Systematic reviews of the evidence regarding chronic cerebral spinal venous insufficiency (CCSVI) and multiple sclerosis
An update for the CIHR Expert Panel
June 4, 2012
From the Canadian Chronic Cerebrospinal Systematic Review Group

Introduction

Our previous report included a systematic review of the studies published about chronic cerebrospinal venous insufficiency (CCSVI) and multiple sclerosis (MS) from 2005 to September, 2011(1). This update focuses on the literature published between September, 2011 and March, 2012. As before, we have only included papers published in the peer-reviewed literature, and have not included abstracts.

In the interest of clarity, we are publishing this update as a stand-alone publication, rather than adding supplementary data to our earlier report. This is because the previous report is quite long, and we are concerned that the information highlighted in this update would be difficult to locate. Readers who have not read the previous report are encouraged to do so (1).

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, the Cochrane Central Register of Controlled Trials and EMBASE. The searches were completed in January and March 2012. 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 to account for plurals and variations in spelling. The detailed search strategies are provided in our previous report (1).

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.

b) Identification of articles for inclusion
Readers are referred to our previous report for a description of the methodological approach used to identify eligible articles and abstract data (1).

c) Sensitivity analysis according to blinding
Blinding the interpreters of a diagnostic test as to whether the study participant has the disease (in this case MS), is an important feature of a high quality study of a diagnostic test. This is particularly true for a test that is subjective, such as ultrasonography. We therefore conducted a sensitivity analysis of the 13 studies that assessed CCSVI with ultrasonography in patients with MS compared to healthy controls.

We evaluated the odds of venous abnormalities (CCSVI diagnosis and the five CCSVI parameters individually) in patients with MS compared to HC, according to method of blinding. For the studies in which double-blinding was not described, we conducted the meta-analysis with and without Zamboni's study. In order to include data from all studies, whenever zeros were present in the numerators of both cells (i.e. when it was not possible to calculate a point estimate, because there were no events), we added a '1' to the numerator of each cell.

We also conducted a meta-regression analysis across all studies, to determine whether blinding had a statistical significant effect upon the magnitude of the odds ratio of the association between CCSVI and MS.

Results

a) Identification of eligible studies
Figures 1 and 2 display the results of the most recent literature searches and evaluation of potentially eligible articles.

Figure 1a: Identification of Studies of Association and Other Diagnostic Studies: Results of Literature Search Update (September 2011 – January, 2012)

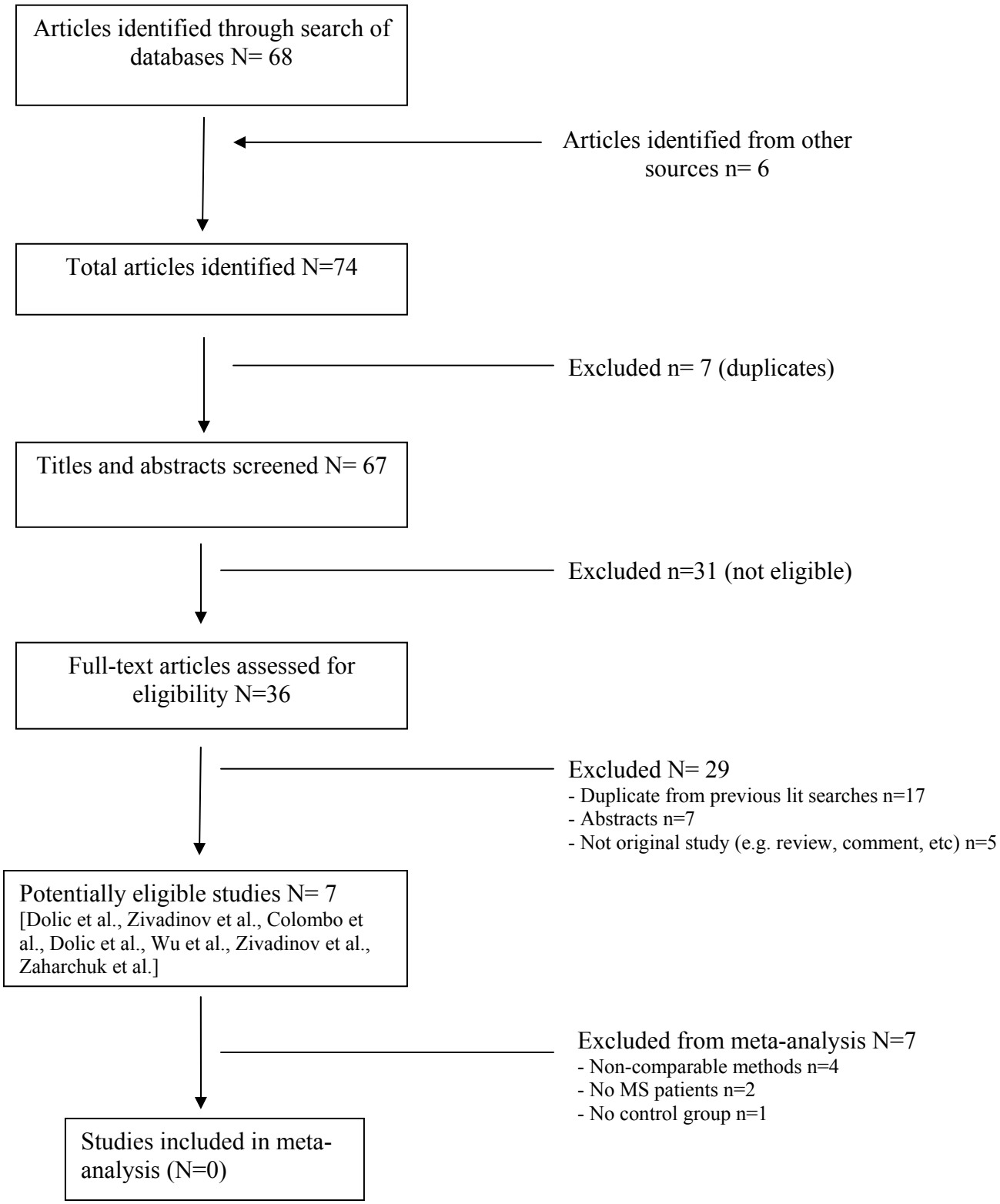


Figure 1b: Identification of Studies of Association and Other Diagnostic Studies: Results of Literature Search Update (January, 2012 – March, 2012)

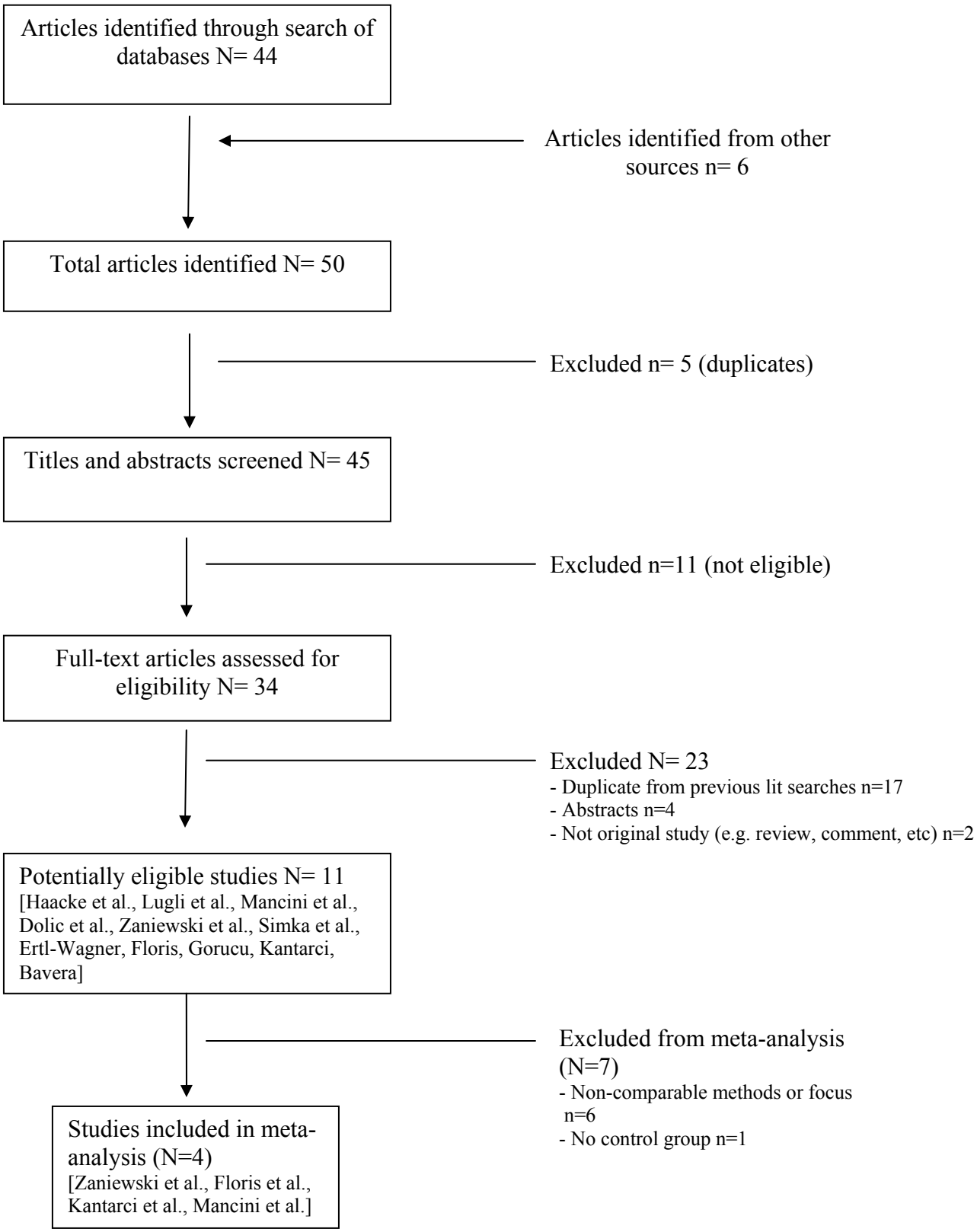


Figure 2a: Identification of Studies of Benefits and Harms of Endovascular Interventions for CCSVI: Results of Literature Search Update (September, 2011 – January, 2012)

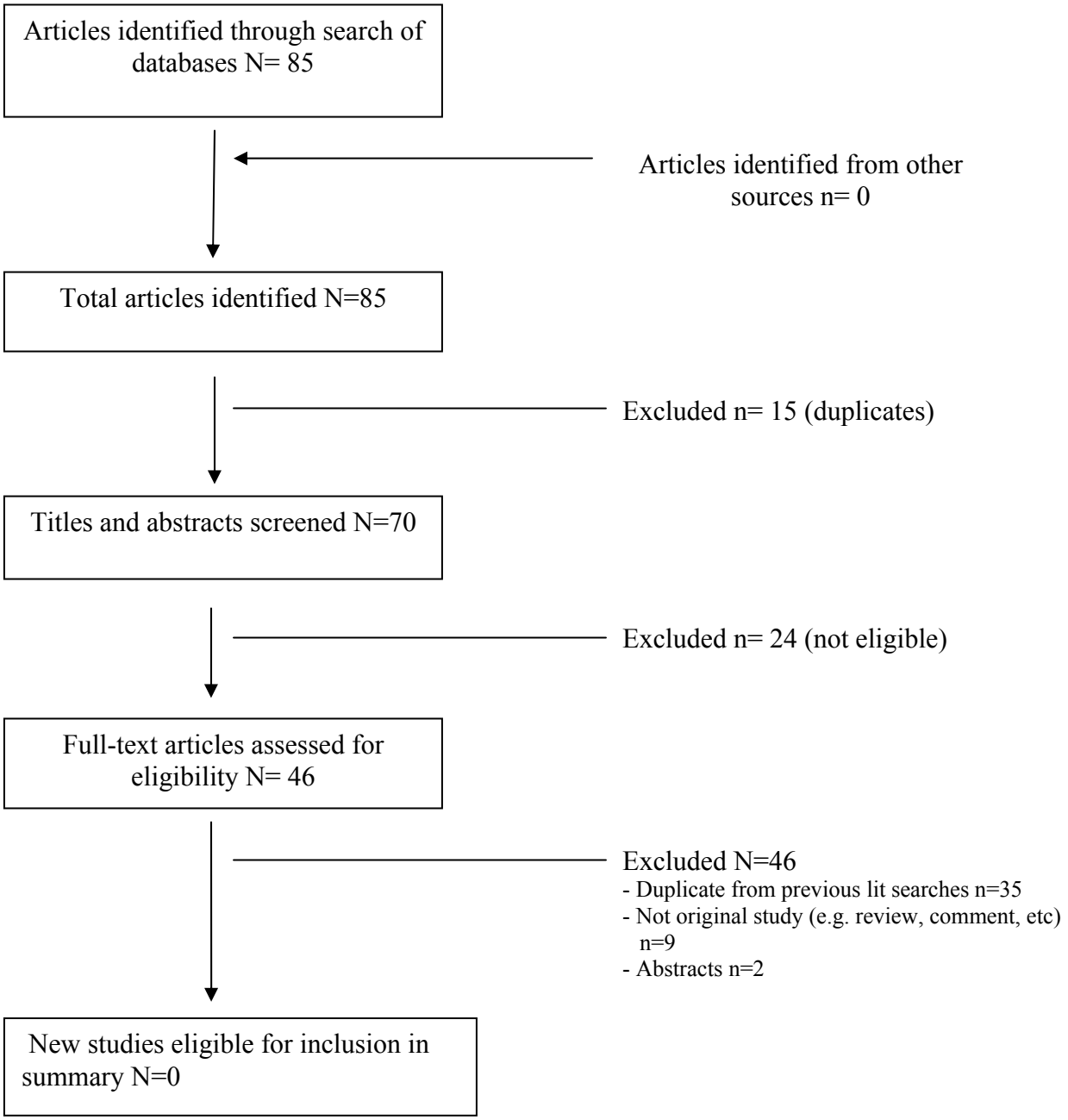
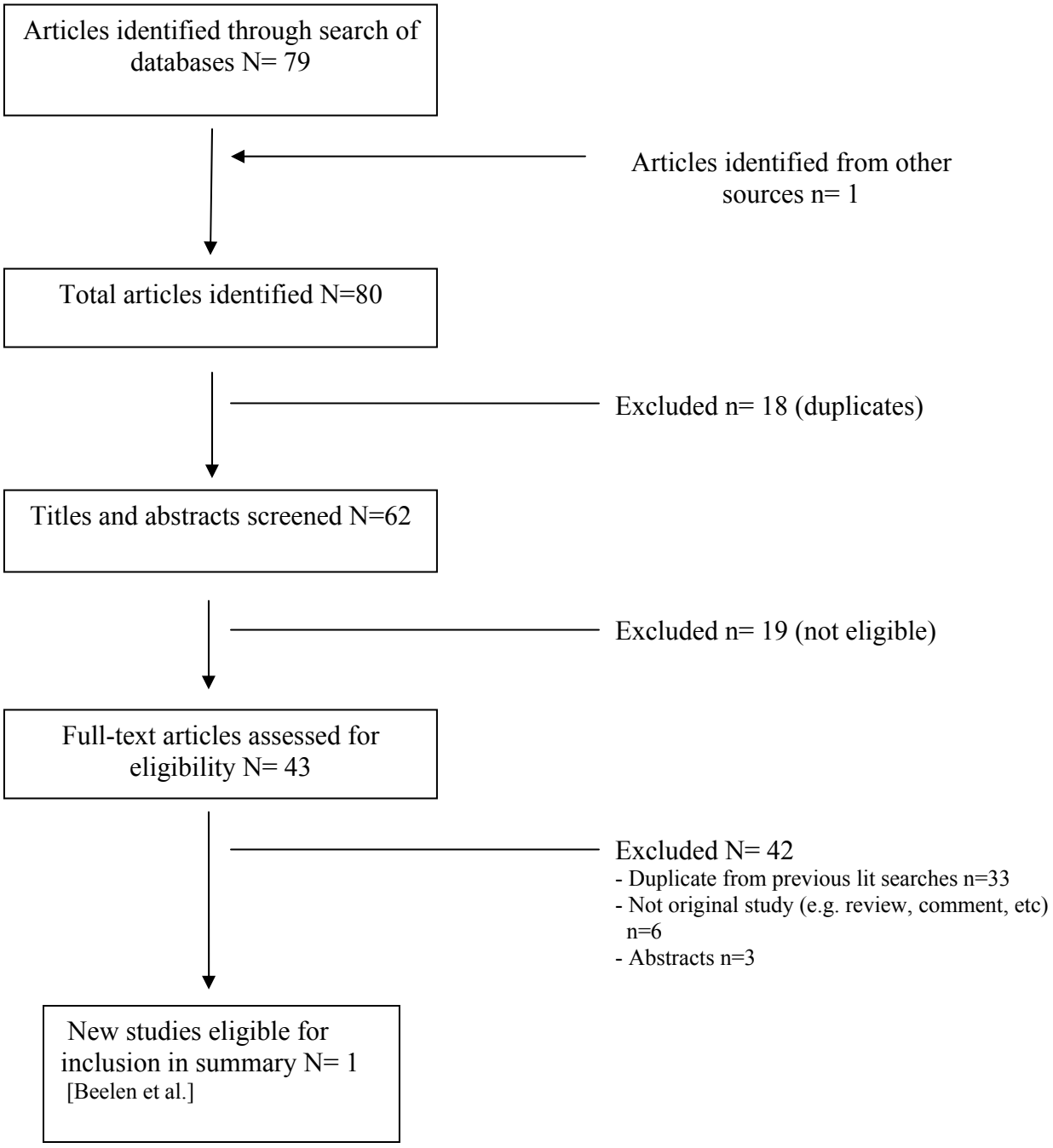


Figure 2b: Identification of Studies of Benefits and Harms of Endovascular Interventions for CCSVI: Results of Literature Search Update (January, 2012 – March, 2012)



b) Association between CCSVI and MS

In our previous report (1), we presented a meta-analysis of 10 studies (including 710 MS patients) evaluating the presence of ultrasound-diagnosed CCSVI as defined by Zamboni in patients with MS and controls [either healthy controls (HC) or controls with other neurological diseases (OND)]. Since then, four new studies (involving 386 MS patients) that meet our inclusion criteria have been published (2-5).The four new studies are described below.

Zaniewski and colleagues from Tychy, Poland studied 181 patients with MS (98 relapsing remitting, 56 secondary progressive, 27 primary progressive) and 50 age- and sex-matched controls (4). The authors described the controls as "volunteers without MS symptoms" and therefore, for the purposes of this systematic review, they were considered to be HCs. This study was not blinded, and it is not clear how the MS patients were recruited.

The authors did not assess reflux in the deep intracerebral veins; consequently, they only assessed 4 of the 5 CCSVI criteria as described by Zamboni. Though the number of participants that were positive for the other 4 CCSVI criteria was described, the total number of patients meeting criteria for a diagnosis of CCSVI was not specified. The frequency of abnormalities in patients with MS (with the values for controls in brackets), was: 54% (4%) for reflux in the internal jugular and vertebral veins, 54% (8%) for stenosis in the internal jugular veins, 10% (0%) for flow not detectable in the internal jugular and vertebral veins and 25% (2%) for abnormal postural control.

Kantarci and colleagues from Istanbul, Turkey performed a blinded assessment of 62 persons with MS (32 relapsing remitting, 13 secondary progressive, 17 primary progressive) and 54 age-matched healthy controls (3). The authors described the blinding protocol, but it is not clear how the MS patients were recruited.

Like Zaniewski, Kantarci and colleagues did not assess the deep cerebral veins. They described the number of study participants positive for the other 4 CCSVI criteria, but did not describe the number of participants who met the criteria for a diagnosis of CCSVI. The frequency of abnormalities in patients with MS, with the values for controls in brackets, was: 44% (39%) for reflux in the internal jugular and vertebral veins, 7% (4%) for stenosis in the internal jugular veins, 16% (6%) for flow not detectable in the internal jugular and vertebral veins and 44% (17%) for abnormal postural control.

Floris and colleagues from Rome, Italy studied 40 patients with MS and 34 age- and sex-matched HCs (2). Correspondence with the author indicated that the study was double-blind, but did not describe the blinding protocol. CCSVI was diagnosed in 55% of MS patients and 35% of healthy controls (odds ratio 2.2, 95% CI 0.9 to 5.7).

The primary purpose of a study of 103 MS patients and 42 controls (of which 26 were healthy and 16 were being investigated for liver disease) conducted in Naples, Italy by Mancini and colleagues was to assess cerebral circulation time; though participants were also assessed for CCSVI using Zamboni's criteria (5). The authors did not provide the

results for the individual diagnostic parameters but indicated that 77% of MS patients and 28% of controls had CCSVI (odds ratio 8.2, 95% CI 3.7 to 18.5). In our meta-analysis, we considered the control participants in this study to be HCs.

The data from these four studies have been added to the tables summarizing the characteristics of the included studies (see Tables 1-4 below). The meta-analysis results are presented below in Figure 3 (diagnosis of CCSVI) and Figure 4 (individual CCSVI parameters).

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. (6)	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 double blinded.
Baracchini et al. (7)	50	110	60	Philips iU22 Extracranial: 5-10 MHz linear array probe. Transcranial: 1-3 MHz phased array probe.	Double blinding not described.
Centonze et al. (8)	84	56	N/A	Esaote Biomedica MyLab-Vinco 25 with a linear LA322 11-3 MHz probe.	Double blinding not described.
Doepp et al. (9)	56	20	N/A	Toshiba Powervision 6000, Extracranial exam: 7.5MHz linear transducer. Transcranial exam: 2.5MHz probe.	Not double blinded.
Krogias et al. (10)	10	2	5	Not described.	Not double blinded.
Mayer et al. (11)	20	20	N/A	Phillips IU22 with an L9-3 probe to assess IJV and VV; S5-1 probe was used for intracranial veins.	Double blinding described.
Zamboni et al. (12)	109	132	45	Esoate-Biosound My lab 25 7.5-10 MHz for extracranial, 2.5 MHz for intracranial.	Double blinding not described.
Zivadinov et	310	163	26	Esaote-Biosound MyLabGOLD25 equipped with	Double

al. (13)				2.5 and 7.5-10 MHz transducers.	blinding described.
Marder et al. (14)	18	N/A	11	Logic 9, GE Healthcare 8MHz linear array probe for extracranial; 2-MHz sector transducer for transcranial examination.	Double blinding not described.
Baracchini et al. (15)	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.	Double blinding described.
Zaniewski et al. (4)	181	50	N/A	GE Logiq US with linear probe at 7.5-10MHz	Not double blinded.
Floris et al. (2)	40	34	N/A	Esaote Biosound MyLab Vinco, equipped with 2.5 and 7.5-13 MHz transducers.	Double blinding not described.
Kantarci et al. (3)	62	54	N/A	Logiq 9 GE with 5-12 MHz linear array transducer.	Double blinding described.
Mancini et al. (5)	103	42	N/A	iU22 US unit with a 9-3-MHz linear-array probe, a 2-1-MHz transcranial phased-array probe, and a 5-8-MHz microconvex probe; Philips, Bothell, Wash.	Double blinding not described.

Note: MS = multiple sclerosis patients, HC = healthy controls, OND = patients with other neurological diseases, N/A = not applicable.

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. (6)	0	21	4	35*	52	N/A	N/A	N/A
Baracchini et al. (7)	50	0	0	33*	70	1.5†	28	N/A
Centonze et al. (8)	0	69	15	39*	62	N/A	82	N/A
Doepp et al. (9)	0	41	15	42*	65	2.7*	N/A	10*
Krogias et al. (10)	0	2	8	42†	30	5.8†	N/A	N/A
Mayer et al. (11)	0	17	3	42*	65	3†	90	13*
Zamboni et al. (12)	0	69	40	40†	59	2†	N/A	6†
Zivadinov et al. (13)	21	191	98	48†	76	3†	89‡	12†
Marder et al. (14)	1	6	11	55*	17	N/A	N/A	21†
Baracchini et al. (15)								
1° progressive	0	0	25	47*	44	6*	N/A	11*
2° progressive	0	0	35	45*	63	6*	N/A	18*
Zaniewski et	0	98	83	41†	61	N/A	N/A	10†

al. (4)								
Floris et al. (2)	0	29	10	41*	68	N/A	N/A	N/A
Kantarci et al. (3)	0	32	30	37*	65	4*	N/A	9*
Mancini et al. (5)	0	41	62	42†	60	4†	71	12†

Note: EDSS = Expanded Disability Status Scale, N/A = information not available. * = mean. † = median.
‡ = calculation based on N=289 MS patients (without CIS subgroup).

Table 3: Characteristics of participants included in the control groups

Study	No. of participants	Age, yr	Female, %
Healthy controls			
Al Omari et al.(6)	25	34‡	52
Baracchini et al. (7)			
Group 1*	50	33‡	70
Group 2†	60	63‡	53
Centonze et al. (8)	56	42‡	64
Doepp et al. (9)	20	41‡	60
Mayer et al. (11)	20	34‡	50
Zamboni et al. (12)			
Group 1*	60	37§	53
Group 2†	72	58§	60
Zivadinov et al. (13)	163	47§	54
Baracchini et al. (15)	60	46‡	55
Zaniewski et al. (4)	50	40§	62
Floris et al. (2)	34	41‡	68
Kantarci et al. (3)	54	37‡	50
Mancini et al. (5)	42	38§	55
Controls with other neurological diseases			
Baracchini et al. (7)	60	64‡	53
Krogias et al. (10)	7	40§	29
Zamboni et al. (12)	45	60§	44
Zivadinov et al. (13)	26	50§	73
Marder et al. ◊ (14)	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 that 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).

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. (6)	No	No	Not sure	No	Convenience	Yes
Baracchini et al. (7)	No	No	Yes	No	Consecutively	Yes
Centonze et al. (8)	Yes	Yes	Yes	No	Convenience	Yes
Doepp et al. (9)	No	No	Yes	No	Convenience	Yes
Krogias et al. (10)	No	No	Not sure	No	Convenience	Not sure
Mayer et al. (11)	No	No	Not sure	No	Convenience	No
Zamboni et al. (12)	Yes	Yes	Not sure	No	Convenience	Yes
Zivadinov et al. (13)	Yes	Yes	Yes	Yes	Convenience	No
Marder et al. (14)	No	No	Not sure	No	Convenience	Yes
Baracchini et al. (15)	No	No	Yes	No	Consecutively	Yes
Zaniewski et al. (4)	No	No	Yes	No	Convenience	Yes
Floris et al. (2)	Not sure	Not sure	Not sure	Not sure	Convenience	Yes

Kantarci et al. (3)	Not sure	Yes	Not sure	Not sure	Convenience	Yes (age)
Mancini et al. (5)	Not sure	Yes	Yes	Yes	Convenience	Yes

Note: MS = multiple sclerosis.
*Methodological quality was assessed using items derived from the Newcastle–Ottawa Quality Assessment Scale tool for observational studies.

As shown below in Figure 3, patients with MS had greater odds of being diagnosed with CCSVI than HCs but there was great heterogeneity in the results [odds ratio: 8.1 (95% CI 2.9-23.1; I^2=84%)]. Patients with MS also had greater odds relative to HCs of being positive for CCSVI criteria 1, 3, 4 and 5, but also with great heterogeneity (see Figure 4).

Because none of the four recently published studies included patients with other neurological diseases, the meta-analysis comparing MS patients and patients with other neurological diseases has not been updated – see our last report for the results of that meta-analysis (1).

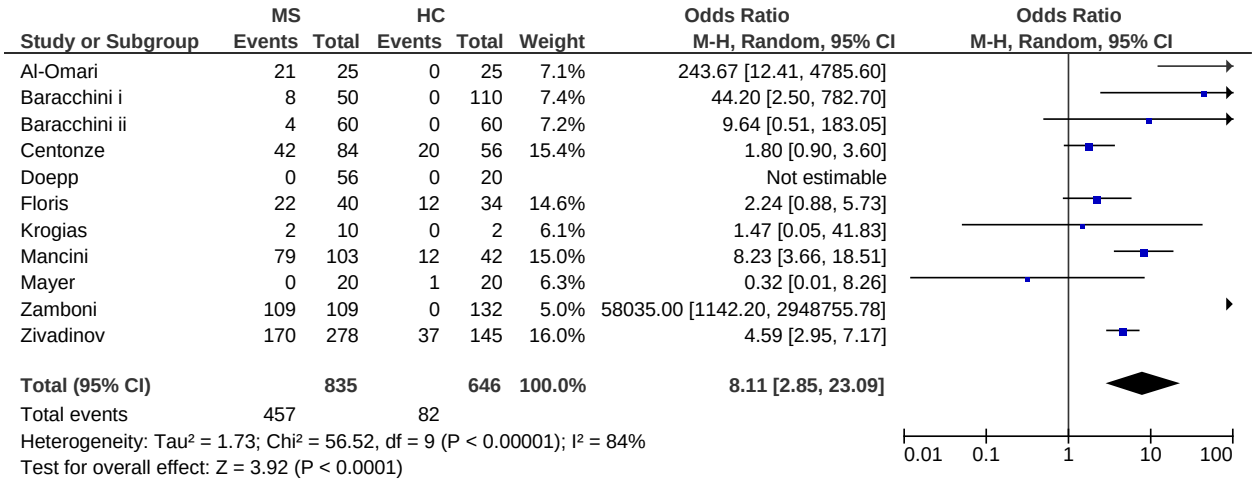


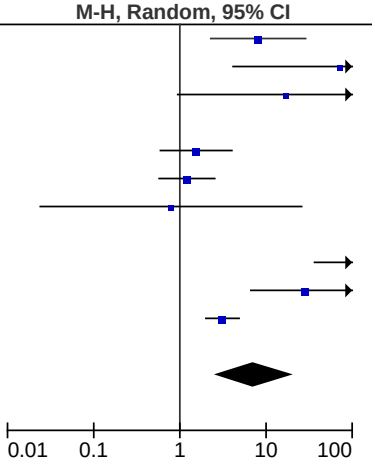
Figure 3: Meta-analysis of a diagnosis of chronic cerebrospinal venous insufficiency (presence of at least two parameters) in patients with multiple sclerosis (MS) versus healthy controls (HC). An odds ratio greater than 1.0 indicates an increased likelihood of a diagnosis of chronic cerebrospinal venous insufficiency in MS patients versus controls. CI = confidence interval, OR = odds ratio.

Study references: Al-Omari(6), Baracchini i (7), Baracchini ii (15), Centonze (8), Doepp (9), Floris (2), Krogias (10), Mancini (5), Mayer (11), Zamboni (12), Zivadinov(13).

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	13.3%	8.14 [2.29, 28.90]
Baracchini i	12	50	0	110	7.4%	71.75 [4.15, 1240.95]
Baracchini ii	7	60	0	60	7.3%	16.96 [0.95, 304.07]
Doepp	0	56	0	20		Not estimable
Floris	17	40	11	34	14.6%	1.55 [0.60, 4.01]
Kantarci	27	62	21	54	15.3%	1.21 [0.58, 2.55]
Krogias	1	10	0	2	5.8%	0.79 [0.02, 25.90]
Mayer	0	20	0	20		Not estimable
Zamboni	76	109	0	132	7.6%	605.15 [36.56, 10016.99]
Zaniewksi	98	181	2	50	12.6%	28.34 [6.68, 120.13]
Zivadinov	137	310	33	163	16.1%	3.12 [2.00, 4.86]
Total (95% CI)		**923**		**670**	**100.0%**	**7.19 [2.52, 20.49]**
Total events	393		73			

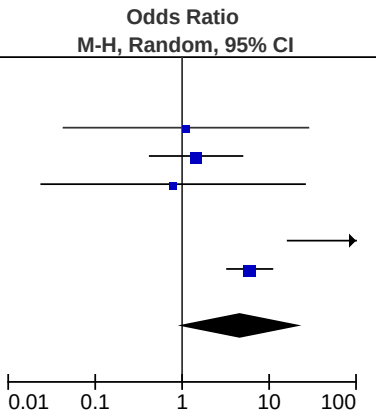
Heterogeneity: Tau² = 1.73; Chi² = 49.83, df = 8 (P < 0.00001); I² = 84%
Test for overall effect: Z = 3.69 (P = 0.0002)



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	14.1%	1.11 [0.04, 28.31]
Floris	8	40	5	34	26.6%	1.45 [0.43, 4.94]
Krogias	1	10	0	2	12.9%	0.79 [0.02, 25.90]
Mayer	0	20	0	20		Not estimable
Zamboni	55	109	0	132	16.3%	269.86 [16.38, 4447.00]
Zivadinov	110	236	15	118	30.0%	5.99 [3.29, 10.91]
Total (95% CI)		**581**		**496**	**100.0%**	**4.64 [0.90, 23.92]**
Total events	175		20			

Heterogeneity: Tau² = 2.24; Chi² = 17.45, df = 4 (P = 0.002); I² = 77%
Test for overall effect: Z = 1.84 (P = 0.07)

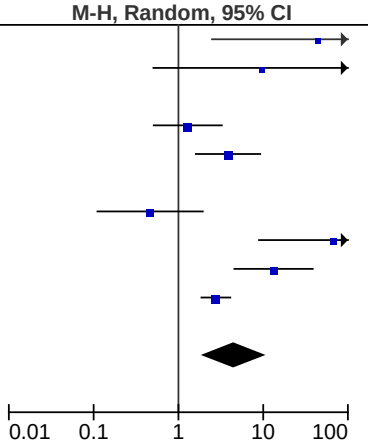


CCSVI Parameter 3

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	6.2%	44.20 [2.50, 782.70]
Baracchini ii	4	60	0	60	6.0%	9.64 [0.51, 183.05]
Doepp	0	56	0	20		Not estimable
Floris	19	40	14	34	15.8%	1.29 [0.51, 3.25]
Kantarci	27	62	9	54	16.1%	3.86 [1.61, 9.25]
Krogias	0	10	0	2		Not estimable
Mayer	13	20	16	20	12.7%	0.46 [0.11, 1.94]
Zamboni	30	109	1	177	9.5%	66.84 [8.96, 498.80]
Zaniewksi	97	181	4	50	15.0%	13.28 [4.59, 38.43]
Zivadinov	197	310	63	163	18.5%	2.77 [1.87, 4.09]
Total (95% CI)		**898**		**690**	**100.0%**	**4.53 [1.89, 10.84]**
Total events	395		107			

Heterogeneity: Tau² = 1.03; Chi² = 32.95, df = 7 (P < 0.0001); I² = 79%

Test for overall effect: Z = 3.39 (P = 0.0007)

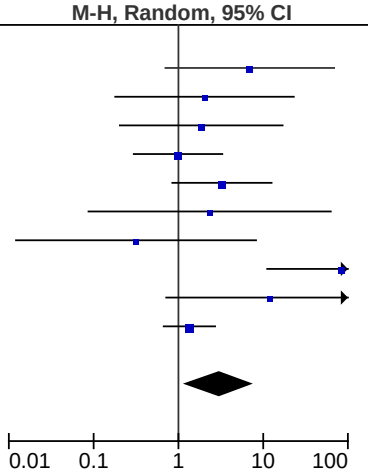


CCSVI Parameter 4

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	8.9%	6.96 [0.71, 68.63]
Baracchini ii	2	60	1	60	8.3%	2.03 [0.18, 23.06]
Doepp	5	56	1	20	9.2%	1.86 [0.20, 16.99]
Floris	7	40	6	34	14.4%	0.99 [0.30, 3.29]
Kantarci	10	62	3	54	13.6%	3.27 [0.85, 12.57]
Krogias	3	10	0	2	5.7%	2.33 [0.09, 62.68]
Mayer	0	20	1	20	5.7%	0.32 [0.01, 8.26]
Zamboni	35	109	1	177	10.1%	83.24 [11.20, 618.93]
Zaniewksi	19	181	0	50	6.9%	12.12 [0.72, 204.32]
Zivadinov	30	310	12	163	17.1%	1.35 [0.67, 2.71]
Total (95% CI)		**923**		**715**	**100.0%**	**3.01 [1.18, 7.67]**
Total events	114		26			

Heterogeneity: Tau² = 1.20; Chi² = 24.02, df = 9 (P = 0.004); I² = 63%

Test for overall effect: Z = 2.31 (P = 0.02)



CCSVI Parameter 5

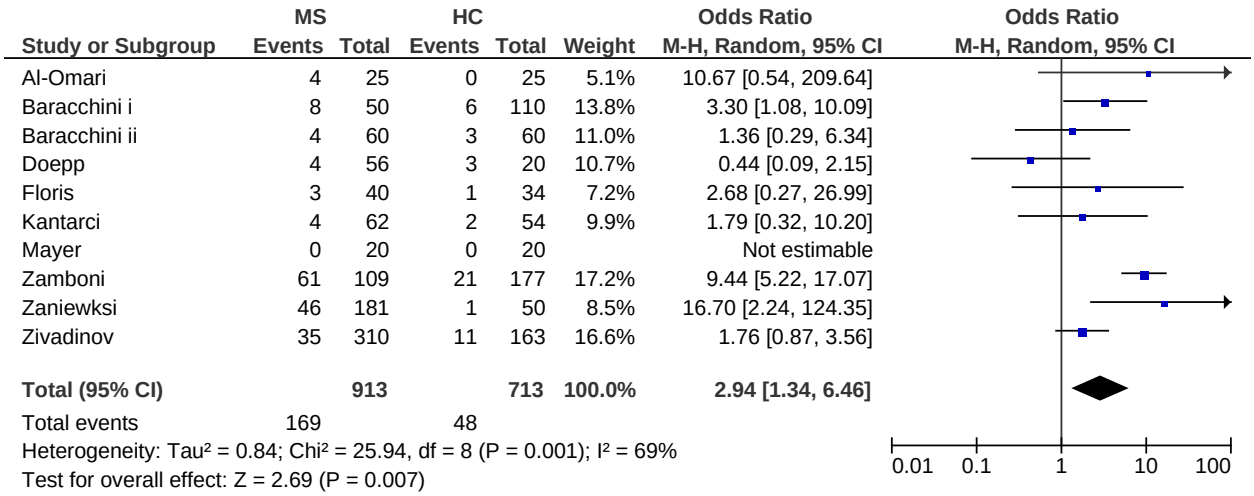


Figure 4: Meta-analysis of individual parameters of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis (MS) versus healthy controls (HC). (1) Reflux in internal jugular veins or vertebral veins; (2) flow reversal in deep cerebral veins; (3) stenoses of internal jugular vein; (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 (6), Baracchini i (7), Baracchini ii (15), Doepp (9), Floris (2), Kantarci (3), Krogias (10), Mayer (11), Zamboni (12), Zaniewski (4), Zivadinov (13).

c) Sensitivity analysis according to blinding

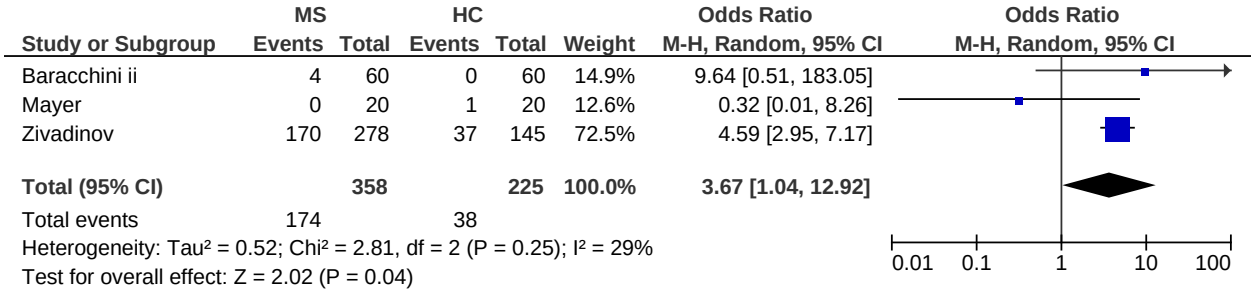
Four studies described their method of blinding well, five indicated that the studies were blinded but did not describe the method of blinding thoroughly, and four were not blinded. Nine studies provided data for both the overall diagnosis of CCVSI and the individual parameters, two provided data for the overall diagnosis only, and two provided data for the parameters only.

The results of the sensitivity analyses of blinding for the diagnosis of CCSVI are shown in Figure 5. The sensitivity analyses of CCSVI parameters 1-5 are presented in Appendix 1. Table 5 summarizes the pooled odds ratios for all of the sensitivity analyses. There was no clear difference in pooled odds ratios according to the method of blinding. In the studies in which double blinding was well described, the pooled odds ratio for CCSVI diagnosis was 3.7 (95% CI 1.04-12.9). None of the pooled odds ratios for any of the 24 analyses were less than 1.0.

The meta-regression found no statistically significant impact of blinding upon the odds ratio for the overall diagnosis of CCSVI. There was a statistically significant effect of

blinding in parameter 1 with Zamboni's study included, parameter 2 without Zamboni's study, and parameter 5 with Zamboni's study included. In all three instances, significant heterogeneity remained after blinding was taken into account.

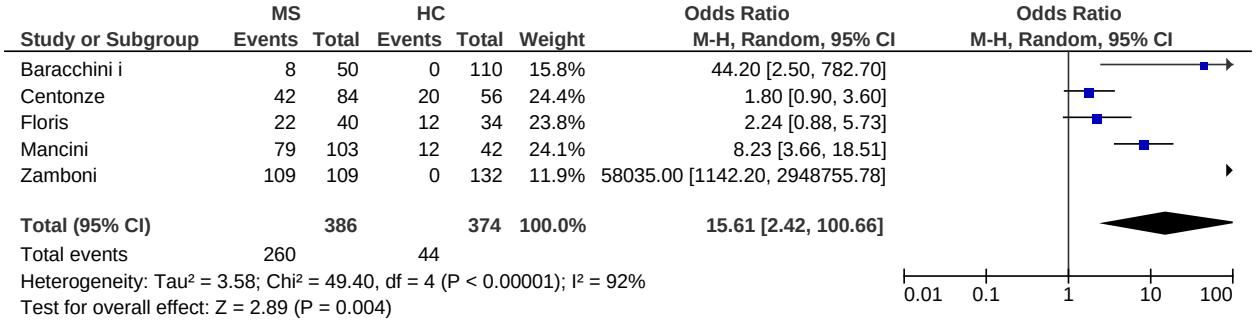
CCSVI diagnosis: studies where double-blinding was described



Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini ii	4	60	0	60	14.9%	9.64 [0.51, 183.05]
Mayer	0	20	1	20	12.6%	0.32 [0.01, 8.26]
Zivadinov	170	278	37	145	72.5%	4.59 [2.95, 7.17]
Total (95% CI)		**358**		**225**	**100.0%**	**3.67 [1.04, 12.92]**
Total events	174		38			

Heterogeneity: Tau² = 0.52; Chi² = 2.81, df = 2 (P = 0.25); I² = 29%
Test for overall effect: Z = 2.02 (P = 0.04)

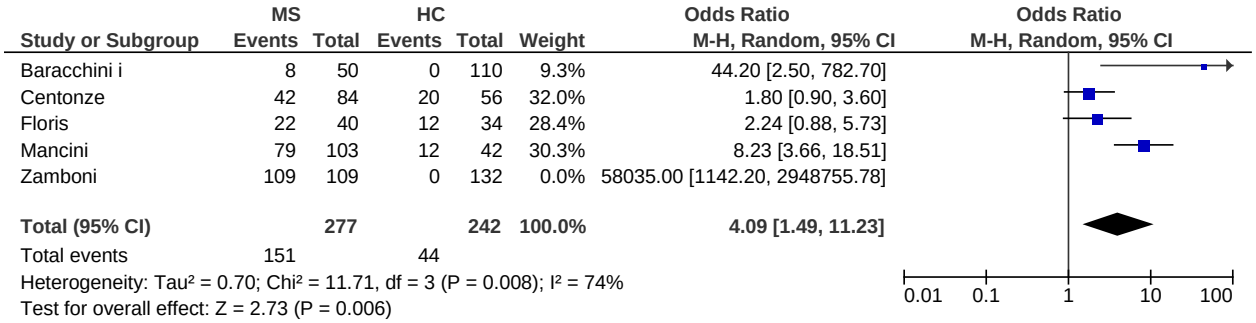
CCSVI diagnosis: studies where double-blinding was not described



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	15.8%	44.20 [2.50, 782.70]
Centonze	42	84	20	56	24.4%	1.80 [0.90, 3.60]
Floris	22	40	12	34	23.8%	2.24 [0.88, 5.73]
Mancini	79	103	12	42	24.1%	8.23 [3.66, 18.51]
Zamboni	109	109	0	132	11.9%	58035.00 [1142.20, 2948755.78]
Total (95% CI)		**386**		**374**	**100.0%**	**15.61 [2.42, 100.66]**
Total events	260		44			

Heterogeneity: Tau² = 3.58; Chi² = 49.40, df = 4 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.89 (P = 0.004)

CCSVI diagnosis: studies where double-blinding was not described, with study by Zamboni et al. excluded



CCSVI diagnosis: studies that were not double-blinded

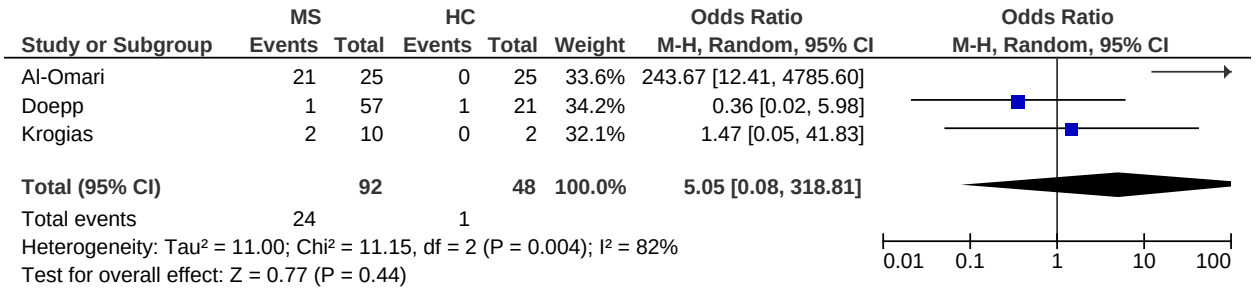


Figure 5: Meta-analysis of a diagnosis of chronic cerebrospinal venous insufficiency (presence of at least two parameters) in patients with multiple sclerosis (MS) versus healthy controls (HC). An odds ratio greater than 1.0 indicates an increased likelihood of a diagnosis of chronic cerebrospinal venous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

Study references: Al-Omari(6), Baracchini i (7), Baracchini ii (15), Centonze (8), Doepp (9), Floris (2), Krogias (10), Mancini (5), Mayer (11), Zamboni (12), Zivadinov(13).

Table 5: Sensitivity analysis according to blinding

	Double-blinding described	Double-blinding not described		Not double-blinded
		With study by Zamboni et al.	Without study by Zamboni et al.	
CCSVI diagnosis	OR= 3.7*	OR= 15.6*	OR= 4.1*	OR= 5.1
CCSVI parameter 1	OR= 2.3	OR= 36.3	OR= 8.6	OR= 4.5
CCSVI parameter 2	OR= 3.5*	OR= 8.7	OR= 1.6	OR= 1.0
CCSVI parameter 3	OR= 2.4*	OR= 11.0	OR= 4.4	OR= 1.3
CCSVI parameter 4	OR= 1.6	OR= 7.8	OR= 2.0	OR= 2.6
CCSVI parameter 5	OR= 1.7	OR= 5.8*	OR= 3.2*	OR= 3.8

* = 95% confidence interval of the pooled odds ratio does not include 1.00 (null value)

d) Recommendations for the standardization of the diagnosis of CCSVI using ultrasonography

Much has been written about the variability of the results of studies that have investigated the frequency of CCSVI in patients with MS as compared to people without MS. One of the factors that may explain the differences in results across studies is a difference in ultrasound technique.

In late 2011, "Recommendations for a protocol" to screen for CCSVI were issued by a group of individuals who attended a meeting about CCSVI in March of that year in Bologna, Italy. The recommendations were prepared in collaboration with the International Union of Angiology, European Venous Forum, International Union of Phlebology, American College of Phlebology, Austral-Asian College of Phlebology, Italian Society for Vascular and Endovascular Surgery, and Italian Society of Pathology of the Vascular Apparatus. The recommendations were published in two different articles (16,17) that appear to be identical.

The articles provide detailed recommendations regarding patient positioning, patient breathing and numerous technical aspects of the ultrasound evaluation of CCSVI, which are very similar to the protocol outlined by Zivadinov. They suggest that because examination of intracerebral reflux is difficult, "…it is not currently recommended as part of the routine procedure…." to examine for CCSVI. CCSVI has traditionally been diagnosed when 2 or more of the 5 CCSVI criteria originally described by Zamboni were positive. When the authors of the new recommendations examined all of the data available to them, they found that omitting intracerebral reflux as a criterion resulted in

reclassification of 7% of patients from positive for CCSVI to negative (these were individuals with 2 positive criteria, 1 of which was intracerebral reflux) (16,17).

e) Reproducibility

One new study by Dolic and colleagues from Buffalo, USA assessed the reproducibility of ultrasonography for the diagnosis of CCSVI (18). Some of the patients in this study were also participants in a study by Zivadinov et al. (13) that was included in our previous report. Dolic found that the kappa for inter-observer agreement in 20 patients with MS and 7 HCs using ultrasonography was 0.64 for the diagnosis of CCSVI (2 or more criteria positive). For the individual criteria, kappa varied from 100 percent agreement for reflux in the IJV and/or VVs (criterion 1) to a kappa of 0.11 for assessment of the deep cerebral veins (criterion 2). Intra-observer agreement was also reported for two ultrasonographers, and the kappa for the diagnosis of CCSVI was 0.34 for one observer and 0.62 for a second observer.

f) Correlation between different methods of assessing cerebral veins

Three studies compared different modalities to assess cerebral veins.

Dolic and colleagues from Buffalo, USA studied 150 patients with MS and 63 age- and sex-matched HCs to compare the types of structural and functional cerebral venous abnormalities detected by ultrasonography and MRV (19). The study participants had also participated in Zivadinov's previously reported ultrasound study (13), and some may also have been participants in Zivadinov's previously published MRV study (20). Ultrasonography and MRV were assessed in a prospective, double-blind manner, and consecutive patients were enrolled.

The intra-rater reliability for the presence of intraluminal, extraluminal and functional venous abnormalities ranged from a kappa of 0.57 to 0.91 when tested in two operators (agreement ranged between 81% and 96%). The inter-rater agreements were poorer – agreement 59% (kappa 0.19) for intraluminal abnormalities, agreement 86% (kappa 0.53) for extraluminal abnormalities and agreement 71% (kappa 0.26) for functional abnormalities. The inter-class correlation coefficient (ICC) was used to assess the intra and inter-rater agreement for numerical values (number of intra, extra and functional venous abnormalities). The ICC for intra-rater agreement ranged from 0.6 to 0.93 in one observer and 0.38 to 0.42 in the other observer. The ICCs for inter-rater agreement were 0.51 for intraluminal, 0.54 for extraluminal and 0.18 for functional venous abnormalities.

A greater difference in venous abnormalities between MS patients and HCs was detected with ultrasonography than with MRV. Patients with MS had a higher number of functional ($p<0.001$), total ($p=0.001$), intraluminal ($p=0.005$) and extraluminal IJV ultrasound abnormalities ($p=0.023$) than HCs. Intraluminal abnormalities included the following: webs, flaps, septa, membranes, and malformed valves; extraluminal abnormalities included stenosis and annulus; and functional abnormalities encompassed reflux/bidirectional flow, paradoxical flow or no flow. Notably and in contradistinction to this group's prior studies, HCs frequently (49%) demonstrated intraluminal abnormalities, although these were more common in patients with MS (68%).

There was no difference in MRV IJV flow morphology (assessed as absent, pinpoint, flattened, crescentric, and ellipsoid) between MS patients and HCs, although MS patients had a higher number of collateral veins (p=0.016). Patients with progressive MS had more extraluminal (p=0.01) and MRV flow abnormalities on TOF (p=0.01) and TRICKS (p=0.006) than patients with relapsing-remitting MS.

The authors concluded that most of the abnormalities in the IJVs in MS patients are caused by intraluminal abnormalities, and that ultrasonography is better at detecting these than is MRV.

Zaharchuk and colleagues from Stanford, USA compared MRV and venography in 39 MS patients (including relapsing-remitting, secondary progressive and primary progressive MS) in a double-blind manner, and the procedures were performed within 24 hours of each other (21). This was a retrospective study, and the criteria used to select patients were not clear.

IJV stenosis was assessed using 2D-TOF and was scored on a four part scale as normal, round or ovoid; mild flattening; moderate flattening; and severe flattening or not visualized. The IJVs were assessed at three levels – high (C1-3), mid (C3-5) and low (C6-T2), and a composite score was calculated for each patient. Collaterals were assessed using TRICKS images temporally remotely blinded to TOF images, which focused mainly on the posterior paraspinal veins using a 4 part scale: none to minimal; mild; moderate; and severe. The same rating system was used for venograms as was used for MRV.

There was moderate agreement between venography and MRV for IJ stenosis overall (kappa = 0.54), but agreement was low for the C6-T2 level (kappa=0.17). The frequency of severe stenosis at any level was 59% for MRV and 46% for venography. If venography is considered to be the gold standard for IJV severe stenosis, the sensitivity of MRV was 0.83, the specificity was 0.67, the positive predictive value was 0.68 and the negative predictive value was 0.82.

The agreement between MRV and venography for the presence of collaterals was less than for IJV stenosis (kappa= 0.30). MRV detected more collaterals than venography (mean 1.76 versus 1.33; p= 0.002) and a higher prevalence of severe collaterals (21% versus 14%).

Lugli and colleagues from Modena, Italy compared the findings on ultrasonography and venography in 366 IJVs (22). This was a retrospective study of 167 patients who were diagnosed as having CCSVI using Zamboni's ultrasound criteria, and who proceeded to undergo venoplasty (note: it is not clear how 366 IJVs could be examined in 167 patients). The ultrasound and venogram findings were congruent in 262/366 IJVs (219 were abnormal, 43 were normal; agreement was 72%). There was a false positive ultrasound result in 91/366 (25%) IJVs and a false negative result in 13/366 (4%) IJVs. An intravascular ultrasound (IVUS) was performed in 18 of the veins where there was

disagreement between the two techniques, and the IVUS agreed with the venogram in 58% and the ultrasound in 42%.

g) Harms associated with endovascular treatment

One new study reported on the short-term harms associated with venoplasty. Lugli and colleagues from Modena, Italy reported a retrospective study of 167 MS consecutive patients with CCSVI who underwent 232 venoplasties (2 of the azygos veins) (22). Patients were treated with low molecular weight heparin for a month after the procedure. Stents were not used. Post-procedure ultrasounds were scheduled at 1, 6 and 12 months, but the number actually performed was not reported. There were no deaths, serious arrhythmias, strokes, myocardial infarctions or major hemorrhages. A femoral cut-down was required to remove a broken balloon in one patient. A left iliac compression (May-Thurner syndrome) occurred in 7 patients (confirmed by IVUS) and an asymptomatic nutcracker syndrome occurred in 1 patient. A transient headache occurred in 13% of patients and an unspecified allergy to contrast dye in one patient. In 12% of ultrasound examinations performed one month after the procedures there was "persistence of altered flow".

h) Benefits of endovascular treatment

No randomized trials have been reported since our last report.

One non-randomized, non-controlled observational study has been reported. Beelen and colleagues from Belgium reported on 67 patients with MS (mean age 45 years; 43 relapsing remitting, 11 secondary progressive, 13 primary progressive) who underwent endovascular treatment (23). The type of treatment was not described. The MSQoL-54 was assessed before and after the procedure, and the Physical and Mental Health Composite Scores were reported. It is not clear whether these patients represent consecutive patients treated, or whether they were selected patients.

The patients were divided into three groups, with outcomes being reported at 3 months in one third, 6 months in a third and 12 months in a third. The mean scores and standard deviations were not reported, but there was a statistically significant improvement in both scores at 3 months ($p<0.005$); the physical health score was statistically significantly improved at 6 months ($p=0.04$) [but not the mental health score ($p=0.15$)] and neither score was statistically significantly improved at 12 months ($p=0.13$).

i) Planned and on-going randomized trials

One randomized trial (principal investigator: Dr. Mehta from Albany, USA) was terminated prematurely after randomization of just two patients. The FDA sent Dr. Mehta a Warning Letter pointing out that he had not received the required FDA approval needed in order to enter patients into the study, and it seems that Dr. Mehta has decided to stop the trial (24).

To our knowledge, there are six randomized trials of venoplasty in patients with MS; two that are currently underway (25,26) and four that are about to get underway (27-30). Four have been registered on www.clinicaltrials.gov (25-28) and one has been registered on

the Australian New Zealand Clinical Trials Registry (29). Funding of the sixth trial has been announced by the Canadian Institutes of Health Research (CIHR) (30), but the details of the investigators or study design have not been provided, and the study is not registered with www.clinicaltrials.gov. A description of the five registered studies is provided in Table 6 (information obtained from clinical trial registries).

The trials vary in sample size from 12 to 679. The primary outcome measures vary markedly, and include MSQOL-54, EDSS, an "integrated functional score", neuromuscular function on electromyography, and serious adverse events. The type of MS (relapsing remitting, primary progressive, secondary progressive) eligible for entry in the trials also varies.

According to www.clinicaltrials.gov, the ongoing study from Albany, USA with a sample size of 130 (not the same one that was mentioned above as having been terminated) has been enrolling patients since August 2010 (25). The investigators were not willing to indicate how many patients have been randomized to date (personal communication, Barbara McDowell).

The largest planned study is a multicentre study from Italy (28), and the first patient is expected to be randomized in June 2012 (personal communication, Dr. Roberto Grilli). This study has two primary outcome measures, both assessed at one year (personal communication Dr. Graziela Filippini, Chair of the Steering Committee). The first is a composite of five validated functional measures. Patients will be considered to have improved if they improved in one or more of the five outcomes and did not worsen on any of the others. The functional outcomes assessed are walking, coordination, vision, bladder function and balance. The second primary outcome consists of MRI findings.

It is not clear whether the patients being entered into the Australian study all have CCSVI – the protocol on http://www.anzctr.org.au lists a variety of venographic abnormalities as inclusion criteria, but does not specifically mention CCSVI (29).

Table 6: Profile of Registered Clinical Trials

Trial and location	Study type/design	Eligibility criteria	Sample size	Primary outcome	Secondary outcome(s)	Treatment arm details
Evaluation of Angioplasty in the Treatment of Chronic Cerebrospinal Venous Insufficiency (CCSVI) in Multiple Sclerosis, Community Care Physicians, P.C NCT01201707 (25) New York, USA Start date: August 2010 Estimated primary outcome measure completion date: August 2012 Estimated study	Interventional Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Outcomes Assessor) Primary Purpose: Treatment	Aged 18-60 years Patients with clinically definite multiple sclerosis by Polman criteria Patients with a history of MS as defined above with an EDSS between 3 and 6. *Exclusion Criteria:* - renal insufficiency based on an estimated GFR <45 - known severe allergy to iodine or gadolinium-based contrast agents which cannot be adequately pre-medicated - known allergy to nickel - pregnancy - contraindication to anticoagulation or anti-platelet medication - contraindication to drugs used for conscious sedation during interventional	Estimated enrollment: 130	Impact of CCSVI treatment on quality of life in patients with MS [Time frame: 1 month, 3 months, 6 months, 12 months, 18 months, 24 months]. Designated as safety issue: No This will be assessed using the Multiple Sclerosis Quality of Life-54 (MSQOL-54), which is a health-related quality of life measure that combines generic and MS-specific items into a single, self-report questionnaire.	Clinical significance of CCSVI in MS patients [Time frame: 1 month, 12 months, 18 months, 24 months] Designated as safety issue: No This will be assessed clinically using annualized relapse rates, Expanded Disability Status Scale (EDSS) change and change in the timed 25 foot walk. Superiority of angioplasty to observation for treatment of CCSVI [Time frame: 1 month, 6 months, 12 months, 18 months, 24 months] Designated as safety issue: No This will be assessed clinically using annualized relapse rates, EDSS change, and change in the timed 25-foot walk. Incidence of CCSVI in patients with MS [Time frame: 0 Months] Designated as safety issue: No This will be assessed on the	<u>Experimental:</u> Treatment of CCSVI with Angioplasty At the time of venography, these patients will have had a significant lesion (blockage) in the internal jugular and/or the azygos vein that will be treated with angioplasty. <u>Procedure:</u> Angioplasty In this procedure, a small catheter (tube) that is approximately the size of a piece of spaghetti is introduced into the vein that is narrowed based on the findings of the venogram. This catheter has a small balloon on it. That balloon is inflated across the narrowing within the vein with the goal of increasing the

completion Date: August 2013 Contact: Barbara J. MacDowell, RN Clinical Research Manager	procedures, including Versed and Fentanyl - history of deep venous thrombosis of the lower extremities - occlusion of the right and left common femoral veins - had any changes in their disease modifying drug regimen for MS during the 6 months prior to enrollment in this trial. (Including addition of any new medications, a change in the dosage of any medications, or the removal of any medications from a patient's drug regimen). - life expectancy <18 month - currently enrolled or plan to enroll in other investigations that conflict with follow-up testing or confounds data in this trial.	basis of the findings on diagnostic venography of the internal jugular and azygos veins, which is the initial procedure performed in these patients. Safety of endovascular treatment of CCSVI [Time frame: 1 month, 3 months, 6 months, 12 months, 18 months, 24 months] Designated as safety issue: Yes This is defined as the number and nature of any procedure-related adverse effects. Target vessel primary and secondary patency [Time frame: 1 month, 3 months, 6 months, 12 months, 18 months, 24 months] Designated as safety issue: No Primary patency is the interval following the initial angioplasty procedure until a reintervention is performed to preserve patency. Secondary patency is defined as the interval following the initial angioplasty procedure until treatment of the vein is abandoned due to an inability to treat the original lesion.	diameter of that vein and improving flow within that vein. <u>Sham Comparator</u>: Observation of CCSVI At the time of venography, these patients will have had a significant lesion (blockage) in the internal jugular and/or the azygos vein that will not be treated with angioplasty. These patients will be observed after treatment and compared to those patients who received treatment. <u>Procedure:</u> Observation Patients in this arm will be diagnosed with CCSVI based on venography but will receive no intervention. They will be followed in the same manner as patients treated with angioplasty.

Trial and location	Study type/design	Eligibility criteria	Sample size	Primary outcome	Secondary outcome(s)	Treatment arm details
Functional Changes Following Percutaneous Venoplasty in Multiple Sclerosis Patients University of Stirling, NCT01555684 (27) Stirling, UK Study start date: April 2012 Estimated study completion date: August 2012 Estimated primary outcome measure completion date: August 2012 **Contact:**	Interventional Allocation: Randomized Endpoint Classification: Safety Study Intervention Model Parallel Assignment Masking: Single Blind (Investigator) Primary Purpose: Treatment Repeated measures design combined with independent blinded neurological assessment. This design allows measurement of the acute neuromuscular response to the treatment and the chronic response to the treatment (6 weeks) to determine the effect on muscular function, mobility and fatigue. Methods: 4 (first 2 to establish baseline variability of measures) repeat visits to the	Age: 18-65 years Diagnosis of CCSVI using transcranial and extracranial colour Doppler sonography in both supine and sitting positions. The diagnosis requires that ≥ 2 of the following 5 criteria are met: - reflux in the internal jugular or vertebral veins, or both, with the head in any position - reflux in the deep cerebral veins - high-resolution B-mode evidence of internal jugular vein stenosis - absence of Doppler-detectable flow in the internal jugular veins and/or vertebral veins - loss of postural control of the main cerebral venous outflow pathways. Ultrasound for CCSVI determination on visits 1 and 3 DEXA scans for alterations in body	Estimated enrollment: 12 (6 patients per group)	Neuromuscular function [Time frame: 52 days] Designated as safety issue: No The venoplasty procedure will be performed at 8 days.	Free living activity [Time frame: 0-7 and 9-52 days] Designated as safety issue: No Measured by accelerometer.	Experimental: venoplasty procedures Half of the participants receive treatment and the other half do not. Procedure: percutaneous venoplasty to alleviate chronic cerebrospinal venous insufficiency percutaneous venoplasty is where a balloon is inserted and inflated into the jugular vein has been developed to improve this drainage of the CNS, reduce venous hypertension and improve symptoms associated with **MS** Placebo Comparator: Control - no treatment Procedure: percutaneous venoplasty to alleviate chronic

Dr Angus Hunter, Health and Exercise Sciences Research Group, University of Stirling	laboratory to establish neuromuscular measures: HDsEMG pre and post-tetanic induced fatigue, muscle fiber conduction velocity as previously described (Hunter et al., 2011).	composition on visits 2 and 4. With the use of accelerometers monitor free living activity on days 0-7 and 9-42 (post-venoplasty). *Exclusion criteria***:** Non-ambulatory				cerebrospinal venous insufficiency percutaneous venoplasty is where a balloon is inserted and inflated into the jugular vein has been developed to improve this drainage of the CNS, reduce venous hypertension and improve symptoms associated with MS.
Trial and location	**Study type/design**	**Eligibility criteria**	**Sample size**	**Primary outcome**	**Secondary outcome(s)**	**Treatment arm details**
BRAVE-DREAMS (BRAin VEnous DRainage Exploited Against Multiple Sclerosis), S. Anna Hospital, NCT01371760 (28) Italy (20 centers; main center is the University Hospital of Ferrara)	Interventional, Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) Primary Purpose: Treatment	patients affected by CCSVI associated with MS relapsing-remitting and\or secondary progressive 18-65 years old EDSS 2-5 Disease duration <10y No relapse in the 30 days preceding the procedure Clinical stability in the last 6 months with disease mod.	Estimated enrollment: 679; each of which will be followed for 12 months.	Clinical parameters in an integrated functional score. [Time frame: Baseline; 12 months] Designated as safety issue: Yes 5 neurological parameters will be measured by means of proper validated tools at 1 year follow-up. The evaluation leads to a score, respectively expressed as improved, stable, fluctuant, worsened.	EDSS [Time frame: Baseline; 12 months] Designated as safety issue: No Chronic fatigue [Time frame: Baseline; 12 months] Designated as safety issue: No Will be measured by M-FIS (Modified-Fatigue Impact Scale). Cognitive function [Time frame: Baseline; 12 months] Designated as safety issue: Yes Will be measured by means of MoCA mental state questionnaire.	Experimental: Intervention The patients will undergo PTA of the extracranial cerebral veins Procedure: Venous PTA PTA of the internal jugular and/or azygous vein Sham Comparator: Controls The patients will undergo sham procedure Other: Catheter Venography The patients will undergo catheter

Study start date: May 2012. Estimated study completion date: July 2013 Estimated primary outcome measure completion date: April 2013 **Contact:** Roberto Grilli Direttore / Director Agenzia Sanitaria e Sociale Regionale / Regional Agency for Health and Social Care	treatments Patients under the best available therapy A neurologist will check that participants meet all inclusion criteria via neurological examination Eco-color Doppler examination by sonographer to verify CCSVI diagnosis. *Exclusion Criteria:* - patients previously treated for CCSVI or in other clinical trials in the last 3 months - under treatment with natalizumab - pregnant or refusing to adopt contraception - presence of significant co-morbidities - alcohol-drug abuse - thrombophilia - contraindication to MR	The parameters are: A) Dynamic Balance Assessment: Balance Master Limits of Stability (LOS). In static platform, swinging to reach the set position of center of pressure. B) Walking Function: The subject walks spontaneously for 10 meters with chronometric measure of time counting the number of steps. The test calculates the walk ratio i.e. ratio between length and step frequency. C) Manual dexterity. Box & Block test, moving wooden cubes. D) Sphincter control: Post-voiding residual by ultrasounds. E) Visual acuity: Low-contrast visual acuity Sloan Letter Chart. MRI outcome measures: T1Gad	Annualized relapse rate [Time frame: Baseline; 12 months] Designated as safety issue: No In the sub population affected by the RR clinical form, the number of relapses will be assessed. Patency rate [Time frame: Baseline; 12 months] Designated as safety issue: No Will be assessed by means of postoperative Doppler sonography. Emotional status [Time frame: Baseline; 1 year] Designated as safety issue: No Anxiety and Depression Scale for use with multiple sclerosis patients will be administered. Memory and cognition [Time frame: Baseline; 1 year] Designated as safety issue: No Will be assessed by means of PASAT - Paced Auditory Serial Addition Test. Overactive Bladder [Time frame: Baseline; 1 year] Designated as safety issue: No	venography but not PTA.

				active lesion.T2 lesion volume MRI evaluation. [Time frame: Baseline; 12 months] Designated as safety issue: Yes Standard MRI parameters will be assessed by the means of a blinded centre of lecture. Outcome measurement will be performed at baseline, 6 months and at 1 year follow-up.	Will be measured by means of validated Overactive Bladder Questionnaire-b.	
Trial and location	**Study type/ design**	**Eligibility criteria**	**Sample size**	**Primary outcome**	**Secondary outcome(s)**	**Treatment arm details**
In multiple sclerosis patients with extracranial and/or azygos vein stenosis, is percutaneous balloon angioplasty more effective than a sham procedure in terms of changes to physical,	Interventional, Purpose of Trial: Treatment. Randomized controlled trial. Sequence generation: The Alfred biostatistician will be asked to generate a randomization list. Participants will be randomized to an angiogram plus the PTA or to just the angiogram without the PTA. Dark	Signed Participant Information and Consent Form Age 18 to 65 years Expanded Disability Disease Scale Score (EDSS) ranging from 0 to 7.5 Diagnosis of MS according to the revised McDonald criteria	Target sample size: 160. recruitment status: completed. Anticipated date of first participant enrollment: 1/04/2012	Outcomes and time points: Change in clinical parameters and disease progression as measured by Kurtzke Extended Disability Status Scale (EDSS) One week; one, three, six and twelve months compared to baseline. Change in clinical	Composite number of procedural and post procedural adverse events (to 12 months) measured Common Terminology Criteria for Adverse Events v 4 (CTCAE), One week; one, three, six and twelve months compared to baseline Restoration of venous outflow (to 75% from normal outflow) as measured by venogram, US and MRV at	<u>Treatment:</u> surgery Percutaneous Transluminal Angioplasty (PTA) is a minimally invasive procedure done under sedation and with image guidance using x-rays called angiography. It takes about 1.5 – 2 hours. A fine wire called a catheter containing a small inflatable balloon is moved through the veins to

neurological and cognitive function? ACTRN12612 000302853. The Alfred Hospital (29) Australia Contact: Helen Kavnoudias Address: Radiology Research Unit Radiology Department	brown envelopes with sequential numbers one to 180 will be prepared. The envelopes will contain the random allocation. The envelopes will be stored in a locked cupboard; they will be given to the radiologist sequentially at the start of the angiography procedure. Blinded (masking used). Who blinded – those receiving treatment, those assessing the outcomes, and those analyzing results. Assignment: Crossover The participants in the control group will cross over to the PTA treatment arm at 12 months. All participants and the neurologists will not know whether the PTA was performed at the start of the study or at 12 months.	Therapy with currently approved disease-modifying treatments Normal renal function or pre-hydration No allergy to contrast media or pre-treatment Abnormal extracranial vein venogram: 1. Stenosis at any level 2. Abnormal filling of vertebral veins following a jugular bulb injection 3. Delayed emptying of the internal jugular vein in the supine position 4. Persistent filling of the internal jugular vein in the erect position 5. Abnormal appearance of the internal jugular valve 6. Stenosis of the thoracic azygos vein 7. Delayed emptying of the thoracic azygos vein.		parameters and disease progression as measured by the Multiple Sclerosis Functional Composite Score (MSFC). One week; one, three, six and twelve months compared to baseline Change in clinical parameters and disease progression as measured by Cognitive Assessment Tool (CogState). One week; one, three, six and twelve months compared to baseline	six and 12 months. Six and twelve months compared to baseline Change in patient reported quality of life measured by the Multiple Sclerosis Quality of Life-54 Instrument (MSQoL-54) One week; one, three, six and twelve months compared to baseline Change in patient reported fatigue as measured by the Fatigue Severity Scale (FSS) One week; one, three, six and twelve months compared to baseline	the point of narrowing. At that point the balloon is inflated, stretching and opening the vein. The catheter and balloon are then pulled back and removed from the veins. <u>Control (placebo):</u> PTA procedure compared to the control group. The control group will get a sham PTA procedure (the angiogram without the ballooning) at the beginning of the study. The control group will cross over to the treatment arm at 12 months.
Trial and location	**Study type/design**	**Eligibility criteria**	**Sample size**	**Primary outcome**	**Secondary outcome(s)**	**Treatment arm details**
Prospective	Interventional	Age 18-65 years	Estimated	Safety [Time	Preliminary efficacy [Time	<u>Active Comparator</u>:

Randomized Endovascular Therapy in Multiple Sclerosis – PREMiSE NCT01450072 University at Buffalo Neurosurgery (26) Buffalo, NY, USA Study start date: June 2010 Estimated study completion date: December 2012 Estimated primary outcome measure completion date: December 2011	Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Single Blind (Subject) Primary Purpose: Treatment	EDSS 0-6.5 (0-5.5 in the phase II of the study) Diagnosis of relapsing MS according to the McDonald criteria (Polman et al., 2005) 1 relapse within the past year or GAD positive lesion on an MRI within the past 3 months (only for phase II of the study) treatment with current FDA approved disease-modifying treatments (excluding Tysabri or steroids, within the last 30 days prior to enrollment) Evidence of ≥2 sonographic parameters of suspicious abnormal extracranial cerebral venous outflow Normal renal function: creatinine clearance level of >60 *Exclusion Criteria:* - relapse, disease	enrollment: 20	frame: 24 hours-1 month] Designated as safety issue: Yes Percent (%) of patients with Severe Adverse Events (SAE) measured at 24 hours (immediate) and 1 month (short-term) post-surgical safety outcome in MS patients diagnosed with CCSVI that underwent therapeutic angioplasty. The 95% confidence interval of the SAE rates for immediate and short terms will be obtained by the exact method, respectively. For Phase II study, the immediate and short term SAE rates will be analyzed, respectively, using the Fisher's exact test.	frame: 1 month, 3 months, 6 months, and 1 year following] Designated as safety issue: No Restoration of venous outflow (more than 75% of normal outflow) as measured by the combined ECD/TCD and MRV at 1 month, 3 months, 6 months, and 1 year following the angioplasty as compared to baseline as well as compared to a parallel control group of MS patients that will undergo only selective venography without balloon angioplasty (sham-angioplasty). These comparisons will be accomplished by the hierarchical linear model which takes into account the correlation within subjects. Based on the residuals, we will check the normality assumptions by the normal quantile plot and skewness.	Active arm therapeutic balloon angioplasty Device: Selective Venography followed by therapeutic balloon angioplasty Venography followed by therapeutic balloon angioplasty <u>Sham Comparator</u>: Control arm Venography and sham angioplasty Other: Control arm Venography and sham angioplasty

	progression and Tysabri and steroid treatment in the 30 days preceding study entry - pre-existing medical conditions known to be associated with brain pathology - severe peripheral chronic venous insufficiency - abnormal renal function - contrast allergy (anaphylaxis) - not willing to undergo endovascular treatment - peripheral vascular disease

j) Miscellaneous studies
Seven studies (5,18,31-35) have been published since our last report which do not meet the inclusion criteria for our meta-analysis, but do address CCSVI and MS. For completeness, we briefly describe them in Appendix 2.

Discussion

Four additional studies comparing the frequency of CCSVI diagnosis in patients with MS and in individuals without MS were published since our last review (2-5) , which brings the total number of studies of this comparison to fourteen (2-15). The four new studies were modest in size and included between 40 and 181 patients with MS; bringing the total number of MS patients in this meta-analysis to almost 1100. Unfortunately, two studies did not describe how many patients had CCSVI (3,4), and only presented data about the individual criteria. Conversely, one study presented information about the diagnosis of CCSVI, but not the individual criteria (5) .

The updated meta-analysis continues to show a strong odds ratio for the association of CCSVI with MS, although the current odds ratio of 8.4 is less than the previous odds ratio of 12.8. Ten of the eleven studies found an odds ratio greater than 1.0. However, there continues to be an exceptionally large amount of heterogeneity in the results, which preclude definitive conclusions.

Studies in which the method of blinding was well-described found that the odds of CCSVI in patients with MS were statistically significantly higher compared to HCs. This was also true for studies that were described as blinded, but did not describe the method of blinding well. The meta-regression found no impact of blinding on the odds ratio for the overall diagnosis of CCSVI. Thus, from this analysis there is no evidence that non-blinded studies are driving the association between CCSVI and MS.

The meta-regression analysis suggested that blinding did impact upon the odds ratio for some of the parameters, but the effect of blinding was not always in the direction expected (i.e. the unblinded studies did not always find the highest odds ratio), and significant heterogeneity remained after adjusting for blinding.

These findings, plus the observation that some studies found no CCSVI in any study participants while others found CCSVI in both MS patients and HCs, suggest that differences in ultrasound technique and interpretation may explain the marked difference in results.

Recently, individuals representing vascular societies from Italy, Europe, the United States and Austral-Asia, as well as Dr. Zamboni and others have published detailed recommendations for standardizing the assessment of CCSVI with ultrasonography (16, 17). Importantly, they suggested that because assessment of criterion 2 (reflux in the deep cerebral veins) requires Quality Doppler Processing (QDP) which is not available on all

ultrasound scanning, it is “not currently recommended as part of the routine procedure”. Later in the paper, criterion 2 is referred to as “potentially an additional criterion”.

It is unusual to change the definition of an entity shortly after it is described. On the other hand, some would consider it appropriate to modify the definition of a newly described entity on the basis of evolving data. Even with QDP, some investigators have found criterion 2 hard to assess (13) and to have poor inter-observer variability. Omitting criterion 2 would only reclassify about 7% of MS patients from positive for CCSVI to negative.

The three studies that compared different modalities for assessing the cerebral veins (MRV compared with ultrasonography; MRV compared with venography; ultrasonography compared with venography) (19,21,22) suggest that each diagnostic modality assesses different aspects of venous morphology and flow, and that one is not the “gold standard” for the others. More research on this topic should clarify this further.

Our previous review identified six studies (including a total of 1148 patients) that reported the frequency of immediate peri-procedure complications (36-41). The most frequent serious complication was a serious arrhythmia, which occurred in 1-2% of patients. Since then, one additional study in 167 patients found no serious complications other than one patient who needed a femoral cut down to remove a broken balloon. The FDA recently released an alert about the potential dangers of endovascular treatment for CCSVI (42). This alert appears to be based upon previously reported cases of serious adverse events, including death. No new data were provided in the FDA warning.

Six randomized trials assessing venoplasty in MS patients with CCSVI are underway or about to start (25-30). They vary markedly in sample size and primary outcome, although they will likely all be collecting similar data. However, given the relatively small samples sizes of most of the trials, the results may not be definitive; particularly with regard to subgroups of interest (e.g. the impact of venoplasty in patients with relapsing-remitting MS compared with progressive MS). Consideration should be given to planning an individual patient meta-analysis, where data from all of the studies are pooled to allow a more robust estimate of the treatment effect, the impact of treatment on the large number of outcomes being assessed, and an exploration of pre-specified subgroup analyses.

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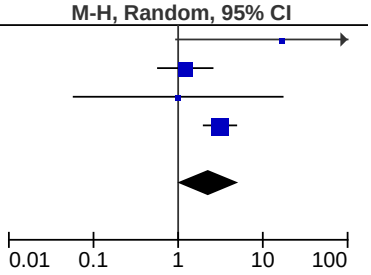
Appendix 1

Sensitivity analysis of CCSVI parameters by type of blinding

A- Double-blinding described

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini ii	7	60	0	60	7.1%	16.96 [0.95, 304.07]
Kantarci	27	62	21	54	38.1%	1.21 [0.58, 2.55]
Mayer	1	21	1	21	7.3%	1.00 [0.06, 17.12]
Zivadinov	137	310	33	163	47.6%	3.12 [2.00, 4.86]
Total (95% CI)		**453**		**298**	**100.0%**	**2.26 [0.99, 5.14]**
Total events	172		55			

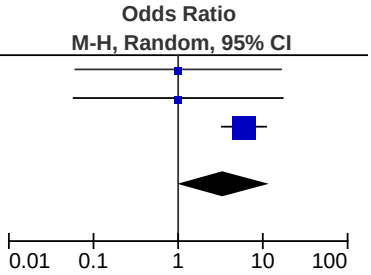
Heterogeneity: Tau² = 0.32; Chi² = 6.76, df = 3 (P = 0.08); I² = 56%
Test for overall effect: Z = 1.94 (P = 0.05)



Parameter 1

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini ii	1	61	1	61	15.5%	1.00 [0.06, 16.36]
Mayer	1	21	1	21	15.1%	1.00 [0.06, 17.12]
Zivadinov	110	236	15	118	69.3%	5.99 [3.29, 10.91]
Total (95% CI)		**318**		**200**	**100.0%**	**3.46 [1.02, 11.74]**
Total events	112		17			

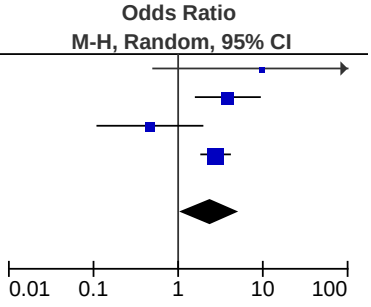
Heterogeneity: Tau² = 0.47; Chi² = 2.85, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 1.99 (P = 0.05)



Parameter 2

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini ii	4	60	0	60	6.5%	9.64 [0.51, 183.05]
Kantarci	27	62	9	54	30.8%	3.86 [1.61, 9.25]
Mayer	13	20	16	20	19.1%	0.46 [0.11, 1.94]
Zivadinov	197	310	63	163	43.6%	2.77 [1.87, 4.09]
Total (95% CI)		**452**		**297**	**100.0%**	**2.36 [1.06, 5.27]**
Total events	241		88			

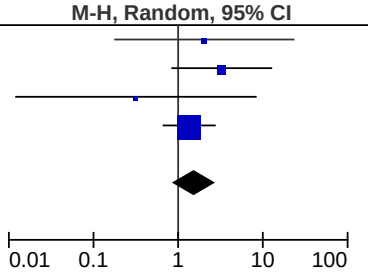
Heterogeneity: Tau² = 0.35; Chi² = 7.19, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 2.10 (P = 0.04)



Parameter 3

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini ii	2	60	1	60	5.9%	2.03 [0.18, 23.06]
Kantarci	10	62	3	54	19.2%	3.27 [0.85, 12.57]
Mayer	0	20	1	20	3.3%	0.32 [0.01, 8.26]
Zivadinov	30	310	12	163	71.6%	1.35 [0.67, 2.71]
Total (95% CI)		**452**		**297**	**100.0%**	**1.56 [0.87, 2.82]**
Total events	42		17			

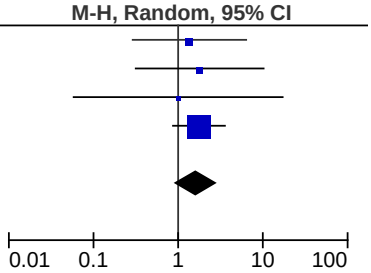
Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)



Parameter 4

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini ii	4	60	3	60	14.6%	1.36 [0.29, 6.34]
Kantarci	4	62	2	54	11.5%	1.79 [0.32, 10.20]
Mayer	1	21	1	21	4.3%	1.00 [0.06, 17.12]
Zivadinov	35	310	11	163	69.6%	1.76 [0.87, 3.56]
Total (95% CI)		**453**		**298**	**100.0%**	**1.66 [0.92, 2.99]**
Total events	44		17			

Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)

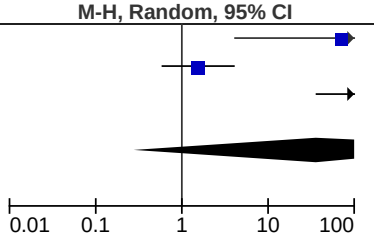


Parameter 5

B- Double-blinding not described

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	12	50	0	110	32.1%	71.75 [4.15, 1240.95]
Floris	17	40	11	34	35.6%	1.55 [0.60, 4.01]
Zamboni	76	109	0	132	32.2%	605.15 [36.56, 10016.99]
Total (95% CI)		**199**		**276**	**100.0%**	**36.33 [0.28, 4637.47]**
Total events	105		11			

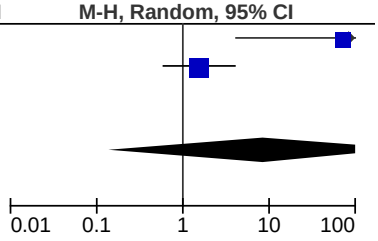
Heterogeneity: Tau² = 16.94; Chi² = 30.02, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.45 (P = 0.15)



Parameter 1

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	12	50	0	110	44.8%	71.75 [4.15, 1240.95]
Floris	17	40	11	34	55.2%	1.55 [0.60, 4.01]
Zamboni	76	109	0	132	0.0%	605.15 [36.56, 10016.99]
Total (95% CI)		**90**		**144**	**100.0%**	**8.62 [0.14, 535.52]**
Total events	29		11			

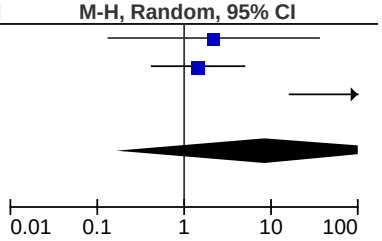
Heterogeneity: Tau² = 7.80; Chi² = 7.63, df = 1 (P = 0.006); I² = 87%
Test for overall effect: Z = 1.02 (P = 0.31)



Parameter 1 (Zamboni excluded from meta-analysis)

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	1	51	1	111	31.8%	2.20 [0.13, 35.89]
Floris	8	40	5	34	36.5%	1.45 [0.43, 4.94]
Zamboni	55	109	0	132	31.7%	269.86 [16.38, 4447.00]
Total (95% CI)		**200**		**277**	**100.0%**	**8.69 [0.17, 441.88]**
Total events	64		6			

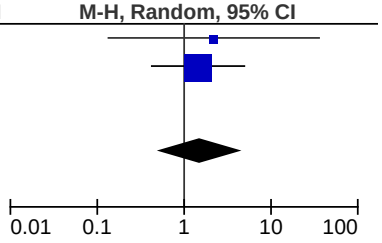
Heterogeneity: Tau² = 10.62; Chi² = 18.52, df = 2 (P < 0.0001); I² = 89%
Test for overall effect: Z = 1.08 (P = 0.28)



Parameter 2

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	1	51	1	111	16.1%	2.20 [0.13, 35.89]
Floris	8	40	5	34	83.9%	1.45 [0.43, 4.94]
Zamboni	55	109	0	132	0.0%	269.86 [16.38, 4447.00]
Total (95% CI)		**91**		**145**	**100.0%**	**1.55 [0.51, 4.76]**
Total events	9		6			

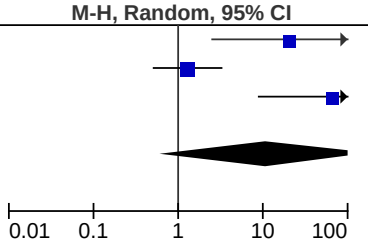
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)



Parameter 2 (Zamboni excluded from meta-analysis)

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	8	50	1	110	31.5%	20.76 [2.52, 171.10]
Floris	19	40	14	34	36.5%	1.29 [0.51, 3.25]
Zamboni	30	109	1	177	32.0%	66.84 [8.96, 498.80]
Total (95% CI)		**199**		**321**	**100.0%**	**10.95 [0.62, 191.98]**
Total events	57		16			

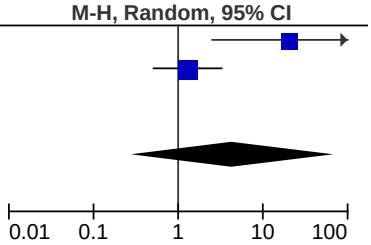
Heterogeneity: Tau² = 5.63; Chi² = 18.02, df = 2 (P = 0.0001); I² = 89%
Test for overall effect: Z = 1.64 (P = 0.10)



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	1	110	44.2%	20.76 [2.52, 171.10]
Floris	19	40	14	34	55.8%	1.29 [0.51, 3.25]
Zamboni	30	109	1	177	0.0%	66.84 [8.96, 498.80]
Total (95% CI)		**90**		**144**	**100.0%**	**4.41 [0.28, 69.70]**
Total events	27		15			

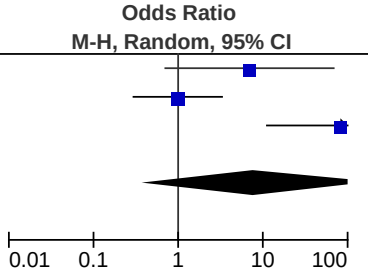
Heterogeneity: Tau² = 3.33; Chi² = 5.83, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 1.05 (P = 0.29)



Parameter 3 (Zamboni excluded from meta-analysis)

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	3	50	1	110	31.3%	6.96 [0.71, 68.63]
Floris	7	40	6	34	36.0%	0.99 [0.30, 3.29]
Zamboni	35	109	1	177	32.7%	83.24 [11.20, 618.93]
Total (95% CI)		**199**		**321**	**100.0%**	**7.76 [0.37, 161.04]**
Total events	45		8			

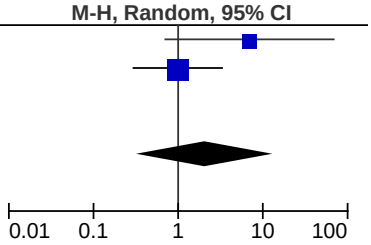
Heterogeneity: Tau² = 6.28; Chi² = 16.99, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 1.32 (P = 0.19)



Parameter 4

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	3	50	1	110	37.0%	6.96 [0.71, 68.63]
Floris	7	40	6	34	63.0%	0.99 [0.30, 3.29]
Zamboni	35	109	1	177	0.0%	83.24 [11.20, 618.93]
Total (95% CI)		**90**		**144**	**100.0%**	**2.04 [0.32, 12.95]**
Total events	10		7			

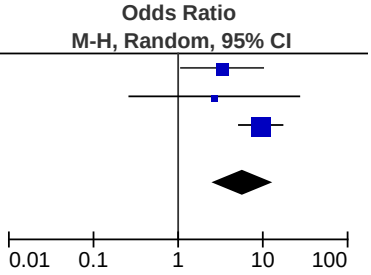
Heterogeneity: Tau² = 1.04; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.76 (P = 0.45)



Parameter 4 (Zamboni excluded from meta-analysis)

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	8	50	6	110	32.6%	3.30 [1.08, 10.09]
Floris	3	40	1	34	11.2%	2.68 [0.27, 26.99]
Zamboni	61	109	21	177	56.2%	9.44 [5.22, 17.07]
Total (95% CI)		**199**		**321**	**100.0%**	**5.82 [2.52, 13.42]**
Total events	72		28			

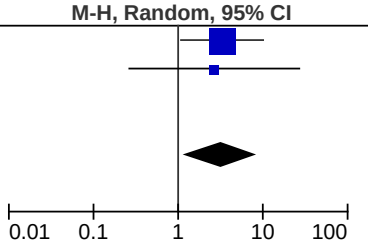
Heterogeneity: Tau² = 0.23; Chi² = 3.38, df = 2 (P = 0.18); I² = 41%
Test for overall effect: Z = 4.13 (P < 0.0001)



Parameter 5

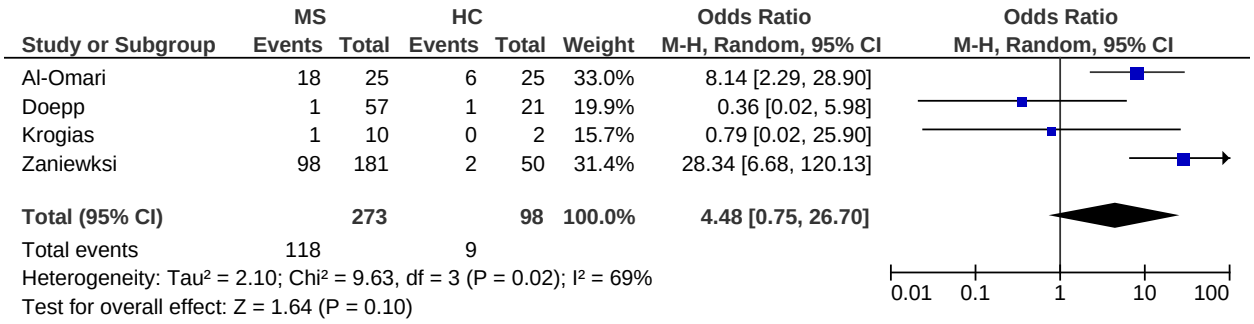
Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Baracchini i	8	50	6	110	81.1%	3.30 [1.08, 10.09]
Floris	3	40	1	34	18.9%	2.68 [0.27, 26.99]
Zamboni	61	109	21	177	0.0%	9.44 [5.22, 17.07]
Total (95% CI)		**90**		**144**	**100.0%**	**3.17 [1.16, 8.68]**
Total events	11		7			

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)

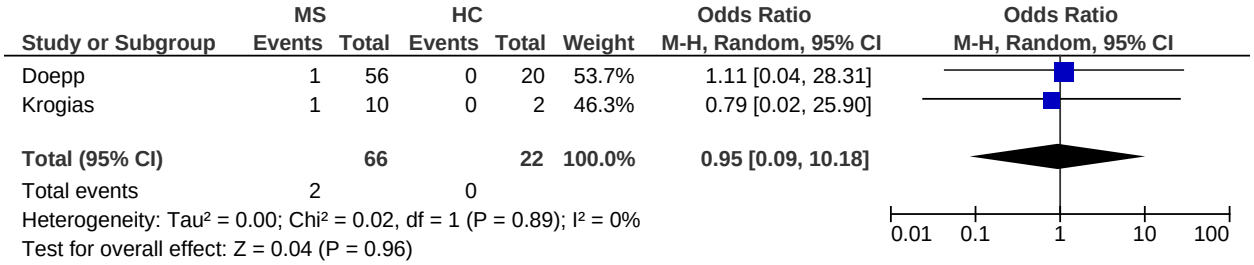


Parameter 5 (Zamboni excluded from meta-analysis)

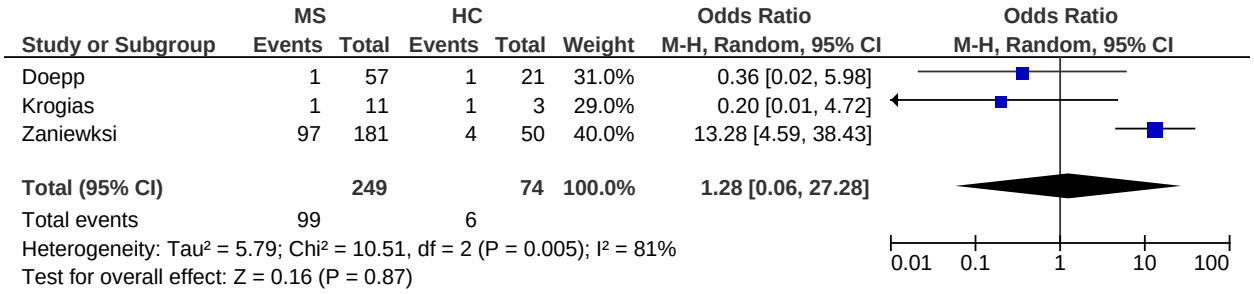
C- Not double-blinded



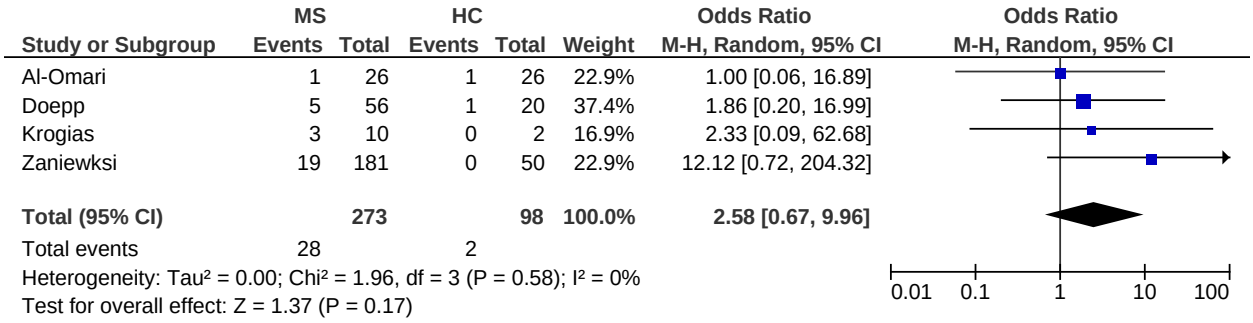
Parameter 1



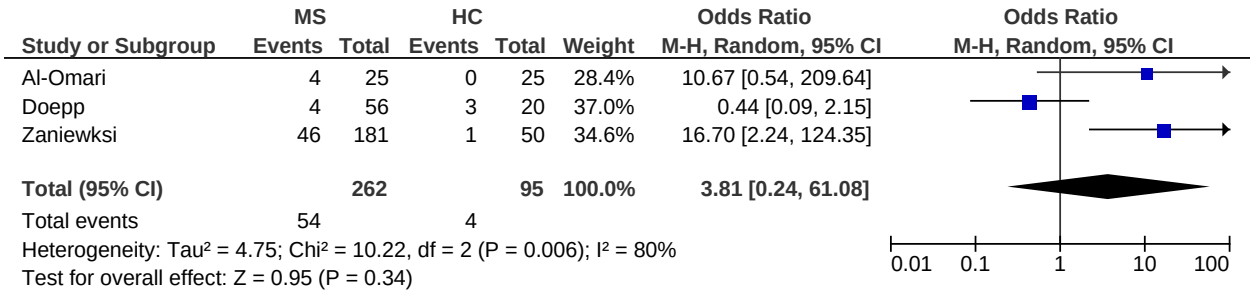
Parameter 2



Parameter 3



Parameter 4



Parameter 5

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 (6), Baracchini i (7), Baracchini ii (15), Doepp (9), Floris (2), Kantarci (3), Krogias (10), Mayer (11), Zamboni (12), Zaniewski (4), Zivadinov (13).

Appendix 2

Studies published between September 2011 and March 2012 that did not meet study inclusion criteria

Dolic and colleagues from Buffalo, USA studied 171 patients with MS and 79 HCs to determine the sensitivity and sensitivity of ultrasonography, MRV and the combination of the two for the diagnosis of hemodynamic abnormalities (18).The participants in Dolic's study were a subset of those included in a previously published study by Zivadinov that evaluated the frequency with which CCSVI was diagnosed with ultrasonography in MS patients and HCs (13).This study was described as double-blind. Zivadinov and colleagues also previously published MRV results from 57 MS patients and 21 HCs (43). It is not clear whether the participants in Zivadinov's MRV study were also included in Dolic's study.

The authors presented the results of a large number of individual ultrasound and MRV parameters, as well as combinations of those parameters, with a focus on how well they distinguished between participants with MS and HCs. The authors provide results for "sensitivity" and "specificity", though what they appear to be describing is the proportion of MS patients who have a positive test result (what they call sensitivity) and the proportion of HCs with a normal test result (what they call specificity). In this report, we will use the terminology used by Dolic and colleagues (18), even though we do not feel it is an accurate use of the term.

Using Zamboni's definition of CCSVI (2 or more ultrasound parameters positive), the sensitivity and specificity were 64% and 62% respectively (positive likelihood ratio 1.7; negative likelihood ratio 0.6). Note – these values differ from the ones reported in the paper, but the authors confirmed (personal communication Dr. Zivadinov) that there were two typographical errors in the paper.

MRV time-of-flight (TOF) distinguished poorly between participants with MS and HCs. Abnormal IJV flow (defined as absent or pinpoint flow) was present in 32% of patients with MS and 24% of HCs (sensitivity 32%, specificity 76%); absent VV flow was present in 14% of MS patients and 18% of HCs (sensitivity 14%, specificity 82%), and presence of collaterals was seen in 91% of MS patients and 91% of healthy controls (sensitivity 91%, specificity 9%).

The authors assessed the sensitivity and specificity of a large number of combinations of ultrasound and MRV criteria, and found that the combinations with a high specificity also had a low sensitivity. For example, the combination of more than one ultrasound VV abnormality and an ultrasound abnormality in the deep cerebral veins and more than one collateral on MRV had a specificity of 95% but a sensitivity of only 6%.

Simka and colleagues from Katwice, Poland reported venographic findings in 586 MS patients (31). It is not clear how these patients were chosen, although the authors state that venography was performed irrespective of the results of non-invasive tests for

CCSVI. Contrast injection was by hand which could reduce reproducibility of findings compared with slow pump injections. No data were provided about catheter French sizes that could influence rates of contrast injection or space occupancy within the lumen of the veins. The following venographic findings were considered abnormal: slowed venous outflow (retention of injected contrast in the vein for longer than one cardiac cycle), reflux (reversal of flow direction), prestenotic dilation of the vein associated with slowed outflow or reflux, no outflow through the vein, hypoplasia or narrowing of the vein associated with any of the above patterns, intraluminal structures (webs, septa, membranes), or complete obstruction or agenesia of the vein.

Simka et al. found one or more of these abnormalities in 96.1% of patients. One vein was abnormal in 44% of patients; two were abnormal in 49% and three or more were abnormal in 3%. Because a control group without MS was not studied, it is not possible to say how much more frequently these abnormalities occur in MS patients than in non-MS patients.

Zivadinov and colleagues (32) studied 59 MS patients and 33 HC with susceptibility-weighted imaging (SWI) venography using MRI, which was used to calculate apparent total venous volume (ATVV). MS patients had decreased ATVV compared to HC ($p<0.0001$), and the severity of CCSVI was significantly correlated with decreased ATVV in patients with MS but not HC.

Haacke and colleagues (33) presented data from two American centres on the frequency of IJV stenosis using TOF MRV in 200 MS patients (100 in each centre). Stenosis was defined as stenosis, atresia or aplasia. The IJV was stenotic in 68% of patients; 56% in one centre and 80% in the other. IJV flow was significantly less in patients with stenosis, compared to those without stenosis. Because no control group was studied, it is not known how the frequency of stenosis detected with MRV in MS patients compares to HC.

Mancini and colleagues (5) from Naples, Italy reported a prospective study of 103 MS patients and 42 controls (26 healthy individuals and 16 patients being evaluated for liver disease) to assess cerebral circulation time (CCT) using contrast-enhanced ultrasonography. None of the MS or control participants had clinical cardiovascular disease or carotid artery stenosis. The study is described as double-blind, but the mechanism of blinding was not described.

The contrast agent used was sulfur hexafluoride. A bolus of 2.4ml was injected into the left antecubital vein, followed by a 10ml saline solution bolus. Three parameters were measured: arrival time, time to peak, and absolute intensity peak. These were assessed at the carotid artery, thyroid tissue and IJV. The CCT was defined as the difference between the carotid and IJV arrival times.

An inter-observer variability study found a mean difference between operators of 0.01 for arrival time at the artery and 0.03 seconds for arrival time at the vein. There was no difference between MS and control participants in the arterial contrast arrival time.

However, average CCT was longer in MS than control participants (5.8 versus 5.0 seconds; p=0.002) and there was a greater difference between the two sides in MS patients (difference 1.6 versus 1.0 seconds; p=0.012). There was not a statistically significant difference in CCT times between MS patients with and without CCSVI (p=0.18). The authors did not indicate whether there was a difference among HC and controls being evaluated for liver disease.

Ertl-Wagner and colleagues (34) from Munich, Germany used TOF MRI to evaluate the craniocervical venous drainage patterns of 27 patients with MS (median age: 25 years) and 26 patients with migraine (median age: 37 years). Each group had their own age- and gender-matched HCs. The MRI results were interpreted without knowledge of participants' clinical status.

MRV was performed using 2D TOF including infratentorial and upper cervical vasculature. Two phase contrast studies were utilized to measure blood flow in both arterial and venous structures at the C2 level. The degree of secondary venous flow in the epidural veins, vertebral veins and deep cerebral veins was characterized as: none, minimal, mild secondary venous outflow, pronounced secondary venous outflow in one of the three pathways, secondary venous outflow in 2 of the 3 pathways, or secondary venous outflow in all 3 pathways. The proportion of measured secondary venous outflow as a percentage of total cerebral blood flow was also calculated.

There was not a significant difference in patterns of secondary venous drainage between participants with MS and those with migraine (p=0.65) or in the secondary venous drainage as a percentage of total cerebral blood flow (p=0.23). However, compared with their respective controls, both MS and migraine patients showed significantly increased relative secondary venous drainage (p=0.004 for MS and p=0.02 for migraine).

Bavera and colleagues (35) from Milan, Italy studied 560 patients with MS using Zamboni's ultrasound protocol, except they did not examine the intracerebral veins. They found the following: abnormal valves at the junction of jugular and brachiocephalic veins in 68% of patients, reflux in the IJ (52%) and vertebral (54%) veins, stenosis of the IJV (88%), abnormal change of the cross-sectional area of the IJV with change in position (43%) and complete occlusion or agenesia of the IJV (2%). Unfortunately, Bavera et al. did not study a control group with whom the frequency of abnormalities could be compared.