NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous venoplasty for chronic cerebrospinal venous insufficiency in multiple sclerosis

It has been suggested that multiple sclerosis symptoms may be caused, or made worse, by blocked veins in the neck or chest (chronic cerebrospinal venous insufficiency). This procedure involves inserting an inflatable balloon to widen veins in the neck and chest. The aim is to improve blood flow and symptoms.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional

procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2018 and updated in November 2018.

Procedure name

- Percutaneous venoplasty for chronic cerebrospinal venous insufficiency in multiple sclerosis.

Specialist societies

- Association of British Neurologists (ABN)
- British Society of Interventional Radiology (BSIR)
- British Society of Neuroradiologists (BSNR)
- The Vascular Society
- Royal College of Radiologists.

Description of the procedure

Indications and current treatment

Multiple sclerosis (MS) is a disease of the central nervous system (brain and spinal cord) that usually starts in early adult life. The disease process is typified by episodes in which white matter within the brain or spinal cord becomes inflamed and then destroyed by the immune system. These inflamed areas become scarred, giving the disease its name: multiple areas of hardening (sclerosis) within the brain or spinal cord. Many of these episodes do not cause any symptoms, but symptoms may occur suddenly and without warning. Although the symptoms may resolve between episodes, once present the disease never goes away and there is no known cure.

At least 3 different patterns of MS are generally recognised:

- Relapsing–remitting MS (RRMS): periods of good health or remission are followed by sudden onset of symptoms or relapses (80% of people at onset).

- Secondary progressive MS (SPMS): symptoms gradually worsen and there are fewer remissions. About 50% of those with RRMS develop SPMS during the first 10 years of their illness.
- Primary progressive MS (PPMS): from disease onset there is gradual continuous worsening of symptoms (10% to 15% of people at onset).

A diagnosis of MS is confirmed if it has 1 of the revised McDonald criteria:

- at least 2 attacks (defined as periods of subjective or objective neurological dysfunction) with objective clinical evidence of at least 2 lesions
- at least 2 attacks with objective clinical evidence of 1 lesion plus lesion dissemination in space shown on magnetic resonance imaging (MRI), or 2 or more MRI lesions consistent with MS plus cerebrospinal fluid findings suggestive of MS or second clinical attack
- 1 attack with objective clinical evidence of at least 2 lesions plus dissemination in time on MRI or a second clinical attack
- 1 attack with objective clinical evidence of 1 lesion, plus dissemination in space shown on MRI or 2 or more MRI lesions consistent with MS plus cerebrospinal fluid findings suggestive of MS and dissemination in time shown on MRI or second clinical attack
- insidious neurological progression suggestive of MS plus 1 year of disease progression determined retrospectively or prospectively, plus 2 of the following: positive brain MRI result (9 T2 lesions or at least 4 T2 lesions with positive visual evoked potential), positive spinal cord MRI result with 2 focal T2 lesions, and cerebrospinal fluid findings suggestive of MS.

Current treatment for MS includes specialist neurological rehabilitation, and medication tailored to the type of disease. The aim of this procedure is to relieve MS symptoms by improving cerebrospinal venous drainage. However, the full mechanism of action is not currently understood.

Proposed diagnostic criteria for chronic cerebrospinal venous insufficiency (CCSVI) amenable to percutaneous venoplasty

Zamboni et al[1] have developed criteria for diagnosing CCSVI using transcranial and extracranial colour doppler sonography in both supine and sitting positions. It is diagnosed if 2 or more 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.

If these criteria are met, percutaneous catheter venography is used to identify venous stenoses that may be the cause of the CCSVI. Lesions on venography that cause more than 50% luminal reduction are regarded as significant.

What the procedure involves

Percutaneous needle puncture of the femoral vein is done under local anaesthesia and a vascular sheath inserted using a standard needle, guidewire and catheter technique. The guidewire is advanced into the superior vena cava under fluoroscopic control. Selective venography of veins, including but not limited to the internal jugular and azygos, is used to identify any abnormal luminal narrowing and collateral circuits. Intravascular ultrasound may also be used. Abnormally narrowed segments are dilated with a standard angioplasty balloon. Sometimes a stent is left in place after the angioplasty. Further venography or ultrasound, or both, are used to assess the outcome of the intervention before the guidewire and sheath are removed.

Outcome measures

Expanded disability status scale (EDSS) quantifies disability in 8 functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other. EDSS scores of 1.0 to 4.5 refer to people with MS who are fully ambulatory. EDSS scores of 5.0 to 9.5 are defined by ambulatory impairment.

Multiple sclerosis impact scale (MSIS-29) measures the impact of MS on day-to-day life during the past 2 weeks. The questionnaire contains 20 items relating to physical impact and 9 items relating to psychological impact. High scores indicate greater impact (disability).

Multiple sclerosis functional composite (MSFC) has 3 components that measure leg function and ambulation (timed 25-foot walk), arm and hand function (9-hole peg test), and cognitive function (Paced auditory serial addition test). The MSFC is measured by a unique Z score where an increase or decrease represents improvement or deterioration in neurological functions, respectively.

Multiple sclerosis quality-of-life instrument (MS-QOL) is a multidimensional health-related quality-of-life measure that combines both generic and MS-specific items into a single instrument. Low scores indicate lower quality of life.

Fatigue severity scale (FSS) consists of 9 questions focusing on physical symptoms with an average score ranging from 1 to 7. Lower scores indicate less fatigue.

Modified fatigue impact scale (MFIS) uses 21 items divided into 3 subscales; physical (9 items), cognitive (10 items) and psychosocial (2 items) functioning. Each item has a score ranging from 0 to 4, with a total score from 0 to 84. Lower scores indicate less fatigue.

Efficacy summary

Relapse rate

In a randomised controlled trial (RCT) of 110 patients with RRMS, the annualised relapse rate was 0.32 (95% confidence interval [CI] 0.2 to 0.4) for patients who had percutaneous transluminal angioplasty (PTA) compared with 0.39 (95% CI 0.2 to 0.5) for patients who had a sham procedure (relative rate 0.82, 95% CI 0.40 to 1.71, p=0.60). 23% (17/73) of patients in the PTA group had at least 1 relapse over the 12 month follow-up compared with 31% (12/39) of patients in the sham group.[1]

In an RCT of 19 patients, there were 4 relapses (in 3 patients) in the PTA group and 1 relapse in the sham group (p=0.389). [2]

In a case-control study of 15 patients who had angioplasty immediately or delayed for 6 months, the proportion of patients who were relapse-free at 1 year was 88% (7/8) and 50% (3/6) respectively, which was not statistically significantly different.[3]

In a case series of 462 patients, the relapse rate was 21% (98/462) of patients at a mean follow-up of 31 weeks.[5]

Functional improvement

In the RCT of 110 patients, the composite functional measure (including walking control balance, manual dexterity, postvoid residual urine volume and visual acuity), was improved for 42% (30/72) of patients who had PTA and 49% (18/37) of patients who had a sham procedure (odds ratio 0.75, 95% CI 0.34 to 1.68, p=0.49). Worsening of function was reported in 13% (9/72) of patients who had PTA compared with 19% (7/37) of patients who had a sham procedure.[1]

In the RCT of 19 patients who had PTA or sham, there were no statistically significant within-group or between-group changes in EDSS, MS Functional Composite, or 6-minute walked distance, except improvement in MS Functional Composite in the sham group (p=0.04).[2]

In the case-control study of 15 patients who had treatment immediately or delayed for 6 months, there were no statistically significant changes in EDSS over 12 months between the 2 treatment groups. There was statistically significant improvement in MSFC compared with baseline over 0 to 6 months (p<0.02) and 0 to 12 months (p<0.02) in both immediate and delayed groups.[3]

In the case series of 462 patients with a mean follow-up of 31 weeks, the mean EDSS score increased from 4.9 at baseline to 5.2 at follow-up but this was not statistically significant; in the subjective evaluation 52.5% of patients had improved symptoms, 36.5% were stable and 11.0% worsened after percutaneous venoplasty.[5]

In a registry study of 102 patients, 20.5% of patients reported that their symptoms were better than before treatment, 53.0% were the same and 26.5% reported they were worse at 6-month follow-up. At 12-month follow-up, 25.3% of patients reported that their symptoms were better than before treatment, 48.2% were the same and 26.5% reported they were worse.[7]

In a case series of 366 patients followed up for 4 years, a statistically significant proportion of patients with RRMS (n=264) reported improvement in diplopia, fatigue, balance coordination, vertigo, sleep disorders, working ability, headache, upper extremity disorders and lower extremity disorders.[8]

Quality of life

In the RCT of 19 patients who had PTA or sham, there were no statistically significant between-group changes in cognitive or quality-of-life outcomes.[2] There were within-group changes in the Multiple Sclerosis Quality of Life-54 physical outcomes in both groups (p=0.0008 for PTA group and p=0.001 for sham group).[2]

New lesions on MRI

In the RCT of 110 patients, the mean number of new combined lesions seen on MRI at 12 months was 1.40 in the PTA group and 1.95 in the sham group (odds ratio 0.72, 95% 0.32 to 1.63, p=0.45). 63% (46/73) of patients in the PTA group were free of new lesions at 12-month follow-up compared with 49% (18/37) of patients in the sham group (odds ratio 1.80, 95% 0.81 to 4.01, p=0.15).[1]

In the RCT of 19 patients, the mean number of new T2 lesions was 2.1 in patients who had PTA and 0.3 in patients who had a sham procedure (p=0.066); the total number of new T2 lesions in each group was 17 and 3 respectively. The mean number of new T1 lesions was 0.8 in patients who had PTA and 0.2 in patients who had a sham procedure (p=0.144); the total number of new T1 lesions in each group was 6 and 2 respectively. The mean number of new contrast-enhancing lesions was 2.4 in patients who had PTA and 0.3 in patients who had a sham procedure (p=0.062); the total number of new contrast-enhancing lesions in each group was 19 and 3 respectively.[2]

In the case-control study of 15 patients who had treatment immediately or delayed for 6 months, the total number of new active lesions seen on MRI was 12 and 5 respectively at 6-month follow-up and 36 and 12 respectively at 12-month follow-up (p value not reported).[3]

In the case series of 462 patients, active lesions (contrast-enhancing or new T2-hyperintense) were seen on MRI in 35.7% (61/171) of patients at a mean follow-up of 29 weeks.[5]

Venous flow restoration

In the RCT of 110 patients, flow was restored in 54% (38/71) of patients in the PTA group and 38% (14/37) of patients in the sham group at 12-month follow-up.[1]

In the RCT of 19 patients, improvement was seen in the PTA group (p=0.02) and the sham group (p=0.04) at 1 month, but this did not reach more than 75% restoration of venous outflow compared with baseline; there were no statistically significant differences in venous haemodynamic insufficiency severity score improvement between the 2 groups (p=0.894).[2]

In a case series of 1,202 patients, successful recanalisation of the azygos vein was reported in 97.4% (911/935) of patients.[4]

Safety summary

Vein rupture

Azygos vein rupture was reported in 1 patient in the case series of 1,202 patients (1,219 procedures). The patient had sudden unexpected severe hypotension needing blood transfusion and stabilisation of vital parameters. Selective phlebography showed a 2 cm vein pseudoaneurysm close to the azygos vein ostium causing severe bleeding in the mediastinum. A self-expandable bare stent

was deployed at the origin of the azygos vein, followed by coil embolisation of the sac. The patient recovered and was discharged 7 days later.[4]

Vein rupture was reported in less than 1% (2/461) of patients in a case series of 461 patients included in a review of 1,157 patients. In the same case series, vein dissection was reported in 3% (15/461) of patients.[6]

A tear in the azygos vein was reported in 1 patient in a registry of 102 patients (104 procedures).[7]

Thrombosis

Thrombosis in the left internal jugular vein within 30 days of the procedure was reported in less than 1% (3/1,219) of procedures in the case series of 1,202 patients. The patients were readmitted to hospital because of sudden pain in the neck.[4]

Jugular thrombosis was reported in 6% (7/462) of patients in the case series of 462 patients; onset ranged from 48 hours to 41 weeks.[5]

Jugular thrombosis within 24 hours was reported in 2% (8/461) and 1% (2/342) of patients in 2 studies included in the review of 1,157 patients. Jugular thrombosis within 30 days was reported in 1% (3/240) of patients in a case series included in the same review. [6]

Periprocedural thrombosis was reported in 1 patient in the registry of 102 patients; 2 patients had thrombosis within the first month.[7]

Unilateral internal jugular vein thrombosis was reported in 2% (7/366) of patients in a case series of 366 patients.[8]

Balloon complications

Balloon ‘deflagration’ was reported in less than 1% (2/1,219) of procedures in the case series of 1,202 patients. Both patients had surgery to remove the fragments from the vein and were discharged home the following day. In another patient, a balloon fragment migrated into the pulmonary artery and was retrieved using a snare catheter.[4]

Open retrieval of a balloon was needed in 1 patient in a case series of 342 patients included in the review of 1,157 patients.[6]

Bursting of the balloon was reported in 1 patient in the registry of 102 patients.[7]

Stent migration or fracture

A case report of stent migration to the right atrium, needing thoracotomy, was described in the review of 1,157 patients.[6]

Bleeding

Severe bleeding at the groin, needing hospital admission, was reported in 1 patient in the case series of 1,202 patients. This was caused by a vein wall tear, likely because of a traumatic introducer sheath advancement following a difficult left common femoral vein puncture. The patient was readmitted 3 days after discharge and had successful treatment with open surgery.[4] A case report of fatal intracranial haemorrhage was described in the review of 1,157 patients.[6]

Groin haematoma was reported in 1% (2/240; 5/461; 4/342) of patients in 3 case series included in the review of 1,157 patients.[6] Bleeding and large haematoma in the right groin was reported in 1 patient in the registry of 102 patients.[7]

Arrhythmia

Symptomatic bradycardia, needing a pacemaker, was reported in 1 patient 24 hours after angioplasty in an RCT of 19 patients. The patient confirmed previous similar episodes that had not been reported to any physicians.[2]

Transient cardiac arrhythmia was reported in 1% (13/1,199) of patients in the case series of 1,202 patients; 4 resolved within 2 hours and 9 patients needed a 24-hour hospital stay before discharge because of atrial fibrillation.[4]

Paroxysmal atrial fibrillation was reported in 1 patient in the case series of 462 patients.[5]

Arrhythmia was reported in 1% (3/240; 6/461; 2/342) of patients in 3 case series included in the review of 1,157 patients.[6]

Arrhythmia was reported in 1 patient in the registry of 102 patients.[7]

Stroke

Stroke was reported in 1 patient in the case series of 462 patients and in 1 patient in the registry of 102 patients.[5,7]

Headache

Headache within 30 days was reported in 10% (23/240) and 9% (6/65) of patients respectively in 2 case series included in the review of 1,157 patients.[6]

Other

Tetraventricular hydrocephalus, status epilepticus, aspiration pneumonia, hypertension and tachycardia after sternotomy, severe bleeding from a bedsore, and myocardial infarction were each reported in 1 patient in the case series of 462 patients.[5]

Acute coronary syndrome was reported in 1 patient in a case series of 461 patients included in the review of 1,157 patients.[6]

Chest pain and depression was reported in 1 patient in the registry of 102 patients.[7]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers did not describe any additional anecdotal or theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous venoplasty for chronic cerebrospinal venous insufficiency in multiple sclerosis. The following databases were searched, covering the period from their start to 2 October 2018: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with chronic cerebrospinal venous insufficiency and multiple sclerosis.
Intervention/test	Percutaneous venoplasty.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on approximately 3,430 patients from 2 RCTs, 1 non-randomised comparative study, 1 systematic review, 4 case series (1 of which is also included in the systematic review) and 1 registry report.[1–8] One paper reported both a case series and an RCT.[2]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in the appendix.

Table 2 Summary of key efficacy and safety findings on chronic cerebrospinal venous insufficiency in multiple sclerosis

Study 1 Zamboni P (2018)

Details

Study type	**Randomised controlled trial (Brave Dreams)**
Country	Italy (6 centres)
Recruitment period	2012 to 2016
Study population and number	**n=115** (76 venous percutaneous transluminal angioplasty [PTA] versus 39 sham [catheter venography without venous angioplasty]) Patients with RRMS
Age and sex	PTA: mean 40 years; 59% (45/76) female Sham: mean 37.5 years; 74% (29/39) female
Patient selection criteria	Age 18 to 65 years; RRMS, according to the 2005 McDonald criteria; SPMS according to Lublin and Reingold; care provided by the recruiting centre for at least 2 years; at least 1 relapse in RRMS in the 2 years before enrolment; baseline Expanded Disability Status Scale (EDSS) score of 2 to 5.5; disease duration of 15 years or less at baseline; stable neurological condition without relapse for at least 30 days before baseline; chronic cerebrospinal venous insufficiency (CCSVI), as determined by colour doppler ultrasonography done in accordance with a screening protocol; and not having MS-specific treatment, immunomodulating, or immunosuppressive therapy without changes for at least 6 months up to baseline. Patients were ineligible if they had previous venous PTA or fingolimod therapy, cladribine therapy, laquinimod therapy, botulinum toxin therapy, infusion pump or neurostimulator implantation, or had participated in any clinical trial within 3 months of baseline.
Technique	All patients had catheter venography, with percutaneous access via the left femoral vein. If venography was positive for CCSVI, patients randomised to the PTA group had venous PTA during the venography session. Those patients allocated to the sham group had catheter venography without venous angioplasty. All procedures were done as day surgery and no patients needed an overnight hospital stay. All patients were offered prophylactic low-molecular-weight heparin for 3 weeks after the procedure.
Follow-up	**12 months**
Conflict of interest/source of funding	Dr Zamboni was the main author of the articles first describing CCSVI and its association with MS as well as the hypothesis of the potential anti-inflammatory action of venous outflow restoration.

Analysis

Follow-up issues: 97% (112/115) of patients completed the 12-month follow-up. One patient in the sham group was lost to follow-up and 2 patients in the venous PTA group withdrew informed consent before the procedure.

Study design issues: Randomised, double-blind, sham-controlled, multicentre trial. A data coordinating centre set up an internet-based computerised central randomisation protocol stratified by centre with variable length blocks, which assigned patients to the PTA or sham group in a 2:1 ratio. Patients, all study investigators apart from the treating surgeon, and operating room and hospital personnel were blinded to assignment. There were 2 primary endpoints at 12 months: a functional one and an MRI endpoint. A new composite functional outcome measure was used for the first time, which used the 5 components of walking control, balance, manual dexterity, postvoid residual urine volume and visual acuity (outcomes and change thresholds of the individual components were validated). The study was underpowered because of low enrolment (final total was 38% of amended target). A post hoc power calculation indicated a power of 30% to detect a difference in the functional endpoint and 17% power to detect the target difference in the MRI endpoint. The analysis was intention to treat.

Study population issues: The 2 groups were similar for baseline characteristics except that patients in the sham group had more women and longer disease duration. The median expanded disability status scale score was 2.5.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **110 (73 venous percutaneous transluminal angioplasty [PTA], 37 sham)**

Results for components of composite functional endpoint and MRI endpoint

	No. (%)		Unadjusted estimated effect of venous PTA		
Finding	PTA (n=73)	Sham (n=37)	OR (95% CI)	p value	Adjusted p value
Composite functional endpoint (n=72 for PTA group)					
Improved	30 (42)	18 (49)	0.75 (0.34 to 1.68)	0.49	-
Stable	17 (24)	8 (22)	-	-	-
Worsened	9 (13)	7 (19)	-	-	-
Mixed	16 (22)	4 (11)	-	-	-
MRI endpoint (new combined lesions at 12 months)					
No. of new lesions, mean (sd)	1.40 (4.21)	1.95 (3.73)	0.72 (0.32 to 1.63)	0.45	0.45
Median (range)	0 (0 to 31)	1 (0 to 8)	-	-	-
No. of patients free of new lesions	46 (63)	18 (49)	1.80 (0.81 to 4.01)	0.15	0.30

OR for improvement in the PTA group compared with sham, adjusted for sex and disease duration=0.70 (95% CI 0.31 to 1.59, p=0.40)

More patients in the PTA group than the sham group improved in visual acuity and manual dexterity, while more patients in the PTA group worsened for postvoid residual urine volume and balance. Walking control remained stable in most patients of both groups.

At 12 months, 68% (50/73) of patients in the PTA group were free of new or enlarged T2 lesions compared with 57% (21/37) of patients in the sham group (OR 1.66, 95% CI 0.73 to 3.75, p=0.22, adjusted p=0.62). 73% (53/73) of patients in the PTA group were free of gadolinium-enhancing lesions compared with 49% (18/37) in the sham group (OR 2.76, 95% CI 1.14 to 6.68, p=0.02, adjusted p=0.08).

7% (8/115) of patients diagnosed as having CCSVI by colour doppler ultrasonography had no abnormalities on venography.

Annualised relapse rate

- PTA=0.32 (95% CI 0.2 to 0.4)
- Sham=0.39 (95% CI 0.2 to 0.5),

Relative rate=0.82 (95% CI 0.40 to 1.71, p=0.60)

Flow restoration at 12 months

- PTA=54% (38/71)
- Sham=38% (14/37)

Safety

There were no serious adverse events attributable to catheter venography or venous PTA.

There were 2 adverse events: 1 vagal reaction and 1 episode of transient neck pain.

Abbreviations used: CI, confidence interval; OR, odds ratio; PTA, percutaneous transluminal angioplasty

Study 2 Siddiqui A (2014)

Details

Study type	**Phase 1 – case series; phase 2 – pilot randomised controlled trial (PREMiSe)**
Country	US
Recruitment period	2010 to 2012
Study population and number	**Phase 1: n=10; phase 2: n=19 (9 venous angioplasty, 10 sham)** Patients with multiple sclerosis (MS) with chronic cerebrospinal venous insufficiency (CCSVI) type venous anomalies.
Age and sex	Phase 1: mean 47 years; 50% (5/10) female Phase 2 treatment arm: mean 43 years; 56% (5/9) female Phase 2 sham arm: mean 45 years; 80% (8/10) female
Patient selection criteria	Inclusion criteria for phase 1: age 18 to 65 years, Expanded Disability Status Scale (EDSS) score 0 to 8.5, diagnosis of clinically definite MS, and fulfilling at the time of screening 2 or more CCSVI venous haemodynamic duplex criteria. Inclusion criteria for phase 2: age 18 to 65 years, EDSS score 0 to 5.5, active relapsing MS, and fulfilling at the time of screening 2 or more venous haemodynamic extracranial duplex criteria. Active relapsing disease was defined as 1 relapse within the past 12 months or presence of contrast-enhancing lesions on postcontrast MRI within the previous 3 months and concomitant treatment with disease-modifying treatments including natalizumab. Exclusion criteria (either phase) included acute relapse, disease progression, or steroid treatment within the previous 30 days, pre-existing medical conditions known to be associated with brain pathology, severe peripheral chronic venous insufficiency, severe contrast media allergy, and abnormal renal function.
Technique	The goal of angioplasty was to restore venous outflow of stenotic internal jugular veins and azygos vein to more than 50% of normal proximal venous diameter at the time of intervention. Angioplasty was only done in the treatment arm, not in the sham arm. All patients had a rigorous sternal rub when the angioplasty balloon was inserted, but the balloon was only inflated in the treatment arm. All patients were prevented from seeing the fluoroscopic images.
Follow-up	**6 months**
Conflict of interest/source of funding	Kaleida Health (New York) provided diagnostic and interventional services at no cost for the study; Direct MS Foundation (Canada), Volcano Corp (California), Covidien/ev3 Corp (California), and Jacquemin Family Foundation (Virginia) provided unrestricted educational grants or donations to Kaleida Health or to the University of Buffalo. There was no involvement from any of the sponsoring organisations in the design, collection, analysis, interpretation of data, writing of the report, or submission for publication.

Analysis

Follow-up issues: There were no losses to follow-up.

Study design issues: Phase 1 was an open-label safety study. Phase 2 was sham-controlled, randomised and double-blind. The sample size was restricted because of the pilot nature of the study, and assumed a 50% treatment effect. Randomisation was done by an independent statistician. All study personnel, except the interventional neurosurgeons, were blind to the assigned procedure, as were the patients. The primary endpoint was safety at 24 hours and 1 month. Preliminary efficacy outcomes were venous outflow restoration of more than 75% at 1 month compared with baseline, as measured by changes in venous haemodynamic insufficiency severity score, and effect of angioplasty on new MRI-based lesion activity and clinical relapse rate over 6 months.

Study population issues: There were no statistically significant differences in baseline characteristics between the 2 groups in phase 2. All patients in phase 2 had relapsing–remitting or relapsing progressive disease. In phase 1, 3 patients had secondary progressive disease and 1 patient had progressive relapsing disease.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 10; 19 (9 angioplasty, 10 sham)

Radiographic venous outflow dilation outcomes
In phase 1, there was improvement of venous haemodynamic insufficiency severity score (VHISS) over 6 months that resulted in >75% restoration of venous outflow compared with baseline (p<0.0001).
In phase 2, improvement was seen in the treatment (p=0.02) and sham (p=0.04) arms at 1 month but did not reach >75% restoration of venous outflow compared with baseline.
No differences in VHISS improvement were found between phase 2 treated and sham groups (p=0.894).

Clinical outcomes
Phase 1: there were no relapses.
Phase 2: there were 4 relapses in the treatment arm (in 3 patients) and 1 in the sham arm (p=0.389). The relapses occurred at 1, 3 (2 relapses) and 6 months in the treated arm and at 5 months in the sham arm.

There were no statistically significant changes in Expanded Disability Status Scale, MS Functional Composite, or 6 minute walked distance in phase 1 patients.
In phase 2, there were no statistically significant within or between-group changes in Expanded Disability Status Scale, MS Functional Composite, or 6 minute walked distance, except improvement in MS Functional Composite in the sham group (p=0.04). There were no statistically significant between-group changes in cognitive or quality-of-life outcomes.

In both phases, there were within-group changes in Symbol Digit Modalities Test (p=0.009 for phase 2 treated arm), Beck Depression Inventory Fast Screen (p=0.01 for phase 2 sham arm), Fatigue Severity Scale (p=0.03 for phase 2 sham arm), MS Neuropsychological Screening Questionnaire (p=0.008 for phase 2 sham arm), and Multiple Sclerosis Quality of Life-54 physical (p=0.02 for phase 1, p=0.0008 for phase 2 treated arm and p=0.001 for phase 2 sham arm) and mental health (p=0.003 for phase 2 sham arm) composites.

MRI outcomes
<table>
<tr><th></th><th>Phase 1 (n=10)</th><th>Phase 2: treatment arm (n=9)</th><th>Phase 2: sham arm (n=10)</th><th>p value</th></tr>
<tr><td>Cumulative number of new T2 lesions, mean (sd)</td><td>0.2 (0.4)</td><td>2.1 (2.9)</td><td>0.3 (0.7)</td><td>0.066</td></tr>
<tr><td>Cumulative number of new T2 lesions, total</td><td>2</td><td>17</td><td>3</td><td></td></tr>
<tr><td>Cumulative number of T1 lesions, mean (sd)</td><td>0</td><td>0.8 (0.9)</td><td>0.2 (0.6)</td><td>0.144</td></tr>
<tr><td>Cumulative number of T1 lesions, total</td><td>0</td><td>6</td><td>2</td><td></td></tr>
<tr><td>Cumulative number of CE lesions, mean (sd)</td><td>0.1 (0.3)</td><td>2.4 (3.2)</td><td>0.3 (0.7)</td><td>0.062</td></tr>
<tr><td>Cumulative number of CE lesions, total</td><td>1</td><td>19</td><td>3</td><td></td></tr>
<tr><td>Active T2 lesion scan, n (%)</td><td>2 (20)</td><td>4 (44.4)</td><td>2 (20)</td><td>0.321</td></tr>
<tr><td>Active T1 lesion scan, n (%)</td><td>2 (20)</td><td>4 (44.4)</td><td>0</td><td>0.118</td></tr>
<tr><td>Active CE lesion scan, n (%)</td><td>2 (20)</td><td>5 (55.6)</td><td>1 (10)</td><td>0.145</td></tr>
<tr><td>Percentage brain volume change</td><td>-0.64 (0.66)</td><td>-0.23 (0.84)</td><td>-0.74 (0.93)</td><td>0.257</td></tr>
<tr><td>Grey matter volume change</td><td>-2.1 (1.2)</td><td>-0.53 (1.6)</td><td>-1.84 (3.1)</td><td>0.320</td></tr>
<tr><td>White matter volume change</td><td>0.9 (1.5)</td><td>0.12 (2.6)</td><td>0.4 (2.9)</td><td>0.841</td></tr>
</table>
Using analysis of covariance, significant cumulative new T2 lesions were related to larger VHISS decrease (p=0.028) and angioplasty (p=0.01) over the follow-up.
</td><td>
Phase 1 (n=10): there were no serious adverse events detected within 6 months. There were no non-serious adverse events that were considered to be related to the procedure.

Phase 2: 1 patient in the treatment arm had a serious adverse event at 24 hours. The patient had an episode of symptomatic bradycardia and a pacemaker was subsequently fitted. The patient confirmed previous similar episodes that had not been reported to any physicians. Further follow-up was uneventful.
A second patient had a serious adverse event at 6 months, which was considered to be unrelated to the procedure (a viral infection caused thrombocytopaenic purpura).

1 patient in the treatment arm reported swelling and soreness at the left side of the neck 6 months after the procedure; no treatment was needed.
</td></tr>
<tr><td colspan="2">Abbreviations used: CE, contrast-enhancing; sd, standard deviation; VHISS, venous haemodynamic insufficiency severity score</td></tr>
</table>

Study 3 Zamboni P (2012)

Details

Study type	**Non-randomised comparative study with delayed treatment arm**
Country	Italy and US
Recruitment period	Not reported
Study population and number	**n=15 (8 immediate treatment at baseline, 7 delayed treatment 6 months later)** Patients with RRMS and duplex detected chronic cerebrospinal venous insufficiency (CCSVI)
Age and sex	Median 36 years (range 23 to 49); 67% (10/15) female
Patient selection criteria	Inclusion criteria: patients with a diagnosis of MS according to the McDonald criteria, who were on treatment with Food and Drug Administration approved disease-modifying treatments, and who were aged between 18 and 65 years. The expanded disability status scale (EDSS) had to range from 0 to 5.5, there had to be more than 2 areas of abnormal extracranial cerebral venous outflow that met venous haemodynamic criteria and normal kidney function. Exclusion criteria: pregnancy, relapse of MS, disease progression and steroid treatment within the 30 days preceding study entry, pre-existing medical conditions known to be associated with brain pathology, and contraindication for having gadolinium-based contrast agents.
Technique	Lesions of the azygos vein were treated with 8 to 10 mm diameter angioplasty balloons between 2 and 6 cm in length, inflated to a maximum pressure of 8 atmospheres. Inflations were held for 30 to 60 seconds and repeated several times, as needed. Angioplasty of stenosed internal jugular veins was done first with a compliant balloon (10 to 12 mm in diameter, 2 to 4 cm in length), which was then inflated to 8 atmospheres. If the initial procedure was unsuccessful, the treatment was repeated with a non-flexible high-pressure balloon (18 to 20 atmospheres) of equal diameter and length to the compliant balloon.
Follow-up	**12 months**
Conflict of interest/source of funding	The study was supported by Hilarescere Foundation and Buffalo Neuroimaging Analysis Center.

Analysis

Follow-up issues: One patient in the delayed group dropped out of the study at 3 months because of family reasons.

Study design issues: Patients were selected to have angioplasty immediately after baseline screening or delayed for 6 months. For the US patients, group selection was based on the availability of an international travel document (only 4 patients had passports available at baseline). The Italian patients were assigned to their groups by alphabetical order. All the interventions were done in Italy. The primary endpoints of the study were safety, patency rate and the effect of angioplasty on brain lesions, as well as relapse rate.

Study population issues: There were no statistically significant differences in baseline characteristics between the 2 groups. The median duration of MS at baseline was 8 years (range 5 to 10). The median EDSS score at baseline was 2.5 (range 1.5 to 5.5).

Other issues: This study is also included in the review by Varatharajan L et al., 2012 (study 6).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 15

Restenosis at 1 year (detected by duplex ultrasound)=27% (4/15) (detected in 2 patients in the delayed group at 9 month follow-up and 1 patient in each group at 12 month follow-up; restenoses were confined to the jugular veins)

Annualised relapse rate
• Immediate=0.12%
• Delayed=0.66%

Proportion of patients who were relapse-free at 1 year
• Immediate=88% (7/8)
• Delayed=50% (3/6), p=not significant
The 1 relapse in the immediate group occurred in a patient who presented at 12 months with 16 new combined active lesions. In the delayed group, 1 patient had 2 relapses and 2 patients had 1 relapse.

There were no statistically significant changes in expanded disability status scale over 12 months between the 2 treatment groups. There was statistically significant improvement in multiple sclerosis functional composite compared with baseline over 0 to 6 months (p<0.02) and 0 to 12 months (p<0.02) in both immediate and delayed groups.

MRI outcomes
<table>
<tr><th></th><th colspan="2">6 month follow-up</th><th colspan="2">12 month follow-up</th></tr>
<tr><th></th><th>Immediate group, n=8</th><th>Delayed group, n=6</th><th>Immediate group, n=8</th><th>Delayed group, n=6</th></tr>
<tr><td>Total number of new combined active lesions, median (range), sum</td><td>0.5 (0 to 3), 12</td><td>1.5 (0 to 3), 5</td><td>3 (0 to 16), 36</td><td>1.5 (0 to 6), 12</td></tr>
<tr><td>Active combined active lesion scans in individual patients, n (%)</td><td>6 (75)</td><td>3 (50)</td><td>5 (62.5)</td><td>4 (66.7)</td></tr>
<tr><td>Total number of new gadolinium lesions, median (range), sum</td><td>0</td><td>0</td><td>0 (0 to 9), 9</td><td>0 (0 to 1), 1</td></tr>
<tr><td>Active gadolinium scans in individual patients, n (%)</td><td>0</td><td>0</td><td>1 (12.5)</td><td>1 (16.7)</td></tr>
<tr><td>Total number of new T2 lesions, median (range), sum</td><td>0.5 (0 to 3), 12</td><td>1.5 (0 to 3), 5</td><td>3.5 (0 to 13), 34</td><td>1.5 (0 to 5), 12</td></tr>
<tr><td>Active T2 scans in individual patients, n (%)</td><td>6 (75)</td><td>3 (50)</td><td>4 (50)</td><td>4 (66.7)</td></tr>
<tr><td>T2 – lesion volume % change, median (range)</td><td>-8.9 (-52.5 to 15.6)</td><td>19.4 (-10.3 to 74)</td><td>-3.8 (-55.6 to 32.8)</td><td>20.3 (-26.3 to 78.5)</td></tr>
<tr><td>T1 – lesion volume % change, median (range)</td><td>-37.6 (-36.3 to 52.7)</td><td>-31.2 (-72.4 to 3.8)</td><td>-36.8 (30.1)</td><td>-15.2 (-53.4 to 28.4)</td></tr>
<tr><td>Percent brain volume change, median (range)</td><td>-1.27 (-6.6 to 1.1)</td><td>-0.57 (-1.8 to -0.3)</td><td>-0.69 (-3.3 to 0.9)</td><td>-0.84 (-1.1 to 1.4)</td></tr>
<tr><td>Lateral ventricle volume % change, median (range)</td><td>1.2 (-17 to 7.2)</td><td>5.6 (0.0 to 14.2)</td><td>9.2 (-6.2 to 16.4)</td><td>2.3 (-9.7 to 10.9)</td></tr>
</table>
</td><td>
There were no major complications.

One patient had vasovagal syncope 3 hours after the procedure.
</td></tr>
</table>

Study 4 Lupattelli T (2013)

Details

Study type	**Case series**
Country	Italy
Recruitment period	2010 to 2012
Study population and number	**n=1,202** Patients with multiple sclerosis (MS) and chronic cerebrospinal venous insufficiency (CCSVI)
Age and sex	Mean 35 years (range 18 to 78); 55% (655/1,202) female
Patient selection criteria	Patients with neurologist-confirmed diagnosis and symptoms of MS. All patients were previously diagnosed with CCSVI at colour doppler sonography, according to Zamboni score. The indication for venography and subsequent endovascular treatment was the presence of at least 2 out of 5 parameters of the Zamboni score.
Technique	Colour doppler sonography guidance was only used at the time of vein puncture when access was difficult. Angioplasty was done at the same time as phlebography. Before balloon dilatation, patients were given unfractionated heparin. A stenosis greater than 50% was considered the threshold for balloon dilatation. However, a luminal diameter reduction less than 50% in patients with a malformed valve, membrane, or septum at the vein outlet was also treated when associated with difficulty passing the guidewire through the ostium or with flow abnormality such as reflux or stasis of the contrast medium. Stenoses and occlusions were treated using high-pressure balloons or standard balloons in the internal jugular vein and azygos vein. Angioplasty was stopped once all detectable lesions in the 3 target veins (left and right internal jugular veins and azygos vein) were treated successfully or after 3 consecutive failing attempts. At least 2 balloons were used for each patient. Stent placement was done after inadequate response to previous attempts at balloon angioplasty only. Self-expandable bare stents were preferred to balloon expandable ones. Most patients had colour doppler sonography of the neck veins the following morning.
Follow-up	**30 days**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up with colour doppler sonography was completed by 85% (874/1,026) of patients at 12 months.

Study design issues: Retrospective case series. The primary endpoint was the combined number of complications at 30 days after the endovascular treatment. The secondary endpoint was the combined number of minor complications during the first 30 days after the procedure. Transient chest pain, neck pain, and headache were regarded as typical symptoms after the procedure and were not registered as adverse events. The study was not intended to evaluate clinical outcomes of the procedure.

Study population issues: 49% (584/1,202) of patients had RRMS, 36% (431/1,202) had secondary progressive, 9% (112/1,202) had primary progressive and the form of MS was unknown in 6% (75/1,202) of patients. The mean duration of MS before the procedure was 11 years (range 0.5 to 43). 87% (1,037/1,199) of patients had the treatment as a primary procedure and 14% (162/1,199) had it as a secondary procedure (reintervention after a venous disease recurrence). Secondary procedures were all done at least 6 months after the previous endovascular intervention.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **1,199** 3 patients did not have endovascular treatment because no significant disease was seen at phlebography, despite evidence of chronic cerebrospinal venous insufficiency at colour doppler sonography. Stents were placed in 14 patients (1.2%) after unsuccessful attempts at azygos vein dilatation. Technical success of the internal jugular vein=90.4% (1,084/1,199) of patients. Persistent stenosis >50% of at least 1 internal jugular vein was seen at confirmation phlebography in 6.8% (81/1,199) of patients. Successful recanalisation of the azygos vein=97.4% (911/935) of patients.	2 patients had inadvertent catheterisation of the left common femoral artery; spontaneous closure devices were used without further sequelae. **Major complications within 30 days, overall rate=0.6% (7/1,219) of procedures** • 1 azygos vein rupture occurred during a standard balloon dilatation with a high-pressure balloon. The patient had sudden unexpected severe hypotension needing blood transfusion and stabilisation of vital parameters. Selective phlebography showed a 2 cm vein pseudoaneurysm close to the azygos vein ostium causing severe bleeding in the mediastinum. A self-expandable bare stent was deployed at the origin of the azygos vein, followed by coil embolisation of the sac. The patient recovered and was discharged 7 days later. • 2 balloon 'deflagrations', both occurred during prolonged dilatation for stenosis in the left internal jugular vein. Both patients had surgical opening of the left common femoral vein. The fragments were removed, the vein was sutured, and the intervention was continued. Both patients were discharged home the following day. • 1 severe bleeding at the groin, needing hospitalisation. This was caused by a vein wall tear, likely because of a traumatic introducer sheath advancement following a difficult left common femoral vein puncture. The patient was readmitted 3 days after discharge and had successful treatment with open surgery. • 3 patients had thrombosis in the left internal jugular vein within 30 days of the procedure. They were readmitted because of sudden pain in the neck. All the major complications occurred during the first 400 procedures. **Minor complications within 30 days, overall rate=2.5% (31/1,219) of procedures** • Transient cardiac arrhythmia=1.1% (13/1,199); 4 resolved within 2 hours and 9 patients needed a 24-hour hospital stay before discharge because of atrial fibrillation. • Slight bleeding or haematomas in the groin=0.8% (10/1,199) • Slight right neck haematomas=0.2% (2/1,199) • Haemotympanum=0.1% (1/1,199); at 25 days after discharge. • Migration of balloon fragment into the pulmonary artery=0.1% (1/1,199); a snare catheter was used to retrieve the fragment. • Mild contrast reactions=0.3% (3/1,199); treated with antihistamine and intravenous fluid administration. • Left common femoral artery pseudoaneurysm=0.1% (1/1,199); the patient had signs of moderate haemoglobin depletion at 3 days after the procedure. The pseudoaneurysm was treated by coil embolisation.

Study 5 Ghezzi A (2013)

Details

Study type	**Case series**
Country	Italy (33 centres)
Recruitment period	2011 to 2012
Study population and number	**n=462** Patients with multiple sclerosis (MS) who had endovascular treatment for chronic cerebrospinal venous insufficiency (CCSVI)
Age and sex	Mean 40 years; 60% (279/462) female
Patient selection criteria	Not reported
Technique	Endovascular CCSVI treatment consisted of balloon dilatation in 93% of patients and stent application in 7% of patients.
Follow-up	**Mean 31 weeks**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: The paper states that data from 462 patients were collected in 33 centres. It is unclear how many patients were eligible for the study.

Study design issues: Multicentre, observational cohort study. All Italian MS centres that were part of the Italian MS Study Group were invited to participate. During the visit to MS centres, patients were regularly asked whether they had endovascular treatment for MS and were consecutively recruited. If the answer was positive, a structured 28-item questionnaire was completed, anonymised and sent to the coordinating centre. Neurological status was scored using the Kurtzke FS and expanded disability status scale (EDSS). Other items of the questionnaire included patient's subjective clinical outcome, adverse events, and other treatments.

Study population issues: 48% (222/462) of patients had RRMS, 23% (107/462) had SPMS and 29% (133/462) had PPMS. The mean duration of MS before the procedure was 13.6 years and the mean EDSS score was 4.9.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **462**

Clinical outcome after endovascular treatment

Follow-up duration (months)	No. of patients	Mean EDSS score		Subjective evaluation		
		Baseline	Follow-up	Improved (%)	Stable (%)	Worsened (%)
<3	121	5.1±2.0	5.2±2.0*	55.4	33.0	11.6
3 to 6	93	5.1±1.9	5.2±2.0*	51.6	34.5	13.9
>6	248	4.8±2.1	5.1±2.1*	48.3	42.0	9.7
Whole cohort	462	4.9±2.0	5.2±2.0*	52.5	36.5	11.0

* p=not significant

Distribution of patients according to EDSS score (%)

EDSS score	Before treatment	After treatment
<2	9	9
2 to 3.5	18	17
4 to 5.5	26	22
>5.5	47	52

No statistically significant difference was found between EDSS scores before and after the procedure in relation to clinical course, gender, age, disability, or disease duration.

Relapse rate=21% (98/462) of patients (144 relapses)

Distribution of relapses after endovascular treatment in relation to the use of pharmacological MS therapy

	Number of patients	Patients with relapses (%)	Number of relapses (relapses per patient)
No previous MS therapy	172	32 (18.3)	36 (1.1)
MS therapy stopped after endovascular treatment	98	26 (26.5)	58 (1.4)
MS therapy continued after endovascular treatment	189	40 (21.1)	50 (1.2)

MRI outcomes (n=171, mean follow-up=29 weeks)

- Active lesions (contrast-enhancing or new T2-hyperintense)=35.7% (61/171)

Safety

Adverse events=10.8% (50/462)

These were considered to be mild in 35 (7.6%) patients and mainly consisted of nausea, headache, cutaneous rash or other skin reactions, and inguinal haematoma.

Severe adverse events=3.3% (15/462)

#	Side effect	Onset from intervention	EDSS change
1	Jugular thrombosis	48 h	No
2	Jugular thrombosis	7 days	2.5 to 3.5
3	Jugular thrombosis	30 days	No
4	Jugular thrombosis	30 days	No
5	Jugular thrombosis	6 weeks	No
6	Jugular thrombosis	10 weeks	5 to 6
7	Jugular thrombosis	41 weeks	No
8	Paroxysmal atrial fibrillation	24 h	No
9	Tetraventricular hydrocephalus	48 h	6 to 6.5
10	Stroke	12 weeks	7.5 to 8.5
11	Status epilepticus	8 weeks	4.5 to 9.5
12	Aspiration pneumonia	7 days	7.5 to 9.0
13	Hypertension and tachycardia after sternotomy	30 days	No
14	Severe bleeding from a bedsore	15 days	No
15	Myocardial infarction	10 weeks	Death

Abbreviations used: EDSS, expanded disability status scale; MS, multiple sclerosis

Study 6 Varatharajan L (2012)

Details

Study type	**Systematic review**
Country	Studies were based in Italy, Bulgaria, Poland and US.
Recruitment period	Search date: March 2012
Study population and number	9 studies were included, 6 of which were included in quantitative synthesis (**n=1,154**). The remaining 3 studies were case reports. Patients with chronic cerebrospinal venous insufficiency (CCSVI) and multiple sclerosis (MS)
Age and sex	Age range 15 to 79 years; mean age ranged from 36 to 49 years. 59% (678/1,154) female
Patient selection criteria	Study inclusion criteria: interventional studies reporting complications following venoplasty of the internal jugular and azygos veins in MS patients. Exclusion criteria: duplicate publication, review articles, letters and abstracts. Case reports were considered qualitatively, as they did not report prevalence statistics. No limits, filters or language exclusions were applied. Authors of conference proceedings were contacted for data and, if they replied, these data were included.
Technique	All procedures were done under local anaesthetic with sedation. All studies described the use of the standard percutaneous venographic technique via a femoral vein. Angioplasty was the primary intention, but stents were placed in 0 to 44% of patients. Four studies described the pressures used during balloon dilatation (4 to 15 atmospheres) and 3 reported the inflation time (30 to 60 seconds). All studies used postoperative antithrombolytic therapy, varying from 1 week of prophylactic dose low-molecular-weight heparin to lifelong aspirin.
Follow-up	**24 hours to 18 months**
Conflict of interest/source of funding	Funded/supported by the National Institute for Health Research Biomedical Research Centre, based at Imperial College Healthcare NHS Trust and Imperial College London. The authors of the systematic review declared no conflicts of interest.

Analysis

Follow-up issues: Six studies followed up patients for at least 24 hours, 4 studies for at least 1 month and 3 for at least 12 months. Two studies had an independent assessor for follow-up.

Study design issues: The review was done according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. After title and abstract screening, full-text articles were assessed independently for methodological quality by 2 reviewers. Authors of articles without clear technical details or follow-up protocols were contacted by email. If they did not respond they were excluded. Of the 6 studies included in the quantitative analysis, 5 were case series and 1 was a pilot randomised controlled trial. Three of the included studies were prospective.

Study population issues: Mean Expanded Disability Status Scale (EDSS) scores at baseline ranged from 2.5 to 6.0. Two studies included severely disabled patients with EDSS scores of up to 9.5 (bed bound or unable to communicate or swallow). Relapsing–remitting disease was found in 36 to 100% of patients across the studies. Mean time from diagnosis of MS was 8 to 11 years.

Other issues: The review includes the study by Zamboni P et al., 2012 (study 3).

Key efficacy and safety findings

Safety

Number of patients analysed: **1,157** (1,154 in 6 case series and 3 case reports)

Complications after venoplasty for chronic cerebrospinal venous insufficiency

	Study (year)					
	Zamboni et al. (2012)	Mandato et al. (2012)	Petrov et al. (2011)	Ludyga et al. (2010)	Malagoni et al. (2010)	Zamboni et al. (2009)
Number of patients treated	15	240	461	342	31	65
Number of procedures	15	257	495	344	NR	65
Follow-up	12 months	1 month	24 hours	24 hours	12 months	18 months
Immediate complications (<24 hours)						
Death	0	0	0	0	0	0
Stroke	NR	NR	NR	0	NR	NR
Major haemorrhage	0	0	0	0	NR	NR
Acute coronary syndrome	NR	NR	1 (0.2%)	NR	n/a	NR
Stent migration	n/a	NR	0	0	n/a	n/a
Jugular thrombosis	n/a	NR	8 (1.7%)	2 (0.6%)	0	0
Open retrieval of balloon needed	0	NR	NR	1 (0.3%)	NR	NR
Groin haematoma	NR	2 (0.8%)	5 (1.1%)	4 (1.2%)	NR	NR
Arrhythmia	NR	3 (1.3%)	6 (1.3%)	2 (0.6%)	NR	NR
Vein rupture	NR	NR	2 (0.4%)	NR	0	0
Vein dissection	NR	NR	15 (3.3%)	NR	NR	NR
Minor contrast reaction	0	7 (2.9%)	NR	NR	0	0
Early complications (<30 days)						
Headache	NR	23 (9.6%)	n/a	n/a	NR	6 (9.2%)
Gastrointestinal bleeding	NR	NR	n/a	1 (0.3%)	NR	NR
Jugular thrombosis	NR	3 (1.25%)	n/a	n/a	NR	0

7 of the 10 immediate jugular thromboses were in-stent thromboses; in 1 centre, 8/8 patients had successful treatment with thrombolysis and catheter aspiration. One group did not re-intervene in patients with in-stent thrombosis and did not follow them further to establish outcome. Of the 3 early jugular thromboses, 2 were in-stent and 1 was in a native vein. The native jugular thrombosis was treated with stenting. Of the 2 in-stent jugular thromboses, 1 was successfully treated with angioplasty. Thrombectomy attempted for the other patient but they developed a life-threatening tachycardia and needed intubation and vasopressor support.

Immediate complications – case reports

- 1 case report of fatal intracranial haemorrhage.
- 1 case report of stent migration to the right atrium, needing thoracotomy.

Early complications – case reports

There were further case reports of symptomatic jugular thrombosis that were treated with thrombectomy, cranial nerve XI and XII palsy from oversized stent placement, extraperitoneal haematoma needing blood transfusion, sigmoid sinus thrombosis needing anticoagulation and asymptomatic transdiaphragmatic azygos stent migration.

Late complications

No late complications were reported by any group.

Abbreviations used: n/a, not applicable; NR, not reported

Study 7 Sadovnick AD (2017)

Details

Study type	**Registry**
Country	Canada
Recruitment period	2011 to 2014
Study population and number	**n=102** Patients with multiple sclerosis (MS) who self-reported venoplasty
Age and sex	Mean 56 years; 73% (74/102) female
Patient selection criteria	British Columbia residents with MS who self-reported venoplasty were invited to telephone or email the registry and leave their contact information. They were then contacted and invited to participate.
Technique	Out of 104 procedures, 89 involved balloon dilatation only, 14 involved balloon dilatation and stent, and 1 was unknown.
Follow-up	**Up to 24 months**
Conflict of interest/source of funding	The study was funded by the British Columbia Ministry of Health. One author has received grant funding from Biogen Idec, Teva Canada Innovation, Sanofi Genzyme and Novartis and partial travel funds from Roche. One author has received consultancy meeting fees from Biogen Idec, is a principal investigator for Novartis and Biogen Idec, and has received fees for seeing study patients. One author has received research support from Sanofi Genzyme, Roche, Biogen Idec and Chugai Pharmaceutical and has served as consultant/adviser for Sanofi Genzyme, Roche, Teva Canada Innovation and Biogen Idec.

Analysis

Follow-up issues: Of the 140 patients who were invited to participate, 38 (27%) chose not to. Of the 102 patients who participated, 91% (93/102) were re-interviewed at 6 months, 81% (83/102) at 12 months and 54% (55/102) were followed up at 24 months (27 patients were beyond the study cut-off date at follow-up, 9 patients refused to complete a follow-up interview, 7 patients could not be contacted, 2 patients had another procedure during the study and restarted data collection, 1 patient moved and 1 patient died).

Study design issues: Information on the registry was disseminated through the official Vancouver Coastal Health research Institute website, University of British Columbia MS clinic visits, and the British Columbia and Yukon Division newsletter of the MS Society of Canada. Patients with MS who self-reported venoplasty were invited to telephone or email the registry and leave their contact information. They were then contacted and invited to participate. 'Initial' and 'follow-up' questionnaires were administered by telephone. The average elapsed time between the most recent venoplasty and the initial interview was 18 months. Follow-up data was also collected from participating physicians, using the Medical Doctor's Adverse Effect Report Form, which was designed and validated for this study.

Study population issues: 13% (13/102) patients reported having PPMS, 10% (10/102) had SPMS, 64% (65/102) had RRMS and 14% (14/102) were unknown or 'other'.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **102**

Patient-reported outcomes by patient-reported MS course at 'initial' interview, n (%) (measured on 5-point Likert-type scale; better=1 [much better] and 2 [somewhat better] and worse=4 [somewhat worse] and 5 [much worse])

	RRMS (n=63)			Progressive/other MS (n=29)		
	Better	Same	Worse	Better	Same	Worse
General health	36 (57.1)	16 (25.4)	11 (17.5)	14 (48.3)	8 (27.6)	7 (24.1)
Fatigue	41 (65.1)	18 (28.6)	4 (6.4)	19 (65.5)	6 (20.7)	4 (13.8)
Pain	20 (31.7)	41 (65.1)	2 (3.2)	8 (27.6)	19 (65.5)	2 (6.9)
Numbness	26 (41.2)	34 (54.0)	3 (4.8)	11 (37.9)	15 (51.7)	3 (10.3)
Tingling	23 (36.5)	39 (61.9)	1 (1.6)	10 (34.5)	15 (51.7)	4 (13.8)
Bladder control	23 (36.5)	34 (54.0)	6 (9.5)	10 (34.5)	17 (58.6)	2 (6.9)
Bowel control	14 (22.2)	47 (74.6)	2 (3.2)	6 (21.4)	22 (78.6)	0
Vision	16 (25.4)	43 (68.3)	4 (6.3)	4 (13.8)	22 (75.9)	3 (10.3)
Balance	33 (52.4)	25 (39.7)	5 (7.9)	12 (41.4)	10 (34.5)	7 (24.1)
Tremor	15 (23.8)	43 (68.3)	5 (7.9)	8 (27.6)	15 (51.7)	6 (20.7)
Concentration	25 (39.7)	32 (50.8)	6 (9.5)	14 (48.3)	13 (44.8)	2 (6.9)
Mobility	27 (42.9)	29 (46.0)	7 (11.1)	11 (37.9)	12 (41.4)	6 (20.7)
Exercise level	29 (46.0)	24 (38.1)	10 (15.9)	19 (65.5)	4 (13.8)	6 (20.7)

Excludes 2 patients who had repeat venoplasty during the study period and 8 patients who did not know their MS course. 1 patient in the progressive group did not answer the question on bowel control.

Patient-reported outcomes relative to status before treatment (%) (measured on 5-point Likert-type scale; better=1 [much better] and 2 [somewhat better] and worse=4 [somewhat worse] and 5 [much worse]); n=82 unless stated otherwise

	6 month follow-up			12 month follow-up		
	Better	Same	Worse	Better	Same	Worse
General health, n=83	20.5	53.0	26.5	25.3	48.2	26.5
Fatigue, n=83	20.5	57.8	21.7	19.3	55.4	25.3
Pain	9.8	70.7	19.5	14.6	69.5	15.9
Numbness	13.4	67.1	19.5	11.0	64.6	24.4
Tingling	9.8	69.5	20.7	8.5	73.2	18.3
Bladder control	17.1	67.1	15.9	11.0	63.4	25.6
Bowel control, n=81	6.2	86.4	7.4	9.9	81.5	8.6
Vision	1.2	73.2	25.6	4.9	70.7	24.4
Balance	9.8	50.0	40.2	13.4	57.3	29.3
Tremor	7.3	75.6	17.1	11.0	74.4	14.6
Concentration	4.9	74.4	20.7	4.9	87.8	7.3
Mobility	12.2	53.7	34.1	15.9	50.0	34.1
Exercise level	31.7	48.8	19.5	29.3	42.7	28.0

Patient rating of outcome (patients who completed all interviews up to 12 month follow-up)

Rating of procedure	Initial interview	6 month follow-up	12 month follow-up
1=not at all helpful	12 (14.8%)	19 (23.5%)	19 (23.5%)
2	13 (16.0%)	11 (13.6%)	12 (14.8%)
3	16 (19.8%)	15 (18.5%)	16 (19.8%)
4	12 (14.8%)	15 (18.5%)	14 (17.3%)
5=extremely helpful	28 (34.6%)	21 (25.9%)	20 (24.7%)
Total	81 (100%)	81 (100%)	81 (100%)

25% (20/80) of the physician reports showed agreement between patient and physician perceptions of the benefit of venoplasty: 8 'significant', 5 'modest', and 7 'none'. In 41.3% (33/80)

Safety

Patient-reported complications during the procedure=11.5% (12/104)

Serious procedure-related complications:

- Tear in azygos vein (n=1)
- Thrombosis (n=1)
- Bursting of balloon (n=1)

8 patients reported procedure-related pain.

Patient-reported complications within the first month after venoplasty=17.3% (18/104)

These included:

- Thrombosis (n=2)
- Allergic reaction to blood thinner, needing hospitalisation on return to Canada (n=1)
- Bleeding and large haematoma in the right groin (n=1)
- Chest pain and depression (n=1)
- Stroke (n=1)
- Arrhythmia (n=1)

Physician-reported periprocedure complications=16.4% (17/104):

- Azygos vein dissection (n=1)
- Menorrhagia (n=1)
- Bleeding and marked bruising (n=1)
- Hypertension needing admission to the coronary care unit for monitoring (n=1)
- Pain (n=1)
- Inadequate sedation (n=1)
- Unspecified (n=11)

Physician-reported complications within the first month=19.2% (20/104), including:

- Pain (n=7)
- Hypertension 3 to 4 hours postoperatively (n=2)
- Anaemia (n=1)

of reports, physicians perceived venoplasty as less beneficial than did patients. 33.7% (26/80) of reports had 'unknown' in 1 or both of the patient's and physician's perceptions.	• Unspecified (n=10)
Abbreviations used: MS, multiple sclerosis	

Study 8 Bavera PM (2016)

Details

Study type	**Case series**
Country	Italy
Recruitment period	Mid-2010
Study population and number	**n=366** Patients with chronic cerebrospinal vein insufficiency (CCSVI) and multiple sclerosis (MS)
Age and sex	65% (238/366) female; age not reported
Patient selection criteria	Not reported
Technique	All patients had percutaneous transluminal angioplasty of the internal jugular veins. No further details were reported.
Follow-up	**4 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: The paper does not discuss completeness of follow-up. The paper states that patients were followed up for 4 years after treatment, but it is unclear whether the reported results are from all patients at the end of the 4 year follow-up.

Study design issues: The main aim of the study was to analyse and classify the symptoms before and after treatment. This new classification was developed from patients' spontaneous descriptions of their own symptoms. Quality of life was assessed using the Spitzer Quality of Life Index, which covers 5 dimensions (activity, daily living, health, support of family and friends, and outlook). Patients were divided into 3 groups (RRMS, SPMS and PPMS), according to their Expanded Disability Status Scale (EDSS) score.

Study population issues: 72% (264/366) patients had RRMS, 17% (62/366) had SPMS, and 11% (40/366) had PPMS.

Other issues: It is sometimes unclear from the paper how many patients had each symptom before the angioplasty. The percentages have been extracted from the table as they are reported.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **366**

Proportion of patients with improved symptoms after percutaneous transluminal angioplasty, n (%)

	Relapsing–remitting	p value	Secondary progressive	p value	Primary progressive	p value
Diplopia	262 (99.2%)	<0.0001	49 (79.0%)	<0.0001	5 (12.5%)	0.884
Fatigue (often combined with headache)	260 (98.5%)	<0.0001	4 (6.5%)	NS	2 (5.0%)	NS
Thermic sensibility (usually combined with extremity disorders)	198 (75.0%)	NS	12 (19.4%)	0.018	5 (12.5%)	0.884
Bladder control	176 (66.7%)	NS	46 (82.1%)	<0.0001	34 (85.0%)	<0.0001
Balance coordination	23/26 (88.5%)	<0.0001	15/62 (24.2%)	0.004	4/40 (10.0%)	NS
Vertigo	30/33 (90.9%)	<0.0001	25/52 (48.1%)	<0.0001	18/32 (56.3%)	0.0007
Sleep disorders	55 (93.2%)	<0.0001	50 (89.3%)	<0.0001	28 (73.7%)	<0.0001
Working ability impairment (often combined with speech and reasoning skills)	260 (98.5%)	<0.0001	5 (8.1%)	0.884	15 (37.5%)	0.0036
Headache (often combined with fatigue, sleep disorders and lack of concentration)	205 (98.6%)	<0.0001	50 (94.3%)	<0.0001	30 (90.9%)	<0.0001
Upper extremity disorders	20/24 (83.3%)	0.0002	35/62 (56.5%)	<0.0001	6/40 (15.0%)	0.495
Lower extremity disorders	13/15 (86.7%)	0.0087	10/62 (16.1%)	0.0531	2/40 (5.0%)	NS

p values were multiple comparisons corrected using Bonferonni's procedure

Safety

Complications

- Unilateral internal jugular vein thrombosis=1.9% (7/366)*

*Reported as 0.19% in the paper

Validity and generalisability of the studies

- Most of the evidence was from Italy.
- The recent RCT was double-blind and sham-controlled, but it was underpowered because of low enrolment.[1]
- The severity of multiple sclerosis (MS) in patients enrolled in the recent RCT was lower than anticipated, in terms of EDSS score and lesion load and patients with active disease may have been underrepresented.[1]
- The recent RCT only enrolled a small number of patients with SPMS, and the results presented are for patients with RRMS only.[1]
- Some studies used stents for a proportion of patients.
- The comparative studies all reported MRI findings as one of the efficacy outcomes.
- The case series included patients with RRMS, SMS and PPMS.
- The longest follow-up was 4 years, but this was for a case series with subjective outcomes only.

Existing assessments of this procedure

A technology brief by the Health Policy Advisory Committee on Technology Australia and New Zealand was published in November 2011.[9] The assessment concluded:

'The role of CCSVI in the pathogenesis of MS remains unclear. In addition, there is a lack of well-designed studies evaluating the safety and efficacy of percutaneous venoplasty for the relief of symptoms in MS patients with CCSVI. The outcomes from randomised, controlled, clinical trials with long-term follow-up of patients will need to be evaluated before this procedure can be widely adopted. Therefore, HealthPACT have recommended that information on this

technology be noted and that no further research by HealthPACT is warranted until results from comparative clinical trials become available.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Percutaneous venoplasty for chronic cerebrospinal venous insufficiency for multiple sclerosis. NICE interventional procedures guidance 420 (2012). Available from http://www.nice.org.uk/guidance IPG420 *[current guidance]*

Technology appraisals

- Cladribine tablets for treating relapsing–remitting multiple sclerosis. NICE technology appraisal 493 (2017). Available from http://www.nice.org.uk/guidance/TA493
- Dimethyl fumarate for treating relapsing‑remitting multiple sclerosis. NICE technology appraisal 320 (2014). Available from http://www.nice.org.uk/guidance/TA320
- Alemtuzumab for treating relapsing‑remitting multiple sclerosis. NICE technology appraisal 312 (2014). Available from http://www.nice.org.uk/guidance/TA312
- Teriflunomide for treating relapsing–remitting multiple sclerosis. NICE technology appraisal 303 (2014). Available from http://www.nice.org.uk/guidance/TA303
- Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis. NICE technology appraisal 254 (2012). Available from http://www.nice.org.uk/guidance/TA254
- Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis. NICE technology appraisal 127 (2007). Available from http://www.nice.org.uk/guidance/TA127

- Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. NICE technology appraisal 32 (2002). Available from http://www.nice.org.uk/guidance/TA32

NICE guidelines

- Multiple sclerosis in adults: management. NICE clinical guideline 186 (2014). Available from http://www.nice.org.uk/guidance/CG186

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two specialist adviser questionnaires for percutaneous venoplasty for chronic cerebrospinal venous insufficiency in multiple sclerosis were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Patient organisation submissions

Submissions were received from 2 patient organisations, which were discussed by the committee.

Issues for consideration by IPAC

None other than those described above.

References

1. Zamboni P, Tesio L, Galimberti S et al. (2018) Efficacy and Safety of Extracranial Vein Angioplasty in Multiple Sclerosis: A Randomized Clinical Trial. JAMA Neurology 75: 35–43
2. Siddiqui AH, Zivadinov R, Benedict RHB et al. (2014) Prospective randomized trial of venous angioplasty in MS (PREMiSe). Neurology 83: 441–49
3. Zamboni P, Galeotti R, Weinstock-Guttman B et al. (2012) Venous angioplasty in patients with multiple sclerosis: results of a pilot study. European Journal of Vascular & Endovascular Surgery 43: 116–22
4. Lupattelli T, Bellagamba G, Righi E et al. (2013) Feasibility and safety of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. Journal of Vascular Surgery 58: 1609–18
5. Ghezzi A, Annovazzi P, Cocco E et al. (2013) Endovascular treatment of CCSVI in patients with multiple sclerosis: clinical outcome of 462 cases. Neurological Sciences 34: 1633–7
6. Varatharajan L, Lane TRA, Thapar A et al. (2012) Complications and safety of jugular and azygous angioplasty in CCSVI patients with multiple sclerosis. Interventional Cardiology (London) 4: 473–79
7. Sadovnick AD, Yee IM, Attwell-Pope K et al. (2017) Patient-Reported Benefits of Extracranial Venous Therapy: British Columbia CCSVI Registry. Canadian Journal of Neurological Sciences 44: 246–54
8. Bavera PM (2016) Chronic cerebrovascular vein insufficiency: How and when jugular vein PTA can influence multiple sclerosis symptoms. Acta Phlebologica 17: 27–32
9. Thavaneswaran P (2011) Technology Brief. Percutaneous venoplasty for the treatment of chronic cerebrospinal venous insufficiency (CCSVI) in multiple sclerosis. Health Policy Advisory Committee on Technology Australia and New Zealand, State of Queensland (Queensland Health)

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	02/10/2018	Issue 10 of 12, October 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	02/10/2018	Issue 9 of 12, September 2018
HTA database (CRD website)	02/10/2018	
MEDLINE (Ovid)	02/10/2018	1946 to October 01, 2018
MEDLINE In-Process (Ovid) & MEDLINE Epubs ahead of print (Ovid)	02/10/2018	October 01, 2018
EMBASE (Ovid)	02/10/2018	1974 to 2018 Week 40

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	exp angioplasty/
2	Endovascular Procedures/
3	Vascular Surgical Procedures/
4	angioplast*.tw.

5	(balloon* adj4 (dilat* or valv*)).tw.
6	(transluminal adj4 dilat*).tw.
7	venoplast*.tw.
8	(liberat* adj4 procedure*).tw.
9	((vascular or intravascular or endovascular) adj4 (procedure* or technique*)).tw.
10	PTA.tw.
11	or/1-10
12	exp Multiple Sclerosis/
13	((disseminat* or multiple) adj4 sclerosis).tw.
14	MS.tw.
15	CDMS.tw.
16	12 or 13 or 14 or 15
17	cerebrovascular disorders/
18	((brain* or intracranial or cerebrovascular) adj4 vascular adj4 (diseas* or disorder*)).tw.
19	CCSVI.tw.
20	Venous Insufficiency/
21	((brain or intracerebral or cerebrospin* or cerebral or extracranial) adj4 (venous or vein*) adj4 (obstruct* or occlusion* or disturb* or drain* or insufficien* or outflow)).tw.
22	((venous or vein*) adj4 (stasis or insufficien* or stenos* or strict* or constrict*)).tw.
23	Constriction, Pathologic/
24	(pathologic* adj4 constrict*).tw.
25	or/17-24
26	16 and 25
27	11 and 26
28	Animals/ not Humans/
29	27 not 28

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Alroughani R, Lamdhade S, Thussu A (2013) Endovascular treatment of chronic cerebrospinal venous insufficiency in multiple sclerosis: a retrospective study. International Journal of Neuroscience 123: 324–8	Case series n=45 FU=1 year	At 1-year follow-up, the proportion of relapse-free patients decreased from 84% to 67% (p=0.085), whereas the mean EDSS score increased (p=0.017). The proportion of patients with new MRI activity increased statistically significantly from 18% to 44% (p=0.012). 36% of patients stopped their disease-modifying therapies.	Small case series with short term follow-up.
Arata M, Sternberg Z (2014) Transvascular autonomic modulation: a modified balloon angioplasty technique for the treatment of autonomic dysfunction in multiple sclerosis patients. Journal of Endovascular Therapy 21: 417–28	Non-randomised comparative study n=42	The combination of balloon angioplasty of anatomically normal veins coupled with external compression during dilation of these veins can improve indicators of autonomic nervous system dysfunction.	Small study, comparing transvascular autonomic modulation with conventional balloon angioplasty.
Arata M, Sternberg Z (2016) Neuroendocrine Responses to Transvascular Autonomic Modulation: A Modified Balloon Angioplasty in Multiple Sclerosis Patients. Hormone & Metabolic Research 48: 123–9	Case series n=72	The intervention resulted in statistically significant reductions in both adrenocorticotropic hormone (ACTH) and cortisol (p<0.001), with a more marked ACTH reduction in males compared with females (p<0.001). This is counter to the stress-mediated increases in serum levels of these hormones, which are expected following an invasive procedure. The clinical implications of this unexpected response warrant further investigations.	Small case series, studying the effect of a modified balloon angioplasty on neuroendocrine responses.
Awad AM, Marder E, Milo R et al. (2011) Multiple sclerosis and chronic cerebrospinal venous insufficiency: a critical review. Therapeutic Advances in Neurological Disorders 4: 231–5	Review	Currently, there is inconclusive evidence to support CCSVI as an aetiological factor in patients with multiple sclerosis. Endovascular procedures should not be done outside of controlled clinical trials.	Review with no meta-analysis. More recent studies are included in table 2.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Barbato L, Conti M, Grasso MA et al. (2017) Surgical repair of PTA-related internal jugular vein occlusion in multiple sclerosis: Report of four cases with chronic cerebrospinal venous insufficiency. Italian Journal of Vascular and Endovascular Surgery 24: 169–172	Case series n=4	Whichever the role of CCSVI in MS patients, percutaneous transluminal angioplasty does not appear to represent a viable solution while surgery is almost invariably feasible and safe and grants a more durable result in terms of vessels patency and symptomatic improvement.	Small case series, focusing on surgical repair after unsuccessful angioplasty.
Beelen R, Maene L, Castenmiller P et al. (2012) Evolution in quality of life and epidemiological impact after endovascular treatment of chronic cerebro-spinal venous insufficiency in patients with multiple sclerosis. Phlebology (27 Suppl 1) 187–9	Case series n=67 FU=12 months	Improvement in the physical health composite was statistically significant ($p<0.05$) in the 3- and 6-month groups. Improvement in the mental health composite was only statistically significant ($p<0.05$) in the 3-month group.	Case series with more patients or longer follow-up are included.
Beggs CB, Giaquinta A, Veroux M et al. (2018) Mid-term sustained relief from headaches after balloon angioplasty of the internal jugular veins in patients with multiple sclerosis. PLoS ONE [Electronic Resource] 13: e0191534	Case series n=286 FU=3.4 years	There was a large and sustained (>3 years) reduction in MIDAS score in both RR and SP MS patients. While a similar initial reduction in FSS score was also observed, this was not maintained in the SP and PP patients, although it remained statistically significant at follow-up (>3 years) in the RR MS patients. This suggests that venoplasty might be a useful intervention for treating patients with persistent headaches and selected concomitant obstructive disease of the internal jugular veins.	Case series with more patients or longer follow-up are included.
Burton JM, Alikhani K, Goyal M et al. (2011) Complications in MS patients after CCSVI procedures abroad (Calgary, AB). Canadian Journal of Neurological Sciences 38: 741–6	Case series n=5	Complications upon investigation and review included internal jugular vein stent thrombosis, cerebral sinovenous thrombosis, stent migration, cranial nerve injury and injury associated with venous catheterisation.	Study is included in the review by Varatharajan L (2012).
Dake MD, Dantzker N, Bennett WL et al. (2012) Endovascular correction of cerebrovenous anomalies in multiple sclerosis: a retrospective review of an	Case series n=40	The angiographic and hemodynamic improvement was associated with improvement in symptomatology, most particularly in cognitive and constitutional symptoms that may be related to cerebrovenous flow. Serious complications included death in	Small case series. The 2 serious complications are included in the review by Varatharajan L (2012).

uncontrolled case series. Vascular Medicine 17: 131–7		one subject and stent embolisation needing open heart surgery in another.	

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Denislic M, Milosevic Z, Zorc M et al. (2013) Disability caused by multiple sclerosis is associated with the number of extra cranial venous stenoses: possible improvement by venous angioplasty. Results of a prospective study. Phlebology 28: 353–60	Case series n=94 FU=12 months	The patient group with the higher disability score had a statistically significantly higher number of venous lesions ($p<0.005$). Statistically significant improvement of clinical disability in patients with RRMS was ($p<0.001$) achieved. In our study no stents were used. Restenosis occurred in 22% of patients.	Case series with more patients or longer follow-up are included.
Dolezal O, Horakova D, Gdovinova Z et al. (2012) Serious complication of percutaneous angioplasty with stent implantation in so called "chronic cerebrospinal venous insufficiency" in multiple sclerosis patient. Prague Medical Report 113: 289–93	Case report n=1	**Stent thrombosis** EDSS worsened after the procedure from 4.5 to 6. Three stents were implanted (2 of them in the right internal jugular vein). After 6 months, patient was referred for independent examination by CT phlebography for right-sided neck pain. Dislocation of stents on the right side and thrombosis of left sided stent was found.	Complication is already described in table 2.
Ferral H, Behrens G, Tumer Y et al. (2013) Endovascular diagnosis and management of chronic cerebrospinal venous insufficiency: Retrospective analysis of 30-day morbidity and mortality in 95 consecutive patients. American Journal of Roentgenology 200: 1358–64	Case series n=95 FU=30 days	Internal jugular vein thrombosis after percutaneous transluminal angioplasty was identified in 3/95 (3%) of the patients who had treatment. Bleeding at the puncture site not needing transfusion occurred in 4/95 patients (4%). There were no reported procedure-related deaths.	Case series with more patients or longer follow-up are included.
Ghezzi A, Annovazzi P, Amato MP et al. (2013) Adverse events after endovascular treatment of chronic cerebro-spinal venous insufficiency (CCSVI) in patients with multiple sclerosis. Multiple Sclerosis 19: 961–3	Case series n=462	Severe adverse events occurred in 15/462 patients at a variable interval after endovascular treatment: jugular thrombosis in 7 patients, tetraventricular hydrocephalus, stroke, paroxysmal atrial fibrillation, status epilepticus, aspiration pneumonia, hypertension with tachycardia, or bleeding of bedsore in the remaining 7 cases. One patient died because of myocardial infarction 10 weeks after endovascular treatment. The risk of severe adverse events related	Study is already included in table 2 (study 5).

		to endovascular treatment for CCSVI must be carefully considered.	

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Hampson CO, Soares GM, Jaffan AA (2012) Reported outcomes after the endovascular treatment of chronic cerebrospinal venous insufficiency. Techniques in Vascular & Interventional Radiology 15: 144–9	Review	Current literature suggests that endovascular treatment strategies for CCSVI in the setting of MS are safe. Available outcomes data are sparse and conflicting. It appears that, in general, patients with progressive forms of MS (as opposed to the relapsing−remitting form) experience fewer benefits after endovascular intervention. Placebo effect has not been excluded in currently available publications.	Review with no meta-analysis. More recent studies are included in table 2.
Hoffer EK (2012) Interventional radiology in the treatment of chronic cerebrospinal venous insufficiency. Journal of Radiology Nursing 31: 3–12	review	The primary criticism of percutaneous intervention for CCSVI is that practice has leapt ahead of science. Patients will hopefully recognise the need to prove the benefit of this new therapy and enrol in prospective randomised studies constructed with that aim.	Review with no meta-analysis. More recent studies are included in table 2.
Hubbard D, Ponec D, Gooding J et al. (2012) Clinical improvement after extracranial venoplasty in multiple sclerosis. Journal of Vascular & Interventional Radiology 23: 1302–8	Case series n=259 FU=6 months	There were statistically significant improvements in the MSIS-29 scores ($p<0.01$) at both 1 and 6 months. At 1 and 6 months, 68% and 54% were improved on the physical scale, respectively, and 53% and 44% were improved on the psychological scale, respectively. Patients with PPMS showed less improvement than did those with RRMS on the psychological scale at 1 month.	Case series with short term follow-up.
Imperial College, CCSVI Investigation Group: Thapar, A, Lane TR, Pandey V et al. (2011) Internal jugular thrombosis post venoplasty for chronic cerebrospinal venous insufficiency. Phlebology 26: 254–6	Case report n=1	**Jugular thrombosis** We report the case of a 33-year-old lady with multiple sclerosis who had left internal jugular venoplasty resulting in iatrogenic jugular thrombosis needing open thrombectomy for symptom relief. This occurred without insertion of a stent and while fully anticoagulated. Clinicians should be aware that endovenous treatment of CCSVI could cause paradoxical deterioration of cerebral venous drainage. Patients with complications post venoplasty are now presenting to	Complication is already described in table 2.

		geographically distant vascular units.	

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Jedynak W, Cieszanowski A (2014) Is there any relation between chronic cerebrospinal venous insufficiency and multiple sclerosis? - a critical review. Polish Journal of Radiology 79: 131–6	review	The main conclusion is that, taking into account results that are currently available, we should remain cautious and routine use of this treatment in patients should not be advisable.	Review with no meta-analysis. More recent studies are included in table 2.
Kazibudzki M, Latacz P, Ludyga T et al. (2016) Efficacy and safety of cutting balloons for the treatment of obstructive lesions in the internal jugular veins. Journal of Cardiovascular Surgery 57: 514–8	Case series n=65 FU=6 months	Failure rate=6% There were no serious adverse events.	Small case series, focusing on the use of cutting balloons.
Kipshidze N, Rukhadze I, Archvadze A et al. (2011) Endovascular treatment of patients with chronic cerebrospinal venous insufficiency and multiple sclerosis. Georgian Medical News 199: 29–34	Case series n=4	There were no complications and mean stenosis was reduced after angioplasty from 60% to 37%. There was positive remission in all patients.	Case series with more patients or longer follow-up are included.
Kostecki J, Zaniewski M, Ziaja K et al. (2011) An endovascular treatment of Chronic Cerebro-Spinal Venous Insufficiency in multiple sclerosis patients - 6 month follow-up results. Neuroendocrinology Letters 32: 557–62	Case series n=36 FU=6 months	The endovascular treatment did not affect the patient's neurological condition; however, there was an improvement in some quality-of-life parameters.	Case series with more patients or longer follow-up are included.
Kugler N, Patel PJ, Lee CJ (2015) Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis: A Failed Concept. Vascular Specialist International 31: 11–14	Review	There is now substantial evidence to say that CCSVI is a failed concept. Extracranial venous angioplasty should be abolished as a treatment in patients with MS.	A non-systematic review with no meta-analysis.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Ludyga T, Kazibudzki M, Simka M et al. (2010) Endovascular treatment for chronic cerebrospinal venous insufficiency: Is the procedure safe? Phlebology 25: 286–95	Case series n=331	There were no major complications (severe bleeding, venous thrombosis, stent migration or injury to the nerves) related to the procedure, except for thrombotic occlusion of the stent in 2 patients (1% of stenting procedures) and surgical opening of femoral vein to remove angioplastic balloon in 1 patient (<1% of procedures). Minor complications included occasional technical problems (2% of procedures): difficulty removing the angioplastic balloon or problems with proper placement of stent, and other medical events (2% of procedures): local bleeding from the groin, minor gastrointestinal bleeding or cardiac arrhythmia.	Study is included in the review by Varatharajan L (2012).
Malagoni AM, Galeotti R, Menegatti E et al. (2010) Is chronic fatigue the symptom of venous insufficiency associated with multiple sclerosis? A longitudinal pilot study. International Angiology 29: 176–82	Case series n=31 FU=12 months	The reestablishment of cerebral venous return reduced chronic fatigue perception.	Case series with more patients or longer follow-up are included.
Mandato KD, Hegener PF, Siskin GP et al. (2012) Safety of endovascular treatment of chronic cerebrospinal venous insufficiency: a report of 240 patients with multiple sclerosis. Journal of Vascular & Interventional Radiology 23: 55–9	Case series n=240 FU=30 days	Headache after the procedure was reported in 8% (21/257) of patients; headache persisted >30 days in 1 patient. Neck pain was reported in 16% (40/257); 53% (21/40) of these patients had stent placement. Three patients experienced venous thrombosis needing retreatment within 30 days. Sustained intraprocedural arrhythmias were observed in 3 patients, and 2 needed hospital admission. One of these patients, who was having retreatment for stent thrombosis, was hospitalised because of a stress-induced cardiomyopathy.	Study is included in the review by Varatharajan L (2012).

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Napolitano M, Bruno A, Mastrangelo D et al. (2014) Endovascular treatment of chronic cerebro spinal venous insufficiency in patients with multiple sclerosis modifies circulating markers of endothelial dysfunction and coagulation activation: a prospective study. Blood Coagulation & Fibrinolysis 25: 716–20	Case series n=110 FU=18 months	55% of patients had favourable outcome within 1 month after treatment, 25% regressed in the following 3 months, 25% did not experience any benefit. Acute recurrence was observed in <1% of patients and it was treated with high-dose immunosuppressive therapy. No major complications were observed.	Case series with more patients or longer follow-up are included.
Petrov I, Grozdinski L, Kaninski G et al. (2011) Safety profile of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. Journal of Endovascular Therapy 18: 314–23	Case series n=461	There were no deaths, major bleeding events, or clinical deterioration of MS. Access site complications included limited groin hematoma (5, 1%); there were no arteriovenous fistulas or puncture site infections. Systemic complications included rare cardiac arrhythmias (6, 1%). Procedure-related complications included vein rupture (2, <1%), vein dissection (15, 3%), acute in-stent/in-segment thrombosis (8, 2%), and acute recoil (1, <1%); there was no stent migration or fracture or distal embolisation.	Study is included in the review by Varatharajan L (2012).
Petrov I, Grozdinski L, Martinov I et al. (2012) Endovascular diagnostics and therapy of chronic cerebrospinal venous insufficiency. Gazzetta Medica Italiana Archivio per le Scienze Mediche 171: 755–65	Case series n=123 FU=3 months	Early clinical improvements were registered in 87% of patients. Clinical improvement was established in 63% of patients at 3 month follow-up. The mean EDSS score improved from 5.3 to 4.7.	Case series with more patients or longer follow-up are included.
Pryse-Phillips W, Stefanelli M, Murphy-Peddle K et al. (2013) An observational study of venoplasty in patients with multiple sclerosis. Canadian Journal of Neurological Sciences 40: 203–9	Case series n=30 FU=12 months	No objective improvement was found at 1 year, although many patients reported a degree of subjective benefit.	Case series with more patients or longer follow-up are included.
Radak D, Kolar J, Sagic D et al. (2014) Percutaneous angioplasty of internal jugular and azygous veins in patients with chronic cerebrospinal venous insufficiency and multiple sclerosis: early and mid-term	Case series n=72 FU=11 months	There were no postoperative complications. Restenosis appeared in 5% of patients. EDSS score was statistically significantly improved ($p<0.01$) and about half of patients reported statistically significant or mild improvement in	Case series with more patients or longer follow-up are included.

results. Phlebology 29: 367–75		disease status and none of them worsening of symptoms.	

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Radak Dj, Tanaskovic S, Antonic Z et al. (2014) Compressive syndrome of internal jugular veins in multiple sclerosis: does it matter? Phlebology 29: 98–104	Case report n=1	Percutaneous transluminal angioplasty of the internal jugular vein confluence resulted in haemodynamic improvement despite the presence of IJV external compression.	Case report.
Salvi F, Bartolomei I, Buccellato E et al. (2012) Venous angioplasty in multiple sclerosis: neurological outcome at two years in a cohort of relapsing-remitting patients. Functional Neurology 27: 55–9	Case series n=29 FU=2 years	Endovascular treatment of concurrent CCSVI seems to be safe and repeatable and may reduce annual relapse rates and cumulative disability in patients with RRMS. Randomised controlled studies are needed to further assess the clinical effects of endovascular treatment of CCSVI in MS.	Case series with more patients or longer follow-up are included.
Samson K (2010) Experimental multiple sclerosis vascular shunting procedure halted at Stanford. Annals of Neurology 67: A13-A15	Case reports n=2	1. Fatal haemorrhage to brain stem while on Coumadin after the procedure. 2. jugular vein stent dislodged into the right ventricle, needing emergency open heart surgery to remove the device.	Report is included in the review by Varatharajan L (2012).
Scalise F, Novelli E, Farina M et al. (2015) Venous Hemodynamic Insufficiency Severity Score variation after endovascular treatment of chronic cerebrospinal venous insufficiency. Phlebology 30: 250–6	Case series n=45 FU=3 months	CCSVI endovascular treatment can induce an improvement in venous haemodynamic parameters and the Venous Hemodynamic Insufficiency Severity Score (VHISS). The neurological disability score (EDSS) also improved after percutaneous venous angioplasty (PVA); however, there was no correlation to the VHISS variation after PVA, MS type and duration.	Case series with more patients or longer follow-up are included.
Sternberg Z, Grewal P, Cen S et al. (2015) Blood pressure normalization post-jugular venous balloon angioplasty. Phlebology 30: 280–7	Case series n=195 FU=24 hours	Balloon angioplasty reduced the average systolic and diastolic blood pressure. Further studies should investigate the association between blood pressure deviation and internal jugular veins narrowing, and whether blood pressure normalisation affects clinical outcomes.	Case series with more patients or longer follow-up are included.
Thibault P, Lewis W, Niblett S (2015) Objective duplex ultrasound evaluation of the extracranial circulation in multiple sclerosis patients undergoing venoplasty of internal jugular vein	Case series n=8	A statistically significant improvement in global arterial cerebral blood flow was evident following venoplasty ($p<0.05$).	Case series with more patients or longer follow-up are included.

stenoses: a pilot study. Phlebology 30: 98–104			

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Tsivgoulis G, Faissner S, Voumvourakis K et al. (2015) "Liberation treatment" for chronic cerebrospinal venous insufficiency in multiple sclerosis: the truth will set you free. Brain and Behavior 5: 3–12	Review	CCSVI appears to be a poorly reproducible and clinically irrelevant sonographic construct. "Liberation treatment" has no proven efficacy, may exacerbate underlying disease activity and has been complicated with SAEs. "Liberation treatment" should stop being offered to MS patients even in the settings of RCTs.	Review with no meta-analysis. A systematic review of complications is included in table 2.
van Zuuren EJ, Fedorowicz Z, Pucci E et al. (2012) Percutaneous transluminal angioplasty for treatment of chronic cerebrospinal venous insufficiency (CCSVI) in multiple sclerosis patients. Cochrane Database of Systematic Reviews 12: CD009903	Cochrane Review	There is currently no high level evidence to support or refute the efficacy or safety of percutaneous transluminal angioplasty for treatment of CCSVI in people with MS.	No randomised controlled trials were identified for the review.
Veroux P, Giaquinta A, Perricone D et al. (2013) Internal jugular veins out flow in patients with multiple sclerosis:a catheter venography study. Journal of Vascular & Interventional Radiology 24: 1790–7	Case series n=313	Balloon angioplasty was immediately able to improve flow in at least 1 internal jugular vein (IJV) in 69% of patients, but venous flow was normalised in both veins in only 37% of patients; severe delayed flow persisted after angioplasty in 32% of patients.	Case series with more patients or longer follow-up are included.
Zagaglia S, Balestrini S, Perticaroli E et al. (2013) Percutaneous transluminal angioplasty for chronic cerebrospinal venous insufficiency in multiple sclerosis: dichotomy between subjective and objective outcome scores. Neurological Sciences 34: 2205–10	Case series n=44 FU=12 months	There was no change in the annualised relapse rate (p=0.829), worsening of disability status (p=0.002) and new lesions at MRI in 30% of patients were found, in contrast to an improvement both in physical and mental domains of MSQoL-54 (p=0.003). Multiple logistic regression showed EDSS score before PTA to be predictor of an increase of >10 points in MSQoL-54 mental domain (OR 0.52, 95% CI, 0.31 to 0.89, p=0.018).	Case series with more patients or longer follow-up are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Zamboni P, Galeotti R, Menegatti E et al. (2009) A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. Journal of Vascular Surgery 50: 1348–58	Case series n=65 FU=18 months	Percutaneous transluminal angioplasty of venous strictures in patients with CCSVI is safe, and especially in patients with RRMS, the clinical course positively influenced clinical and quality-of-life parameters. Restenosis rates are elevated in the internal jugular veins but very promising in the azygos veins, suggesting the need to improve endovascular techniques in the former. The results of this pilot study warrant a subsequent randomised controlled trial.	Case series with more patients or longer follow-up are included.
Zecca C, Gobbi C (2011) Chronic cerebrospinal venous insufficiency (CCSVI) and multiple sclerosis (MS): a critical review. CNS & Neurological Disorders Drug Targets 10: 757–61	review	The available data are insufficient to establish conclusively a clear relationship between MS and CCSVI and do not support the role of CCSVI as the primary cause of MS. Until credible scientific evidence replicates the original results, any proposed invasive treatments of CCSVI should be discouraged.	Review with no meta-analysis. More recent studies are included in table 2.
Zivadinov R, Magnano C, Galeotti R et al. (2013) Changes of cine cerebrospinal fluid dynamics in patients with multiple sclerosis treated with percutaneous transluminal angioplasty: a case-control study. Journal of Vascular & Interventional Radiology 24: 829–38	Case-control study n=15 FU=12 months	Percutaneous transluminal angioplasty in patients with MS with CCSVI increased cerebrospinal flow and decreased cerebrospinal fluid velocity, which are indicative of improved venous parenchyma drainage.	Other outcomes from the same study are already included in table 2 (study 3).