Systematic reviews of the evidence regarding chronic cerebral spinal venous insufficiency (CCSVI) and multiple sclerosis
An update for the CIHR Expert Panel
December 18, 2012

From the Canadian Chronic Cerebrospinal Venous Insufficiency Systematic Review Group
(Andreas Laupacis, Erin Lillie, Richard Aviv, Andrew Dueck, Jodi Burton, Laure Perrier, Sharon Straus, Tom Feasby, Kevin Thorpe)

Introduction

This is the fourth report from the Canadian Chronic Cerebrospinal Venous Insufficiency Systematic Review Group. The previous reports can be found at http://ccsvireviews.ca/our-findings/. This update focuses on the literature published between March, 2012 and September, 2012. As before, we have only included papers published in the peer-reviewed literature, and have not included abstracts.

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 September 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 reports (1-3).

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 reports for a description of the methodological approach used to identify eligible articles and abstract data (1-3).

Results

a) Identification of eligible studies

From the literature search for studies of association between cerebral venous abnormalities and multiple sclerosis, 38, 1, and 49 articles were retrieved from Medline, the Cochrane Central Register of Controlled Trials, and EMBASE, respectively. There were 4 duplicates. Eleven additional articles were identified from scanning reference lists and hand-searching. Of the 95 articles screened, 43 were selected at level 1 (title and abstract) and 23 at level 2 (full text). Four studies were added to the meta-analysis and 4 others are summarized in the report.

From the literature search for studies of the benefits and harms of endovascular treatment of CCSVI, 36, 7, and 33 articles were retrieved from Medline, the Cochrane Central Register of Controlled Trials, and EMBASE, respectively. There were 7 duplicate articles. Two additional articles were identified from scanning reference lists and hand-searching. Of the 71 articles that were screened, 37 were selected at level 1 (title and abstract) and 5 at level 2 (full text). All five articles are summarized in the report.

Reasons for exclusion at level 2 screening were either that the article did not meet inclusion criteria or had been already included or considered in a past report (1-3).

b) Association between CCSVI and MS

In our last report (3) we presented a meta-analysis of 14 studies (including 1128 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 277 MS patients) meeting our inclusion criteria have been published (4-7). The four studies are described below, along with a fifth study that used ultrasound to diagnose CCSVI in MS patients and HC but did not follow Zamboni's protocol and therefore could not be added to the meta-analysis (8).

Chambers and colleagues from Heidelberg, Australia studied 70 patients with clinically isolated syndrome (CIS) or mild MS (EDSS scores 2 or less) and 70 matched healthy controls (HC) (6). The ultrasonographer had experience acting as a demonstrator for Dr. Zamboni during a trip he made to Australia. The ultrasonographer was blinded and the method of blinding was well-described. This is the only study to test whether blinding was successful, and it appears to have been. Only one of the patients, a healthy control, was identified as having CCSVI. The CCSVI parameter that was most commonly detected was internal jugular vein (IJV) stenosis, which was present in 17 MS patients and 9 controls (p=0.13).

Patti and colleagues from Catania, Italy studied 148 MS patients, 20 patients with CIS, 40 patients with other neurological diseases (OND) and 172 matched HC (7). The MS patients were a random selection of the MS patients seen in their MC clinic. The ultrasonographer had previously trained with Dr. Zamboni and was blinded to the identity of the study participants. The method of blinding was described but the success of blinding was not tested. CCSVI was found in 19% of MS patients, 10% of CIS patients, 5% of patients with OND and 6% of HC. The difference in CCSVI frequency between MS patients and HC was statistically significant (p=0.001) and among MS patients, CCSVI was detected more frequently in those who had MS for longer than 144 months, as compared to those with MS for a shorter period of time (p= 0.03).

Amato and colleagues from Florence, Italy studied 15 patients with pediatric onset MS (POMS) and 16 HC (4). The median age of MS patients was 18 years; with disease duration of a median of 6 years, a median EDSS score of 1.2 and all with relapsing- remitting MS (RRMS). The neurosonologists in the study were blinded, but the success of blinding was not reported. Specific training of the ultrasonographers in the diagnosis of CCSVI was not described. CCSVI was diagnosed in 27% of MS patients and 19% of HC (p=0.60).

Blinkenberg and colleagues from Copenhagen, Denmark studied 23 MS patients with RRMS and 16 HC (5). The study was described as blinded, but blinding of the ultrasonographers was not well-described and the success of blinding was not tested. They also did not describe any specific training of the ultrasonographers related to the diagnosis of CCSVI. They did not find CCSVI in any study participants.

The data from these four studies have been added to **Tables 1-4** summarizing the characteristics of the included studies. The meta-analysis results are presented in **Figure 1** (diagnosis of CCSVI) and **Figure 2** (individual CCSVI parameters).

The fifth study that compared the frequency of ultrasound findings in patients with MS and HC was conducted by Mehrpour and colleagues from Tehran, Iran. They studied 84MS patients (20 of whom had CIS) and 115 HC (8). The study was not blinded, and there was no description of specific training of the ultrasonographers for the diagnosis of CCSVI. They did not assess CCSVI criterion 4 (non-detectable flow in the IJV or vertebral veins (VV) and therefore, it was not possible to determine how many patients met the diagnosis of CCSVI.

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

Study	**No. of patients with MS**	**No. of controls**		**Ultrasound equipment used**	**Blinding**
		Healthy controls	Patients with other neurological diseases		
Al-Omari et al.	25	25	N/A	Philips ATL HDI 5000 4-7MHz linear probe and/or 5-8Mhz curved probe, Transcranial Doppler not performed (probe not available).	Not blinded.
Baracchini et al.	50	110	60	Philips iU22 Extracranial: 5-10 MHz linear array probe. Transcranial: 1-3 MHz phased array probe.	Described as blinded but did not describe how blinding ensured or whether blinding tested.
Centonze et al.	84	56	N/A	Esaote Biomedica MyLab-Vinco 25 with a linear LA322 11-3 MHz probe.	Described blinding process but did not describe whether blinding achieved.
Doepp et al.	56	20	N/A	Toshiba Powervision 6000, Extracranial exam: 7.5MHz linear transducer. Transcranial exam: 2.5MHz probe.	Not blinded.
Krogias et al.	10	2	5	Not described.	Not blinded.
Mayer et al.	20	20	N/A	Phillips IU22 with an L9-3 probe to assess IJV and VV; S5-1 probe was used for intracranial veins.	Described blinding process but did not describe whether blinding achieved.
Zamboni et al.	109	132	45	Esoate-Biosound My lab 25 7.5-10 MHz for extracranial, 2.5 MHz for intracranial.	Described as blinded but did not describe how blinding undertaken or whether blinding achieved.
Zivadinov et al.	310	163	26	Esaote-Biosound MyLabGOLD25 equipped with 2.5 and 7.5-10 MHz	Described blinding process but did not describe whether

				transducers.	blinding achieved.
Marder et al.	18	N/A	11	Logic 9, GE Healthcare 8MHz linear array probe for extracranial; 2-MHz sector transducer for transcranial examination.	Described as blinded but did not describe how blinding ensured or whether blinding tested.
Baracchini et al.	60	60	N/A	Phillips IU22 with a 5-10 MHz linear probe for extracranial and 1-3 MHz phased-array TCD for intracranial veins.	Described blinding process but did not assess the effectiveness of blinding.
Zaniewski et al.	181	50	N/A	GE Logiq US with linear probe at 7.5-10MHz	Not blinded.
Floris et al.	40	34	N/A	Esaote Biosound MyLab Vinco, equipped with 2.5 and 7.5-13 MHz transducers.	Described as single-blinded, but did not give description of blinding process.
Kantarci et al.	62	54	N/A	Logiq 9 GE with 5-12 MHz linear array transducer.	Blinded.
Mancini et al.	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.	Described as double-blinded but did not give description of blinding process.
Amato et al.	15	16	N/A	My Lab Vinco Esaote, Italy; 7.5MHz linear and 6.5 MHz microconvex transducers for IJV and vertebral veins; 2MHz phased array probe for transcranial examination	Double-blinded. Described blinding process but did not assess the effectiveness of blinding.
Blinkenberg et al.	24	15	N/A	Philips IU22, transducers were linear array L9-3 for cervical scans and phased array S5-1 for transcranial examination	Described as blinded but blinding process not well-described and did not assess the effectiveness of blinding.
Chambers et al.	70	70	N/A	Siemans Antares	Blinded. Blinding well-described and ultrasonographer appears to have been blinded.

Patti et al.	168	172	40	GE Vivid E Ultrasound (GE Health Care, Norway); 8L-RS (4-12MHz) linear array transducer if IJV and VV; 3S-RS Secor Array Probe (1.5-3.6MHx) transducer for the deep cerebral veins.	Blinded. Described blinding process but did not assess the effectiveness of blinding.

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

Study references, in order of appearance in table: Al-Omari (9), Baracchini (10), Centonze (11), Doepp (12), Krogias (13), Mayer (14), Zamboni (15), Zivadinov (16), Marder (17), Baracchini (18), Zaniewski (19), Floris (20), Kantarci (21), Mancini (22), Amato (4), Blinkenberg (5), Chambers (6), Patti (7).

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

Study	Type of MS; no. of MS patients			Age, yr	Female, %	EDSS score	Use of disease-modifying medications, %	Duration of MS, yr
	Clinically isolated syndrome	Relapsing-remitting	Other					
Al-Omari et al.	0	21	4	35*	52	N/A	N/A	N/A
Baracchini et al.	50	0	0	33*	70	1.5†	28	N/A
Centonze et al.	0	69	15	39*	62	N/A	82	N/A
Doepp et al.	0	41	15	42*	65	2.7*	N/A	10*
Krogias et al.	0	2	8	42†	30	5.8†	N/A	N/A
Mayer et al.	0	17	3	42*	65	3†	90	13*
Zamboni et al.	0	69	40	40†	59	2†	N/A	6†
Zivadinov et al.	21	191	98	48†	76	3†	89‡	12†
Marder et al.	1	6	11	55*	17	N/A	N/A	21†
Baracchini et al.								
1° progressive	0	0	25	47*	44	6*	N/A	11*
2° progressive	0	0	35	45*	63	6*	N/A	18*
Zaniewski et al.	0	98	83	41†	61	N/A	N/A	10†
Floris et al.	0	29	10	41*	68	N/A	N/A	N/A
Kantarci et al.	0	32	30	37*	65	4*	N/A	9*
Mancini et al.	0	41	62	42†	60	4†	N/A	12†
Amato et al.	0	15◊	0	18†	60	1.2†	N/A	6†
Blinkenberg et al.	0	24	0	37*	67	3.2*	N/A	10*

Chambers et al.	4	66	0	43*	84	All <=2	>90	6.5*
Patti et al.	20	105	43	44*	63	N/A	65	15*

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

Study references, in order of appearance in table: Al-Omari (9), Baracchini (10), Centonze (11), Doepp (12), Krogias (13), Mayer (14), Zamboni (15), Zivadinov (16), Marder (17), Baracchini (18), Zaniewski (19), Floris (20), Kantarci (21), Mancini (22), Amato (4), Blinkenberg (5), Chambers (6), Patti (7).

Table 3: Characteristics of participants included in the control groups

Study	No. of participants	Age, yr	Female, %
Healthy controls			
Al Omari et al.	25	34‡	52
Baracchini et al.			
Group 1*	50	33‡	70
Group 2†	60	63‡	53
Centonze et al.	56	42‡	64
Doepp et al.	20	41‡	60
Mayer et al.	20	34‡	50
Zamboni et al.			
Group 1*	60	37§	53
Group 2†	72	58§	60
Zivadinov et al.	163	47§	54
Baracchini et al.	60	46‡	55
Zaniewski et al.	50	40§	62
Floris et al.	34	41‡	68
Kantarci et al.	54	37‡	50
Mancini et al.	42	38§	55
Amato et al.	16	18§	44
Blinkenberg et al.	15	37‡	73
Chambers et al.	70	44‡	84
Patti et al.	172	43‡	58
Controls with other neurological diseases			
Baracchini et al.	60	64‡	53
Krogias et al.	7	40§	29
Zamboni et al.	45	60§	44
Zivadinov et al.	26	50§	73
Marder et al. ◊	11	55‡	36
Patti et al.	40	46‡	60

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

Study references, in order of appearance in table: Al-Omari (9), Baracchini (10), Centonze (11), Doepp (12), Mayer (14), Zamboni (15), Zivadinov (16), Baracchini (18), Zaniewski (19), Floris (20), Kantarci (21), Mancini (22), Amato (4), Blinkenberg (5), Chambers (6), Patti (7), Baracchini (10), Krogias (13), Zamboni (15), Zivadinov (16), Marder (17), Patti (7).

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

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

Blinkenberg et al.	No	No	Not sure	Not sure	Convenience	Yes
Chambers et al.	Yes	No	Not sure	Not sure	Convenience	Yes
Patti et al.	Yes	Yes	Yes	Yes	Random sample	Yes

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

Study references, in order of appearance in table: Al-Omari (9), Baracchini (10), Centonze (11), Doepp (12), Krogias (13), Mayer (14), Zamboni (15), Zivadinov (16), Marder (17), Baracchini (18), Zaniewski (19), Floris (20), Kantarci (21), Mancini (22), Amato (4), Blinkenberg (5), Chambers (6), Patti (7).

As shown below in **Figure 1**, patients with MS had greater odds of being diagnosed with CCSVI than HC but there was great heterogeneity in the results [odds ratio: 5.1 (95% CI 2.3-11.5; I^2=80%)]. Patients with MS also had greater odds relative to HC of being positive for CCSVI criteria 1, 3, 4 and 5, but also with great heterogeneity (see **Figure 2**).

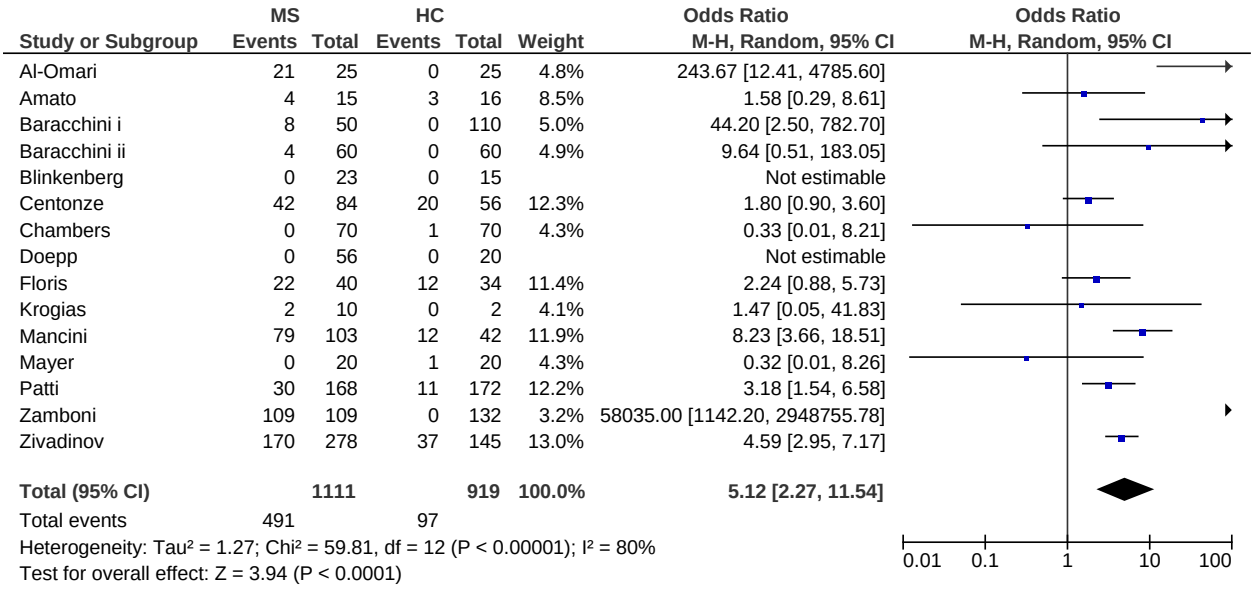


Figure 1: Meta-analysis of a diagnosis of chronic cerebrospinal venous insufficiency (presence of at least two parameters) in patients with multiple sclerosis (MS) versus healthy controls (HC). An odds ratio greater than 1.0 indicates an increased likelihood of a diagnosis of chronic cerebrospinal venous insufficiency in MS patients versus controls. CI = confidence interval, OR = odds ratio.

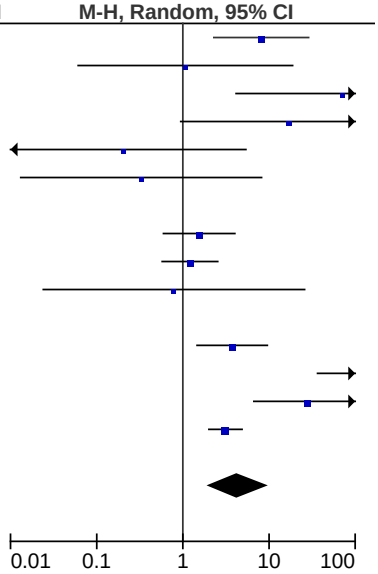
Study references: Al-Omari (9), Amato (4), Baracchini (10), Baracchini (18), Blinkenberg (5), Centonze (11), Chambers (6), Doepp (12), Floris (20), Krogias (13), Mancini (22), Mayer (14), Patti (7), Zamboni (15), Zivadinov (16).

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	10.1%	8.14 [2.29, 28.90]
Amato	1	15	1	16	5.1%	1.07 [0.06, 18.82]
Baracchini i	12	50	0	110	5.2%	71.75 [4.15, 1240.95]
Baracchini ii	7	60	0	60	5.1%	16.96 [0.95, 304.07]
Blinkenberg	0	23	1	15	4.3%	0.21 [0.01, 5.39]
Chambers	0	70	1	70	4.4%	0.33 [0.01, 8.21]
Doepp	0	56	0	20		Not estimable
Floris	17	40	11	34	11.2%	1.55 [0.60, 4.01]
Kantarci	27	62	21	54	11.9%	1.21 [0.58, 2.55]
Krogias	1	10	0	2	4.0%	0.79 [0.02, 25.90]
Mayer	0	20	0	20		Not estimable
Patti	20	168	6	172	11.3%	3.74 [1.46, 9.56]
Zamboni	76	109	0	132	5.3%	605.15 [36.56, 10016.99]
Zaniewksi	98	181	2	50	9.4%	28.34 [6.68, 120.13]
Zivadinov	137	310	33	163	12.7%	3.12 [2.00, 4.86]
Total (95% CI)		**1199**		**943**	**100.0%**	**4.35 [1.90, 9.97]**
Total events	414		82			

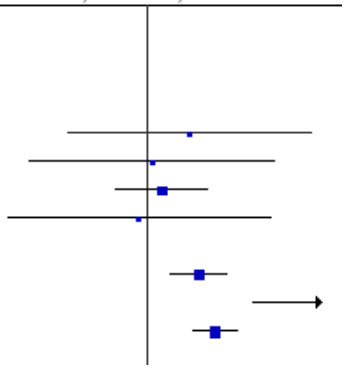
Heterogeneity: Tau² = 1.36; Chi² = 54.12, df = 12 (P < 0.00001); I² = 78%

Test for overall effect: Z = 3.47 (P = 0.0005)



CCSVI parameter 2**

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Amato	0	15	0	16		Not estimable
Baracchini i	0	50	0	110		Not estimable
Baracchini ii	0	60	0	60		Not estimable
Blinkenberg	0	23	0	15		Not estimable
Chambers	1	70	0	70	7.0%	3.04 [0.12, 75.99]
Doepp	1	56	0	20	6.9%	1.11 [0.04, 28.31]
Floris	8	40	5	34	20.1%	1.45 [0.43, 4.94]
Krogias	1	10	0	2	6.2%	0.79 [0.02, 25.90]
Mayer	0	20	0	20		Not estimable
Patti	30	168	9	172	24.8%	3.94 [1.81, 8.58]
Zamboni	55	109	0	132	8.6%	269.86 [16.38, 4447.00]
Zivadinov	110	236	15	118	26.5%	5.99 [3.29, 10.91]



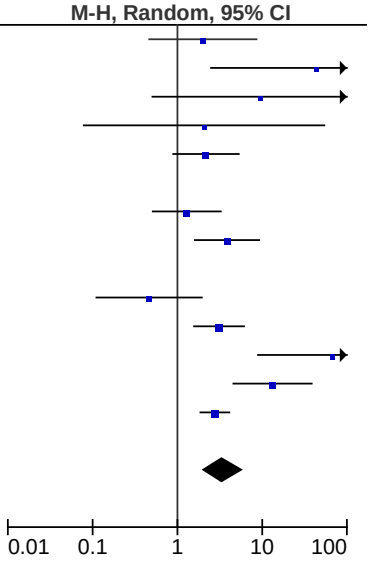
** As many studies either did not report criterion 2 or did not assess it, we did not meta-analyze the data for this criterion. If provided, the point estimates from each of the studies are shown.

CCSVI parameter 3

Study or Subgroup	MS Events	MS Total	HC Events	HC Total	Weight	Odds Ratio M-H, Random, 95% CI
Amato	10	15	8	16	7.6%	2.00 [0.47, 8.56]
Baracchini i	8	50	0	110	3.1%	44.20 [2.50, 782.70]
Baracchini ii	4	60	0	60	2.9%	9.64 [0.51, 183.05]
Blinkenberg	1	23	0	15	2.5%	2.07 [0.08, 54.12]
Chambers	17	70	9	70	11.3%	2.17 [0.89, 5.28]
Doepp	0	56	0	20		Not estimable
Floris	19	40	14	34	11.0%	1.29 [0.51, 3.25]
Kantarci	27	62	9	54	11.3%	3.86 [1.61, 9.25]
Krogias	0	10	0	2		Not estimable
Mayer	13	20	16	20	7.8%	0.46 [0.11, 1.94]
Patti	34	168	13	172	12.7%	3.10 [1.57, 6.12]
Zamboni	30	109	1	177	5.2%	66.84 [8.96, 498.80]
Zaniewksi	97	181	4	50	10.0%	13.28 [4.59, 38.43]
Zivadinov	197	310	63	163	14.6%	2.77 [1.87, 4.09]
Total (95% CI)		**1174**		**963**	**100.0%**	**3.43 [1.96, 6.01]**
Total events	457		137			

Heterogeneity: Tau² = 0.52; Chi² = 33.58, df = 11 (P = 0.0004); I² = 67%

Test for overall effect: Z = 4.31 (P < 0.0001)

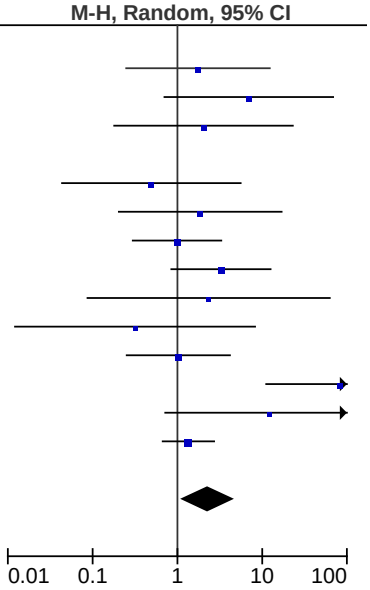


CCSVI parameter 4

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
Amato	3	15	2	16	7.7%	1.75 [0.25, 12.28]
Baracchini i	3	50	1	110	6.4%	6.96 [0.71, 68.63]
Baracchini ii	2	60	1	60	6.0%	2.03 [0.18, 23.06]
Blinkenberg	0	23	0	15		Not estimable
Chambers	1	70	2	70	6.0%	0.49 [0.04, 5.56]
Doepp	5	56	1	20	6.7%	1.86 [0.20, 16.99]
Floris	7	40	6	34	11.5%	0.99 [0.30, 3.29]
Kantarci	10	62	3	54	10.7%	3.27 [0.85, 12.57]
Krogias	3	10	0	2	3.9%	2.33 [0.09, 62.68]
Mayer	0	20	1	20	3.9%	0.32 [0.01, 8.26]
Patti	4	168	4	172	10.4%	1.02 [0.25, 4.16]
Zamboni	35	109	1	177	7.5%	83.24 [11.20, 618.93]
Zaniewksi	19	181	0	50	4.9%	12.12 [0.72, 204.32]
Zivadinov	30	310	12	163	14.5%	1.35 [0.67, 2.71]
Total (95% CI)		**1199**		**988**	**100.0%**	**2.27 [1.08, 4.76]**
Total events	122		34			

Heterogeneity: Tau² = 0.86; Chi² = 26.31, df = 12 (P = 0.010); I² = 54%

Test for overall effect: Z = 2.17 (P = 0.03)



CCSVI parameter 5

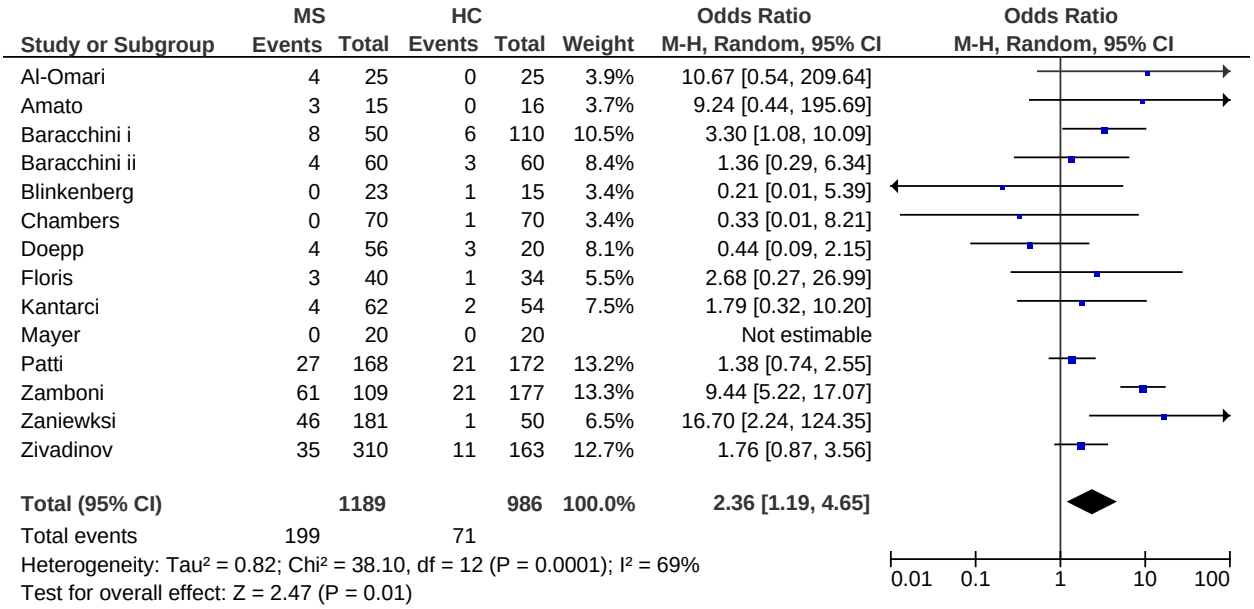


Figure 2: Meta-analysis of individual parameters of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis (MS) versus healthy controls (HC). (1) Reflux in internal jugular veins or vertebral veins; (2) flow reversal in deep cerebral veins; (3) stenoses of internal jugular vein; (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.

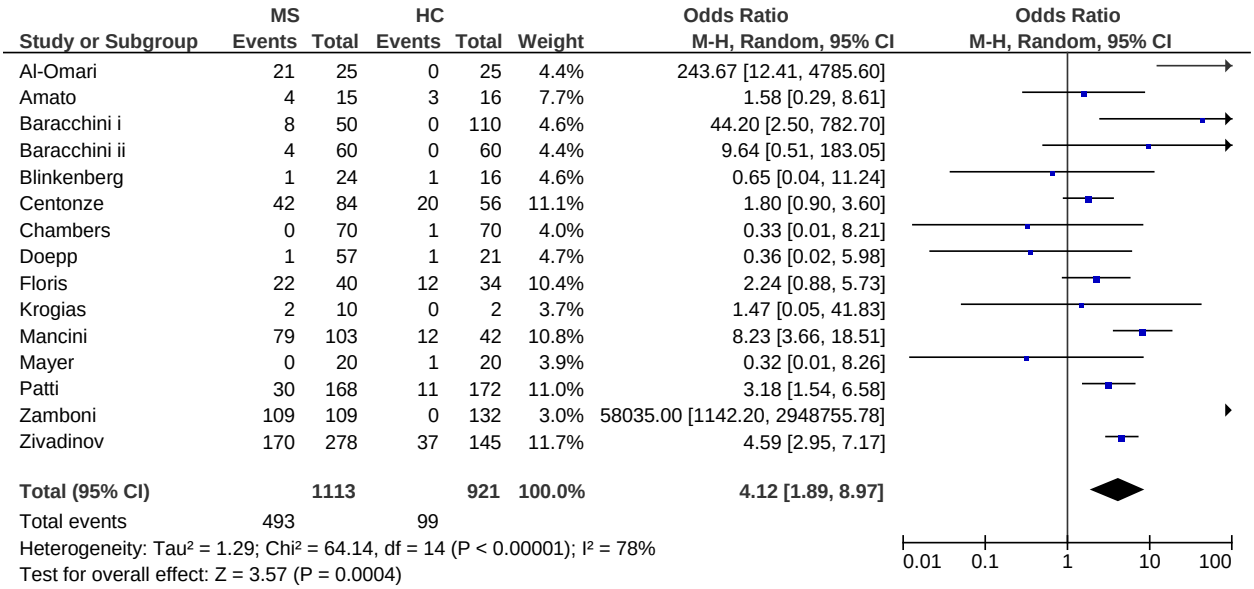
Study references: Al-Omari (9), Amato (4), Baracchini (10), Baracchini (18), Blinkenberg (5), Chambers (6), Doepp (12), Floris (20), Kantarci (21), Krogias (13), Mayer (14), Patti (7), Zamboni (15), Zaniewski (19), Zivadinov (16).

c) Sensitivity analyses

One of the four recently reported studies did not find CSSVI in any of the MS patients or HC (5). Studies with "zero cells" (or no events across both groups) do not contribute to the results of a meta-analysis. Therefore, we conducted a sensitivity analysis in which we added '1' to each of the four cells for this study, as well as to previous studies that had zero cells. The results of this analysis found an OR of 4.1 (95% CI 1.9-9.0; I^2=78%)

We repeated the sensitivity analysis just described, and at the same time excluded Zamboni's study which found CCSVI in 100% of MS patients and none of the HC (15). This analysis found an OR of 3.2 (95% CI 1.8-5.6; I^2=58%). The results of the sensitivity analyses of the diagnosis of CCSVI are shown in **Figure 3**.

CCSVI diagnosis: with +1 to all Doepp, Blinkenberg cells



CCSVI diagnosis: with +1 to all Doepp, Blinkenberg cells, and study by Zamboni excluded

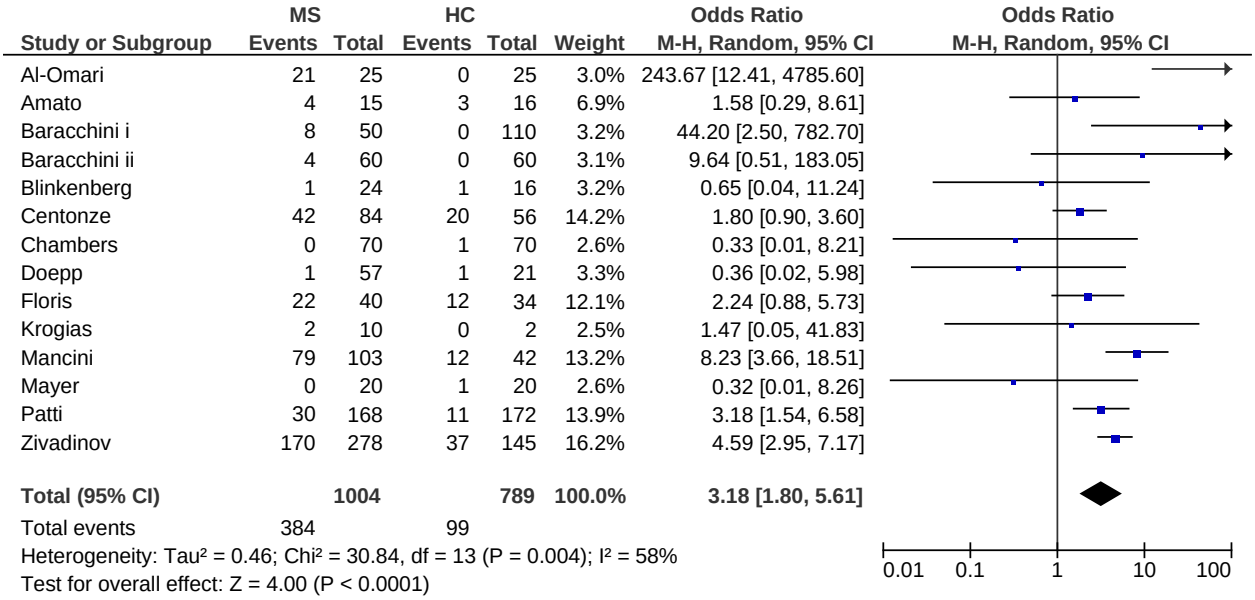


Figure 3: Meta-analysis of a diagnosis of chronic cerebrospinal venous insufficiency (presence of at least two parameters) in patients with multiple sclerosis (MS) versus healthy controls (HC). An odds ratio greater than 1.0 indicates an increased likelihood of a diagnosis of chronic cerebrospinal venous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

Study references: Al-Omari (9), Amato (4), Baracchini (10), Baracchini (18), Blinkenberg (5), Centonze (11), Chambers (6), Doepp (12), Floris (20), Krogias (13), Mancini (22), Mayer (14), Patti (7), Zamboni (15), Zivadinov (16).

d) Reproducibility of the assessment of CCSVI

Patti and colleagues studied intra-observer agreement in 30 patients examined one week apart, and found a kappa of 0.79, which is in the range of the results of other studies (7).

e) Comparison of different methods of assessing cerebral veins

Blinkenberg and colleagues compared phase-contrast magnetic resonance (MR) imaging with Doppler ultrasonography in 24 MS patients and 17 HC (5). The investigators were blinded to the participants' diagnosis. Very few abnormalities were found in either group. The MR and ultrasound findings were consistent except for one patient with no identifiable IJV on ultrasound and a normal MRI venogram (although the phase-contrast MR showed reduced blood flow).

Simka and colleagues from Poland compared catheter venography and ultrasound for the assessment of 116 IJVs in 58 MS patients (23). Blinding of the investigators to the results of the other modality was not described. Venograms were considered abnormal if the following conditions were met: no outflow through the vein, venous outflow was slowed down (retention of injected contrast in the examined vein longer than one cardiac cycle); reversed flow direction (reflux); outflow through collaterals; intraluminal structures (webs, septa, or membranes), hypoplasia or narrowing of the vein compromising outflow (incurring the retention of injected contrast, reflux or collateral flow); prestenotic dilation of the vein associated with slowed down flow or reflux; or complete occlusion or agenesis of the vein. Venous valves in the junction of the IJV and brachiocephalic vein were only considered abnormal if the valve compromised the outflow in a similar way as the other intraluminal structures. The ultrasound criteria described by Zamboni and similar criteria described by the International Society for Neurovascular Disease (ISNVD) (24) were used, though deep cerebral veins were not imaged.

Seventy-eight percent of the IJVs were considered abnormal by venography and 92% of IJVs were abnormal for at least one of Zamboni's criteria when examined by ultrasonography. However, the correlation between venography and ultrasonography was extremely poor. If the venogram was considered the "gold standard"; the sensitivity of the 4 Zamboni ultrasound criteria varied from 0 (reflux) to 89% (stenosis/B mode anomalies). The specificity varied from 12% (stenosis/B mode anomalies) to 100% (reflux). Similarly, poor correlations between venography and the ISNVD criteria were found.

f) Assessment of the cerebral veins with magnetic resonance imaging

Blinkenberg and colleagues used phase-contrast MR to assess the veins of 23 MS patients and 14 HC (5). The venograms were normal in 21MS patients and 2 patients had stenosis between 1-49% in one IJV. Two HC had stenosis of the left IJV between 50-69%, with the other patients

having normal IJVs. Thus, there was no difference in the frequency of IJV stenosis as assessed by MRI between MS patients and HC. There was also no difference in mean blood flow in the IJV or carotid artery between the two groups.

McTaggart and colleagues from Stanford used 2D-TOF neck MRV and TRICKS MRV to assess IJV flattening and collaterals in 19 MS patients and 20 age- and sex-matched HC (25). The mean age of the MS patients was 45 years, and their mean EDSS scores was 4.2. The radiologists were unaware of the participants' clinical status. Flattening scores were graded as 0, normal (0-25% narrowed); 1, mild (25-50% narrowed); 2, moderate (50-75% narrowed) and 3, absent, nearly absent or pinpoint (75-100% narrowed). Collateral scores were 0, none; 1, mild (collaterals in the posterior paraspinal soft tissues of the neck but neither the vertebral artery venous plexus nor the deep cervical vein could be seen inserting on the low IJV near the IJV-subclavian confluence); 2, moderate (prominent collateral veins with clear insertion of the deep cervical veins on the low IJV near the confluence) and 3, severe (same as 2, but with additional prominence of upper thoracic paraspinal collateral veins).

MS patients had statistically significant higher flattening scores than HC ($p=0.002$). Although there was a trend towards a higher collateral score in the MS patients, this did not reach statistical significance ($p=0.06$). There was a weak but statistically significant correlation between flattening and collateral scores ($r=0.32$; $p=0.005$). In the MS patients, there was a correlation between EDSS scores and flattening scores ($r=.45$; $p=0.004$) but not between EDSS and collateral scores ($r=0.01$; $p=0.97$).

Feng and colleagues evaluated the IJVs of 200 patients with MS and 14 HC, using MR venography (26). They found IJV stenosis in 57% of MS patients, but did not compare their findings with the HC because of the small number of HC patients. They found lower IJV flow in MS patients with IJV stenosis than those without stenosis.

g) Harms associated with endovascular treatment

Dake and colleagues from Stanford USA treated 38 MS patients with stents (27). In a retrospective chart review, they reported that "approximately 80%" of patients described local neck discomfort and headaches after the procedure which resolved in 4-5 days. Twelve percent of patients developed shoulder muscle weakness; sometimes associated with pain 7-10 days after the procedure, which in some cases persisted for up to 3-4 months. Two patients suffered serious harm – a fatal intracranial hemorrhage 10 weeks after the procedure in a patient taking warfarin, and stent migration to the tricuspid valve requiring thoracotomy and surgical stent extraction.

Hubbard and colleagues from San Diego, USA reported on 259 patients who underwent venoplasty (28). There was one deep venous thrombosis at the venous access site that required systemic anticoagulation. No serious peri-operative complications were reported. Patients were not followed in the clinic beyond the peri-operative period, and 29% were lost to follow-up. Thus, serious side-effects from venoplasty days to weeks after treatment may have been missed.

h) Benefits of endovascular treatment

Randomized trials

No results of randomized trials of endovascular treatment for CCSVI in patients with MS have been published since our last report.

The protocol of the Italian Brain Venous Drainage Exploited Against Multiple Sclerosis (BRAVES) randomized trial has been published (29). The sample size is 645 (423 patients with relapsing remitting and 222 with secondary progressive MS), and patients will be randomized in a ratio of 2:1 to venoplasty: sham venoplasty.

Since our third report, the Canadian Institutes of Health Research has announced that it has funded a randomized trial of 100 patients led by Dr. Anthony Traboulsee at the University of British Columbia (30,31). The study has not yet been registered with www.clinicaltrials.gov.

Thus, we are aware of 7 randomized trials of endovascular treatment for CCSVI in MS patients that are either underway or about to get underway; with sample sizes varying from 12 to 645 – please refer to our third report for details regarding study design(s) (3).

Non-randomized studies of the benefits of endovascular treatment for CCSVI in MS patients

Since our last report, 4 non-randomized studies of venoplasty, with no untreated control patients, have been published.

Hubbard and colleagues from the United States studied 259 consecutive patients who underwent venoplasty; 76% of whom were not on disease-modifying drugs (28). Stents were inserted in 6 (2.3%) patients. There was considerable loss to follow-up – 27% at one month and 29% at 6 months. The Multiple Sclerosis Impact Scale (MSIS-29) was completed in the facility before treatment, and online 1 and 6 months later. The MSIS-29 Physical and Psychological Scores both improved significantly in those who completed the questionnaire (p values all <0.01). No neurological examinations or MR imaging techniques were performed.

Salvi and colleagues from Bologna and Ferrara, Italy reported on 29 patients who had undergone venoplasty and who had been followed for two years before and after the procedure (32). These patients appear to have been a subset of the 65 patients that were previously described by Dr. Zamboni. There was a small improvement in mean EDSS scores after treatment (1.98 versus 2.27; $p=0.04$), and the mean annual relapse rate was also lower (0.45 versus 0.76; $p= 0.02$). The proportion of patients with relapses, along with MRI findings, was not reported. Forty-five percent of patients underwent one or two subsequent procedures to treat re-stenosis.

In a retrospective review of 38 stent placements at Stanford (USA), Dake and colleagues reported a statistically significant improvement in the Modified Fatigue Impact Scale 2 months and one year after treatment (27). Seventy one percent of patients reported a subjective improvement in heat intolerance. MRI scans were performed before and 2 months after the procedure; but results were not presented other than to say that there were “no new or enlarging

lesion(s)" on the 2-month scan. EDSS scores were measured, but the change in EDSS scores after treatment was not reported.

Kipshidze and colleagues from Tbilisi, Georgia reported on 4 patients who underwent venoplasty (33). Because of the small number of patients and the poor quality of the paper, it will not be considered further.

Discussion

The papers that have been published since our last report in June 2012 do not change what we know about the diagnosis and endovascular treatment of venous abnormalities in patients with MS in a substantial way.

Four small studies (with number of MS patients ranging from 15 to 148) used ultrasonography to diagnose CCSVI in patients with MS and HC. The two strongest studies (6,7) in terms of methodology, found CCSVI in zero and 19% of MS patients, which is much lower than what was described in Zamboni's initial study and in some other studies. However, when the results of these studies were added to the previously published studies, there was no substantial change to the results of the meta-analysis examining the association of CCSVI with MS – CCSVI was found more frequently in patients with MS, but the heterogeneity continues to be so large that definitive conclusions cannot be reached.

A large Italian study of ultrasonography in 1200 patients with MS has been reported in abstract form (34). The authors have published their "advanced sonological protocol" (35) but have not yet published a more complete description of their protocol, and the results have not been published in a peer-reviewed journal. Their publication is awaited with great interest.

There are still no published results of randomized trials of the treatment of CCSVI in patients with MS (a recent Cochrane review also did not identify any published randomized trials (36)), and until this occurs, the impact of treatment on disease activity and patient symptoms remains unclear.

References:

(1) Laupacis A, Lillie E, Dueck A, Aviv R, Straus S, Perrier L, et al. Systematic reviews of the evidence regarding chronic cerebral spinal venous insufficiency (CCSVI) and multiple sclerosis. First Report for CIHR Expert Panel. August 19, 2011 (www.ccsvireviews.ca).

(2) Laupacis A, Lillie E, Dueck A, Aviv R, Straus S, Perrier L, et al. Systematic reviews of the evidence regarding chronic cerebral spinal venous insufficiency (CCSVI) and multiple sclerosis. Second Report for CIHR Expert Panel. November 21, 2011 (www.ccsvireviews.ca).

(3) Laupacis A, Lillie E, Dueck A, Aviv R, Straus S, Perrier L, et al. Systematic reviews of the evidence regarding chronic cerebral spinal venous insufficiency (CCSVI) and multiple sclerosis. An update for the CIHR Expert Panel from the Canadian Chronic Cerebrospinal Systematic Review Group. 2012; June 4, 2012 (www.ccsvireviews.ca).

(4) Amato M, Saia V, Hakiki B, Giannini M, Pastò L, Zecchino S, et al. No association between chronic cerebrospinal venous insufficiency and pediatric-onset multiple sclerosis. Multiple Sclerosis Journal 2012 April 18, 2012.

(5) Blinkenberg M, Akeson P, Sillesen H, Lövgaard S, Sellebjerg F, Paulson O, et al. Chronic cerebrospinal venous insufficiency and venous stenoses in multiple sclerosis. Acta Neurol Scand 2012.

(6) Chambers B, Chambers J, Cameron H, Macdonell R. Chronic cerebrospinal venous insufficiency is not more prevalent in patients with mild multiple sclerosis: a sonographer-blinded, case-control ultrasound study. Multiple Sclerosis Journal September 7, 2012.

(7) Patti F, Nicoletti A, Leone C, Messina S, D'Amico E, Fermo SL, et al. Multiple Sclerosis and CCSVI: A Population-Based Case Control Study. PLoS ONE 2012; 7(8):e41227.

(8) Mehrpour M, Najimi N, Fereshtehnejad S, Safa FN, Mirzaeizadeh S, Motamed MR, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: A case-control study from Iran. Perspectives in Medicine 2012 (1–12): 375.

(9) Al-Omari MH, Rousan LA. Internal jugular vein morphology and hemodynamics in patients with multiple sclerosis. International Angiology April 2010; 29(2):115-120.

(10) Baracchini C, Perini P, Calabrese M, Causin F, Rinaldi F, Gallo P. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. Ann Neurol January 2011; 69(1):90-99.

(11) Centonze D, Floris R, Stefanini M, Rossi S, Fabiano S, Castelli M, et al. Proposed CCSVI criteria do not predict MS risk nor MS severity. Annals of Neurology 2011.

(12) Doepp F, Paul F, Valdueza JM, Schmierer K, Schreiber SJ. No cerebrocervical venous congestion in patients with multiple sclerosis. Ann Neurol August 2010; 68(2):173-183.

(13) Krogias C, Schroder A, Wiendl H, Hohlfeld R, Gold R. ["Chronic cerebrospinal venous insufficiency" and multiple sclerosis: critical analysis and first observation in an unselected cohort of MS patients]. Nervenarzt 2010 Jun; 81(6):740-746.

(14) Mayer CA, Pfeilschifter W, Lorenz MW, Nedelmann M, Bechmann I, Steinmetz H, et al. The perfect crime? CCSVI not leaving a trace in MS. Journal of Neurology, Neurosurgery & Psychiatry April 1, 2011; 82(4):436-440.

(15) Zamboni P, Menegatti E, Galeotti R, Malagoni AM, Tacconi G, Dall'Ara S, et al. The value of cerebral Doppler venous haemodynamics in the assessment of multiple sclerosis. J Neurol Sci 2009; 282(1-2) (pp 21-27).

(16) R. Zivadinov, K. Marr, G. Cutter, M. Ramanathan, R.H.B. Benedict, C. Kennedy, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. Neurology 2011;77:000-000.

(17) Marder E, Gupta P, Greenberg BM, Frohman EM, Awad AM, Bagert B, et al. No Cerebral or Cervical Venous Insufficiency in US Veterans With Multiple Sclerosis. Arch Neurol August 8, 2011:archneurol.2011.185.

(18) Baracchini C, Perini P, Causin F, Calabrese M, Rinaldi F, Gallo P. Progressive multiple sclerosis is not associated with chronic cerebrospinal venous insufficiency. Neurology August 30, 2011; 77(9): 844-850.

(19) Zaniewski M, Kostecki J, K,W., Z,D., Opala G, S´wiat M, et al. Neck duplex Doppler ultrasound evaluation for assessing chronic cerebrospinal venous insufficiency in multiple sclerosis patients. Phlebology 2012:1-8.

(20) Floris R, Centonze D, Fabiano S, Stefanini M, Marziali S, Del Giudice C, et al. Prevalence study of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: preliminary data. La Radiologia Medica: 1-10.

(21) Kantarci F, Albayram S, Demirci N, Esenkaya A, Uluduz D, Uysal O, et al. Chronic cerebrospinal venous insufficiency: does ultrasound really distinguish multiple sclerosis subjects from healthy controls? European Radiology 2012; 22(5): 970-979.

(22) Mancini M, Morra VB, Di Donato O, Maglio V, Lanzillo R, Liuzzi R, et al. Multiple sclerosis: cerebral circulation time. Radiology 2012 Mar; 262(3):947-955.

(23) Simka M, Ludyga T, Latacz P, Kazibudzki M. Diagnostic accuracy of current sonographic criteria for the detection of outflow abnormalities in the internal jugular veins. Phlebology April 23, 2012.

(24) Nicolaides AN, Morovic S, Menegatt E, Viselner G, Zamboni P. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound. Recommendations for a protocol. Funct Neurol October-December 2011; 26(4):229-248.

(25) McTaggart RA, Fischbein NJ, Elkins CJ, Hsiao A, Cutalo MJ, Rosenberg J, et al. Extracranial Venous Drainage Patterns in Patients with Multiple Sclerosis and Healthy Controls. Am J Neuroradiol September 1, 2012; 33(8):1615-1620.

(26) Feng W, Utriainen D, Trifan G, Sethi S, Hubbard D, Haacke EM. Quantitative flow measurements in the internal jugular veins of multiple sclerosis patients using magnetic resonance imaging. Rev Recent Clin Trials 2012 May; 7(2):117-126.

(27) Dake MD, Dantzker N, Bennett WL, Cooke JP. Endovascular correction of cerebrovenous anomalies in multiple sclerosis: A retrospective review of an uncontrolled case series. Vascular Medicine (United Kingdom) June 2012; 17(3):131-137.

(28) Hubbard D, Ponec D, Gooding J, Saxon R, Sauder H, Haacke M. Clinical Improvement after Extracranial Venoplasty in Multiple Sclerosis. Journal of Vascular and Interventional Radiology 2012 10; 23(10):1302-1308.

(29) Zamboni P, Bertolotto A, Boldrini P, Cenni P, D'Alessandro R, D'Amico R, et al. Efficacy and safety of venous angioplasty of the extracranial veins for multiple sclerosis. Brave Dreams Study (Brain Venous Drainage Exploited Against Multiple Sclerosis): study protocol for a randomized controlled trial. Trials 2012; 13(1):183.

(30) Canadian Institutes of Health Research. Frequently Asked Questions - Information on the Phase I/II Clinical Trial. 2012; Available at:http://cihr-irsc.gc.ca/e/45920.html. Accessed 11/16, 2012.

(31) Vancouver Coastal Health Research. MS-CCSVI PHASE I/II TREATMENT TRIAL. 2012; Available at:http://www.vchri.ca/ms-ccsvi-phase-iii-treatment-trial. Accessed 11/16, 2012.

(32) Salvi F, Bartolomei I, Buccellato E, Galeotti R, Zamboni P. Venous angioplasty in multiple sclerosis: neurological outcome at two years in a cohort of relapsing-remitting patients. Funct Neurol 2012 Jan-Mar; 27(1):55-59.

(33) Kipshidze N, Rukhadze I, Archvadze A, Kipiani V, Kipshidze N, Lapiashvili E, et al. Endovascular treatment of patients with chronic cerebrospinal venous insufficiency and multiple sclerosis. Georgian Med News 2011 Oct (199): 29-34.

(34) Comi G, Battaglia MA, Bertolotto A, Del Sette M, Ghezzi A, Malferrari G, et al. Chronic Cerebro-Spinal Venous Insufficiency (CCSVI) and global venous haemodynamics in multiple sclerosis: the CoSMo study. Mult Scler 2012; 18:509.

(35) Malferrari G, Sette MD, Zedde M, Sanguigni S, Carraro N, Baracchini C, et al. Italian multicenter study on venous hemodynamics in multiple sclerosis: Advanced Sonological Protocol. Perspectives in Medicine 2012; 1(1-12): 399.

(36) van Zuuren EJ, Fedorowicz Z, Pucci E, Robak EW. Percutaneous transluminal angioplasty for treatment of chronic cerebrospinal venous insufficiency (CCSVI) in multiple sclerosis patients (Review). The Cochrane Library 2012, Issue 12 (www.thecochranelibrary.com)