



**HealthPACT**  
Health Policy Advisory Committee  
on Technology  
Australia and New Zealand

## **Technology Brief**

# **Percutaneous venoplasty for the treatment of chronic cerebrospinal venous insufficiency (CCSVI) in multiple sclerosis**

**November 2011**



Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
Surgical

© State of Queensland (Queensland Health) 2011



This work is licensed under a Creative Commons Attribution Non-Commercial No Derivatives 2.5 Australia licence. In essence, you are free to copy and communicate the work in its current form for non-commercial purposes, as long as you attribute the authors and abide by the licence terms. You may not alter or adapt the work in any way.

To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/2.5/au/>.

For further information, contact the HealthPACT Secretariat at:

HealthPACT Secretariat

c/o Access Improvement Service, Centre for Healthcare Improvement,

Queensland Health

Floor 3, Forestry House

160 Mary Street, Brisbane QLD, AUSTRALIA 4000

Email: [HealthPACT@health.qld.gov.au](mailto:HealthPACT@health.qld.gov.au) Telephone: (07) 3234 0624.

For permissions beyond the scope of this licence contact: Intellectual Property Officer, Queensland Health, GPO Box 48, Brisbane Qld 4001, email [ip\\_officer@health.qld.gov.au](mailto:ip_officer@health.qld.gov.au), phone (07) 3234 1479.

**DISCLAIMER:** This brief is published with the intention of providing information of interest. It is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements to health technologies. This brief is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

The State of Queensland acting through Queensland Health (“Queensland Health”) does not guarantee the accuracy, currency or completeness of the information in this report. Information may contain or summarise the views of others, and not necessarily reflect the views of Queensland Health.

This brief is not intended to be used as medical advice and it is not intended to be used to diagnose, treat, cure or prevent any disease, nor should it be used for therapeutic purposes or as a substitute for a health professional's advice. It must not be relied upon without verification from authoritative sources. Queensland Health does not accept any liability, including for any injury, loss or damage, incurred by use of or reliance on the information.

This brief was commissioned by Queensland Health, in its role as the Secretariat of the Health Policy Advisory Committee on Technology (HealthPACT). The production of this brief was overseen by HealthPACT. HealthPACT comprises representatives from health departments in all States and Territories, the Australian and New Zealand governments and MSAC. It is a sub-committee of the Australian Health Ministers’ Advisory Council (AHMAC), reporting to AHMAC’s Clinical, Technical and Ethical Principal Committee (CTEPC). AHMAC supports HealthPACT through funding.

This brief was prepared by Dr Prema Thavaneswaran from ASERNIP-S.

# TECHNOLOGY BRIEF

**REGISTER ID**

**WP057**

**NAME OF TECHNOLOGY**

**PERCUTANEOUS VENOPLASTY**

**PURPOSE AND TARGET GROUP**

**TO RELIEVE THE SYMPTOMS OF MULTIPLE SCLEROSIS BY IMPROVING CEREBROSPINAL VENOUS DRAINAGE**

## STAGE OF DEVELOPMENT (IN AUSTRALIA)

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established  |
| <input type="checkbox"/> Experimental             | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational          | <input type="checkbox"/> Should be taken out of use   |
| <input type="checkbox"/> Nearly established       |   |

## AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes  
 No  
 Not applicable

## INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials underway or completed	Limited use	Widely diffused
Bulgaria	✓		
Italy	✓		
Poland	✓		
Portugal	✓		
United Kingdom	✓		
United States	✓		

## IMPACT SUMMARY

Recent research has suggested that venous obstruction or abnormal venous outflow from the central nervous system, which has been termed chronic cerebrospinal venous insufficiency (CCSVI), may play a role in the pathogenesis of multiple sclerosis (MS). As a result, there has been increasing interest in the role that endovascular therapies, including angioplasty and stent implantation, may play in the relief of MS symptoms.

Specifically, it has been suggested that percutaneous venoplasty may reduce the symptoms of MS by opening blocked veins in the neck and/or trunk and thus improving blood flow to the brain.

## **BACKGROUND**

Multiple sclerosis (MS) is a chronic, progressive disease of the central nervous system (CNS). Approximately 75% of MS cases are female, and the average age of symptom onset and diagnosis is 30 years. Most patients with MS (80%) begin with relapsing-remitting MS (RRMS), a disease course characterised by periods of good health followed by the sudden onset of symptoms or relapses (Lublin and Reingold 1996). This is often followed by disability progression outside of relapses, which is defined as secondary progressive MS (SPMS). A small proportion of patients (10-15%) begin with primary progressive MS (PPMS), with disease progression and continuous worsening of symptoms from the onset (Lublin and Reingold 1996).

The symptoms of MS and the severity of these symptoms are completely unpredictable and vary enormously. Symptoms include extreme fatigue (particularly during hot weather), loss of balance and co-ordination, impaired vision, limb weakness, tremors, stiffness, slurred speech, problems with memory and concentration, loss of bladder and bowel control, and in severe cases partial or complete paralysis. People suffering from MS may experience one, several, or all of these symptoms, collectively or in isolation. Within 10 years of diagnosis, more than 50% of people start to experience significant and worsening mobility problems, and within 20 years of diagnosis, 80% of people require mobility assistance.

The pathophysiology of MS, although not fully understood, includes early inflammatory cell infiltration of the CNS affecting primarily the white matter (Duddy et al 2011). Axonal damage, resulting in permanent clinical disability, begins from the earliest stages of the disease. Parameters including magnetic resonance imaging (MRI) data and the number of attacks in the first two years partly predict long-term outcome in MS patients, and form the basis of the modified McDonald criteria, which is used to make a definitive diagnosis of MS (Duddy et al 2011).

Recent research has suggested that venous obstruction or abnormal venous outflow from the CNS, which has been termed chronic cerebrospinal venous insufficiency (CCSVI), may play a role in the pathogenesis of MS. Further support for this hypothesis has come from a recent meta-analysis by Laupacis et al (2011), in which the data from eight studies of CCSVI and MS was combined and analysed. The findings from this study showed a statistically significant association between CCSVI and MS. Zamboni et al (2009) have developed criteria for the diagnosis of CCSVI using transcranial and extracranial colour

Doppler ultrasound. The diagnosis requires that two or more of the following five criteria are met:

- reflux in the internal jugular (IJV) or vertebral veins, or both, with the head in any position
- reflux in the deep cerebral veins
- high-resolution B-mode evidence of IJV stenosis
- absence of Doppler-detectable flow in the IJVs and/or vertebral veins
- loss of postural control of the main cerebral venous outflow pathways.

Percutaneous catheter angiography is used to identify venous stenosis that may be the cause of CCSVI in patients who meet these criteria. On angiography, lesions that cause a >50% luminal reduction are regarded as significant.

As a result of these reports, which suggest a treatable cause of MS, there has been increasing interest in the role that endovascular therapies, including angioplasty and stent implantation, may play in the relief of MS symptoms. Specifically, it has been suggested that percutaneous venoplasty may reduce the symptoms of MS by opening blocked veins in the neck and/or trunk and thus improving blood flow to the brain.

The procedure involves a percutaneous needle puncture of the femoral vein, which is performed under local anaesthesia. A vascular sheath is then inserted using a standard needle, guidewire and catheter technique, and the guidewire is then advanced into the superior vena cava under fluoroscopic control. Angiographic images of the internal jugular and azygous veins are then taken, and used to identify any abnormal luminal narrowing and collateral circuits, which are characteristic of CCSVI. Segments that are abnormally narrowed are dilated using a standard angioplasty balloon, the diameter of which is comparable with that of the adjacent normal venous segment. The balloon is then inserted across the stenosis and inflated. In cases where the result of balloon angioplasty is inadequate, a metal stent may be placed to hold open the stricture. Further venography or ultrasound, or both, are used to assess the outcome of the intervention. Once dilation of the vessel is confirmed, the guidewire and sheath are removed and manual compression is applied to the puncture site.

### **CLINICAL NEED AND BURDEN OF DISEASE**

Currently in Australia, MS is thought to directly affect over 18,000 people, and indirectly affect hundreds of thousands of family members, friends and colleagues of those suffering from the disease (MS Australia 2011). Around 1000 people are newly diagnosed with MS each year. Australia has a higher incidence rate of MS compared with many other countries, particularly in the cooler climates of South Eastern Australia.

At present, 79% of people living with MS in Australia rate their level of disability as being mild to moderate (MS Australia 2011). It is currently unclear what proportions of MS patients in Australia meet the diagnostic criteria for CCSVI.

MS is a chronic and highly disabling condition that represents a significant burden for Australian society, both financially and socially. This disease has an early onset, and can affect adults from the age of 20 years, impacting on their ability to establish careers, relationships and families. As MS progresses, patients suffer increasing disability, and are often forced to work fewer hours, take more sedentary and possibly lower paid jobs, or even stop working (Taylor et al 2007). Patients are faced with a decrease in their income and productivity, and an increase in the cost of their healthcare. In addition, families of MS sufferers are often burdened with their care. In 2005, the burden of disease of MS in Australia was estimated to be 8,968 DALYs lost (Access Economics, 2005), which was greater than DALYs lost due to chronic back pain, machinery accidents and rheumatic heart disease (AIHW 2001).

## **DIFFUSION**

Currently in Australia, percutaneous venoplasty is not being used routinely for the relief of symptoms in MS patients with CCSVI. It is still unclear what proportion of the MS patient population meets the diagnostic criteria for CCSVI, and would therefore benefit from this procedure. The Multiple Sclerosis Network of Care, a patient advocacy organisation for people affected by MS, has suggested there is strong evidence that testing for possible CCSVI irregularities should be mandatory during the diagnostic stages of MS (Multiple Sclerosis Network of Care, 2011). They have suggested that the Australian government could tie its immunotherapy subsidies for MS to requirements that:

- information be provided to individual patients about possible vascular irregularities in MS, and
- vascular (including CCSVI) screening be undertaken.

Authorising general practitioners to refer patients for Doppler ultrasound CCSVI screening may be a key step in achieving this (Multiple Sclerosis Network of Care, 2011).

Much of our understanding of the role of CCSVI in MS has come from studies conducted in Europe, particularly Italy, where 20 CCSVI/MS clinical trial centres have been established in the last few years. Similarly, in Canada the National Government has announced that it will provide funding, through the Public Health Agency of Canada, to support the development of a national monitoring system, which will capture information

to help identify disease patterns and track CCSVI treatments and long-term outcomes for people living with MS (Multiple Sclerosis Network of Care, 2011).

In 2010, the Society of Interventional Radiology (SIR) in the US published a position statement on interventional endovascular management of CCSVI in patients with MS, which was also endorsed by the Canadian Interventional Radiology Association (Vedantham et al 2010). In this document, the SIR acknowledged the need for more effective treatments for MS patients and the public's interest in rapidly making such therapies available to this patient group, but stated that patients with MS constitute a particularly vulnerable population, whose safety must be protected as new therapeutic approaches are evaluated. In addition, the SIR considers the current published evidence to be inconclusive on whether CCSVI is a clinically important factor in the development and/or progression of MS, and on whether balloon angioplasty and/or stent placement are clinically effective in patients with MS. The SIR stated strong support for the urgent performance of high-quality clinical research to determine the safety and efficacy of interventional MS therapies.

## **COMPARATORS**

Current treatments for MS include supportive care, symptomatic management, and disease-modifying agents which impact on lesions and reduce relapses, and may delay disability progression. Importantly, drugs that are thought to have an effect on MS progression are significantly more costly than drugs used only to prompt recovery from relapse (Taylor et al 2007). In addition, effective pharmacological treatments for fatigue and refractory neuropathic pain associated with MS are also available.

## **SAFETY AND EFFECTIVENESS ISSUES**

Three case series studies which assessed the safety and efficacy of percutaneous venoplasty for the relief of symptoms in MS patients with CCSVI were eligible for inclusion in this technology brief. Two studies evaluated the safety of the procedure (Petrov et al 2011, Zamboni et al 2009), and two studies evaluated the procedure's efficacy (Malagoni et al 2010, Zamboni et al 2009).

### *Study profile*

The aim of the study by Petrov et al (2011) was to evaluate the safety of endovascular treatment for CCSVI in patients with MS. MS patients who attended the institution from January 2010 were screened with Doppler ultrasound, and those patients who met at least two of the five sonographic criteria of abnormal venous outflow as defined by Zamboni et al (2009), were diagnosed as CCSVI-positive. By the end of 2010, 472 MS patients had been screened, and a total of 461 (97.7%) patients (261 women; mean age 45.4 years,

range 21-79) were diagnosed as CCSVI-positive. Diagnostic venography documented venous flow obstruction in 100% of the CCSVI-positive patients. Of these patients, 117 (25.4%) had PPMS, 169 (36.7%) had RRMS and 175 (37.9%) had SPMS. The baseline Expanded Disability Status Scale (EDSS) score was 5.2 (range 0-9.5), the mean duration of MS from diagnosis was 124.3 months, and 60.6% of patients were receiving medicinal treatment for MS.

All 461 patients agreed to endovascular treatment for CCSVI. The protocol for endovascular treatment included balloon angioplasty in the IJVs and the azygous vein, in order to improve blood flow. Where there was more than one lesion in the same vessel, the interventional strategy was selected based on the operator's judgement; however, in most cases, all identified lesions were treated. Stent implantation was used to treat dilation-resistant lesions, recoil leading to persistent residual venous outflow obstruction, significant and resistant twisting of the vein, and iatrogenic dissection significantly compromising blood flow.

In order to evaluate safety, the following categories of complications were developed:

- *Major adverse events*, which included death, major bleeding requiring transfusion and/or major surgical intervention, and clinical deterioration of MS during hospital stay as determined by patient complaint and neurological examination.
- *Access-site complications*, which included groin haematoma, arteriovenous (AV) fistula formation, and puncture site infection.
- *Procedure-related complications not associated with angioplasty*, which included dysrhythmias and vascular injury during diagnostic manoeuvres.
- *Angioplasty complications*, which included acute (within 24 hours of the procedure) target vessel failure due to vein wall rupture or dissection, acute in-stent or in-segment thrombosis or recoil (verified by Doppler ultrasound), stent migration or fracture, and distal embolisation.

The study by Malagoni et al (2010), aimed to assess the effect on chronic fatigue (CF) of the balloon dilatation of stenosing lesions affecting the main extracranial veins of MS patients with CCSVI. Patients were included in the study if they had clinically defined MS, according to the revised McDonald criteria, as well as CF. Other inclusion criteria included age between 18 and 65 years, a diagnosis of CCSVI pointed out by  $\geq 2$  transcranial and extracranial Echo-Color Doppler-high resolution (TCCS-ECD) criteria, the presence of fatigue symptoms for  $>6$  months, a mean score of the Fatigue Severity Scale (FSS)  $>4$ , and normal renal function. Patients were excluded from the study due to relapse or disease progression in the previous three months, the presence of depression or other major diseases, and the intake of medications affecting fatigue in the past three months (for example corticosteroids, antidepressants, amantadine, or modafinil). Patients were allowed to remain on their disease-modifying therapies for MS throughout the study.

All patients were screened by means of a TCCS-ECD examination, and those patients who met at least two of the five criteria of abnormal venous outflow as defined by Zamboni et al (2009), were diagnosed as CCSVI-positive. This diagnosis was then confirmed by selective phlebography of the lumbar veins, left renal vein, azygous vein and IJVs. This procedure also enabled treatment of the identified venous obstructive lesion by percutaneous transluminal angioplasty (PTA).

Fatigue was assessed in all patients at baseline (the day before the endovascular procedure), and at 1, 6, and 12 months follow-up. All assessments of fatigue were undertaken by a trained interviewer who was not involved in the neurological or surgical assessment, and was blinded to the vascular outcome of the patient. Fatigue was assessed using the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS). The FSS is a questionnaire consisting of nine questions focused on physical symptoms, with an average score ranging from one to seven, and lower scores indicating less fatigue. The MFIS is a questionnaire consisting of 21 items divided into three 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 ranging from 0 to 84, and lower scores indicating less fatigue. Mobility was assessed in all ambulatory patients at baseline and one-month follow-up. Patients were asked to walk up and down a 22 meter corridor at their own pace for six minutes, and the distance covered during this time (6MWD) was recorded.

Thirty-five consecutive patients were initially recruited into the study; however, four of these patients were eventually excluded due to FSS scores <4. Thirty-one patients (16 males, age  $46.2 \pm 9.4$  years) were finally enrolled in the study. The mean EDSS score at baseline was  $3.8 \pm 2.2$ , and the mean duration of MS from diagnosis was  $10.8 \pm 7.1$  years. Thirteen (42%) patients had RRMS, 8 (26%) had PPMS, and 10 (32%) had SPMS.

The purpose of the case series by Zamboni et al (2009) was to assess the safety, feasibility and vascular and clinical outcomes of PTA, in MS patients with CCSVI. Patients were included in the study if they had clinically defined MS, according to the revised McDonald criteria. Other inclusion criteria included age between 18 and 65 years, an EDSS score between 0 and 6.5, therapy with current FDA approved disease-modifying treatments, at least two of the five sonographic criteria of abnormal venous outflow as defined by Zamboni et al (2009), and normal renal function. Patients were excluded from the study due to relapse or disease progression, and steroid treatment in the previous 30 days, pre-existing medical conditions known to be associated with brain pathology, including neurodegenerative disorders, cerebrovascular disease, and a history of alcohol abuse, abnormal renal function, and refusal to undergo the endovascular treatment.

All patients were screened by means of an Echo-Color Doppler (ECD) examination, and those patients who met at least two of the five criteria of abnormal venous outflow as defined by Zamboni et al (2009), were diagnosed as CCSVI-positive. This diagnosis was then confirmed by selective venography of the lumbar veins, left renal vein, azygous vein and IJVs. This procedure also enabled treatment of the identified venous obstructive lesion by PTA, which was performed exclusively at the levels of the azygous vein and IJVs when significant stenoses (>50% reduction in venous lumen) were identified.

A number of vascular outcome measures were assessed, including preoperative and postoperative venous pressure (measured in the azygous vein and IJVs), patency rate (measured at 1, 3, 6, 12, 15 and 18 months follow-up), and the postoperative course and rate of complications, including patients' tolerance of the procedure as indicated by visual analog scale (VAS) pain scores. Neurologic outcomes were assessed by a nonblinded team of neurologists. Outcomes included disease severity, assessed using the Multiple Sclerosis Functional Composite (MSFC), which measures leg function and ambulation (timed 25-foot walk), arm and hand function (9-hole peg test) and cognitive function (paced auditory serial addition test), and is expressed as unique Z score where an increase or decrease represents an improvement or deterioration in neurological function, respectively. Other neurological outcomes assessed were the rate of relapse in RRMS patients, and quality of life, assessed using the Multiple Sclerosis Quality of Life (MS-QOL) instrument, a 54-item questionnaire that addresses physical and mental status in MS patients, where low scores indicate lower quality of life.

Sixty-five consecutive patients (30 males, age  $41.7 \pm 12.2$  years) were enrolled in the study. The mean EDSS score at baseline was  $3.0 \pm 2.3$ , and the mean duration of MS from diagnosis was  $8.6 \pm 7.1$  years. Thirty-five (53.8%) patients had RRMS, 10 (15.4%) had PPMS, and 20 (30.8%) had SPMS.

### *Safety*

Petrov et al (2011) reported that 461 patients underwent 495 endovascular procedures, of which 34 (6.9%) procedures were reinterventions for restenosis (n=11), in-stent/in-segment subacute and chronic thrombosis (n=20), and an inadequate initial procedure (n=3). A total of 1012 veins (mean 2.2 lesions per intervention) were treated for angiographic obstruction >50% in the right IJV (379, 37.4%), left IJV (394, 38.9%) and azygous vein (239, 23.6%). Balloon angioplasty was the technique used in the majority of patients; however, in 66 (14.3%) patients, nitinol self-expanding stents were implanted for recoil or recalcitrant lesions. In addition, 11 stents were implanted in 10 (2.2%) patients during reinterventions for restenosis or thrombosis.

Table 1 presents an overview of the complications following endovascular treatment for CCSVI.

**Table 1: Complications following endovascular procedures for CCSVI (Petrov et al 2011)**

Adverse event category	n (%)
<b>Major adverse events</b>	
Death	0 (0%)
Major bleeding	0 (0%)
Clinical deterioration of MS	0 (0%)
<b>Access-site complications</b>	
Groin haematoma	5 (1.0%)
AV fistula formation	0 (0%)
Puncture site infection	0 (0%)
<b>Procedure-related complications</b>	
Cardiac arrhythmias	6 (1.2%)
Vascular injury during diagnostic manoeuvre	0 (0%)
<b>Interventional complications</b>	
Vein rupture	2 (0.4%)
Vein dissection	15 (3.0%)
Acute in-stent/in-segment thrombosis	8 (1.6%)
Acute recoil	1 (0.2%)
Stent migration and/or fracture	0 (0%)
<b>Total</b>	<b>37 (7.5%)</b>

AV: Arteriovenous; MS: Multiple Sclerosis

No deaths, major bleeding events or clinical deterioration of MS were observed. Groin haematomas were the only access-site complications reported, and all resolved spontaneously without any additional measures. Of the six reported cardiac arrhythmias, there were four cases of atrial fibrillation, which were all reversed to sinus rhythm. There was one reported ventricular fibrillation in a patient with previously undiagnosed significant left main coronary artery disease (CAD), who was successfully stented during the same hospitalisation. Ventricular tachycardia associated with ST elevation was reported in another patient, who exhibited no evidence of CAD. With regard to angioplasty-related complications, both of the azygous vein ruptures were successfully resolved by prolonged balloon inflation and stenting. None of the reported vein wall dissections progressed or led to a clinically significant disorder, and in three of the 15 cases, a self-expandable nitinol stent was inserted. All of the reported cases of acute thrombosis occurred within 24 hours of the procedure, and all thrombotic lesions were recanalised by selective fibrinolysis, mechanical thromboaspiration, and additional

balloon angioplasty. The single case of vessel recoil was identified following balloon angioplasty, and the lesion was retreated. There were no reported cases of stent migration or fracture, or pulmonary embolism.

The case series by Zamboni et al (2009) reported that the procedure was well tolerated, with a mean VAS pain score of  $3.4 \pm 0.3$ . There were no reported cases of complications such as vessel rupture, thrombosis, or side effects to the contrast media, during or after the procedure; however, minor haemorrhages with hematomas at the vascular access sites did occur, albeit infrequently. A total of six (9.3%) patients reported a postoperative headache that was transitory and resolved spontaneously.

### *Effectiveness*

Table 2 presents the outcome of fatigue assessment in patients at baseline, and up to one year follow-up, as reported by Malagoni et al (2010). FSS and MFIS scores significantly improved from preoperative values, and this positive trend was maintained at one year follow-up ( $P < 0.001$  for both).

At one-month follow-up, the 6MWD had improved significantly compared with baseline ( $332 \pm 190\text{m}$  to  $378 \pm 200\text{m}$ ,  $P = 0.0002$ ). In addition, an inverted correlation between 6MWD and MFIS-physical subscale was found in the subgroup of eight patients with no lower limb motor impairment ( $r = -0.74$ ,  $P = 0.035$ ).

**Table 2: FSS and MFIS scores in the study population (n=31) at baseline and 1, 6, and 12 months follow-up (Malagoni et al 2010)**

	Baseline	1 month	6 months	12 months	P Value <sup>b</sup>
FSS	$5.1 \pm 1.0$	$3.2 \pm 1.5^a$	$3.2 \pm 1.8^a$	$3.5 \pm 1.8^a$	<0.001
MFIS (Total)	$34.9 \pm 14.8$	$15.9 \pm 13.4^a$	$20.3 \pm 14.9^a$	$22.5 \pm 13.7^a$	<0.001
MFIS (Physical subscale)	$21.2 \pm 8.0$	$10.5 \pm 7.8^a$	$13.3 \pm 9.7^a$	$13.5 \pm 9.7^a$	<0.001
MFIS (Cognitive subscale)	$9.2 \pm 9.5$	$3.7 \pm 6.4^a$	$5.1 \pm 6.4$	$6.0 \pm 6.3$	0.03
MFIS (Psychological subscale)	$4.5 \pm 2.1$	$1.8 \pm 1.9^a$	$1.9 \pm 2.1^a$	$2.5 \pm 2.1^a$	<0.001

Data are expressed as mean  $\pm$  SD; FSS: Fatigue severity scale; MFIS: Modified fatigue impact scale.

<sup>a</sup>A significant decrease in the perception of fatigue compared with baseline.

<sup>b</sup>12 months compared with baseline.

Zamboni et al (2009) reported that the rate of relapse-free patients ( $P<0.0014$ ) and patients with MRI Gad+ lesions ( $P<0.0001$ ), as well as measures of quality of life ( $P=0.0097$  and  $P=0.003$ ) and neurological function ( $P=0.008$ ), were all significantly improved up to 18 months after endovascular treatment in RRMS patients (Table 3). Similarly, PPMS patients demonstrated significant improvements in physical ( $P<0.03$ ) and mental ( $P<0.01$ ) quality of life measures 18 months after endovascular treatment; however, no improvements were observed in neurological function (Table 4). In SPMS patients, no improvements in quality of life or neurological function were observed at 18 months follow-up (Table 4) (Zamboni et al 2009).

**Table 3: Preprocedural and postprocedural changes in clinical outcome, MRI, QOL and disability scale in RRMS patients (n=35) (Zamboni et al 2009)**

Variable	Pre-PTA	18-month FU	P Value
Annualised relapse rate	0.9 ± 0.8	0.7 ± 1.0	0.11
Patients free of relapse, %	27	50	<0.0014
Patients with MRI Gad+ lesions, % <sup>a</sup>	50	12	<0.0001
MSQOL Physical health component, mean ± SD <sup>b</sup>	66 ± 18	84 ± 16	0.0097
MSQOL Mental health component, mean ± SD <sup>c</sup>	61 ± 22	82 ± 13	0.003
MSFC, mean ± SD <sup>d</sup>	5.5e <sup>-18</sup> ± 0.7	0.65 ± 0.5	0.008

5.5e<sup>-18</sup>: Infinitesimal negative baseline value of the MSFC; FU: Follow-up; PTA: Percutaneous transluminal angioplasty; RRMS: Relapse remitting multiple sclerosis.

<sup>a</sup>Magnetic resonance imaging-active gadolinium-enhanced lesions.

<sup>b</sup>Score of physical health component of the Multiple Sclerosis Quality of Life 54-item Instrument.

<sup>c</sup>Score of mental health component of the Multiple Sclerosis Quality of Life 54-item Instrument.

<sup>d</sup>Multiple Sclerosis Functional Composite, a disability scale expressed by the *Zeta* score, which integrates evaluation of the motility of the upper and lower extremities with cognitive function.

**Table 4: Preprocedural and postprocedural changes in QOL and disability scale in SPMS and PPMS patients reported by Zamboni et al (2009)**

Variable	Pre-PTA	18-month FU	P Value
<i>SPMS (n=20)</i>			
MSQOL Physical health component, mean $\pm$ SD <sup>a</sup>	47 $\pm$ 12	62 $\pm$ 16	<0.08
MSQOL Mental health component, mean $\pm$ SD <sup>b</sup>	65 $\pm$ 3	70 $\pm$ 18	>0.10
MSFC, mean $\pm$ SD <sup>c</sup>	0 $\pm$ 0.8	0.5 $\pm$ 0.6	>0.10
<i>PPMS (n=10)</i>			
MSQOL Physical health component, mean $\pm$ SD <sup>a</sup>	53 $\pm$ 13	66 $\pm$ 12	<0.03
MSQOL Mental health component, mean $\pm$ SD <sup>b</sup>	60 $\pm$ 15	78 $\pm$ 9	<0.01
MSFC, mean $\pm$ SD <sup>c</sup>	-0.001 $\pm$ 0.5	0.04 $\pm$ 0.6	>0.10

FU: Follow-up; PPMS: Primary progressive multiple sclerosis; PTA: Percutaneous transluminal angioplasty; SPMS: Secondary progressive multiple sclerosis.

<sup>a</sup>Score of physical health component of the Multiple Sclerosis Quality of Life 54-item Instrument.

<sup>b</sup>Score of mental health component of the Multiple Sclerosis Quality of Life 54-item Instrument.

<sup>c</sup>Multiple Sclerosis Functional Composite, a disability scale expressed by the *Zeta* score, which integrates evaluation of the motility of the upper and lower extremities with cognitive function.

## COST IMPACT

In Australia, MS represents a significant economic burden both to the individual patient and to society. A 2005 economic assessment of the costs of MS to Australian society reported that the annual cost of MS is approximately \$2 billion (Access Economics 2005). This included the burden of disease of MS (estimated to be 8,968 DALYs lost in 2005) which cost approximately \$1.34 billion, as well as \$659 million in direct costs (MS health expenditure) for patient care, drug therapy, loss of productivity (3,195 people were prevented from working due to MS in 2005), and other costs.

A study by Taylor et al (2007) aimed to provide information about the cost structure of MS in Australia from a societal perspective, including all relevant costs to society for the treatment, secondary prevention, rehabilitation and long-term care of people with MS, both within and outside the healthcare system. In this study, detailed questionnaires were completed for 100 patients over a six month period (12 months for hospitalisation costs). The annual average direct cost of MS in this study was \$20,396/patient, with the majority being spent on three items: immunomodulating therapy, consultations and

hospitalisations. The annual average indirect cost was \$15,085/patient, with district nursing a major contributor. There were a number of factors that significantly increased overall direct costs, including SPMS, severe MS symptoms and higher EDSS scores (Taylor et al 2007). Therefore, it is clear that in order to reduce the economic burden of MS on society, as well as improve the quality of life of MS sufferers, the aim of MS treatment should be to stabilise patients on a low disability (low cost) level at an early stage of the disease using cost-effective therapies.

Percutaneous venoplasty is an established, routine procedure, with a proven safety and efficacy. However, this procedure has not been formally assessed in a trial setting for use in the treatment of CCSVI in patients with MS. Therefore, the cost-effectiveness of percutaneous venoplasty for this new indication cannot be determined at this time; however, it is unlikely that the costs associated with performing this procedure for the new indication would differ significantly from the cost of existing percutaneous venoplasty procedures. It is still unclear what proportion of the MS patient population meets the diagnostic criteria for CCSVI, and would therefore benefit from this procedure. Given that an estimated 1000 patients are newly diagnosed with MS each year in Australia, the potential cost impact of routine Doppler ultrasound screening during the diagnostic stages of MS will need to be considered.

#### **ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

There were no issues identified from the retrieved material.

#### **OTHER ISSUES**

Of the three studies included in this brief, one study explicitly stated that the authors had no commercial, proprietary, or financial interest in any procedure or companies described in the article (Petrov et al 2011). The two remaining studies failed to provide any statement regarding potential conflicts of interest (Malagoni et al 2010, Zamboni et al 2009).

There are a number of ongoing clinical trials assessing the use of percutaneous venoplasty for the relief of symptoms in MS patients with CCSVI being conducted in Italy (NCT01371760), Poland (NCT01264848) and the US (NCT01089686, NCT01201707 and NCT01205633). MS Australia has reported actively encouraging Australian researchers who wish to pursue research into CCSVI; however, this has resulted in only two small scale projects (MS Australia, 2011). Searches of clinical trials registers failed to identify any ongoing trials in Australia.

## **SUMMARY OF FINDINGS**

The evidence available for this brief was limited to lower level case series studies. These studies were heterogeneous in terms of the measures used to assess patient outcomes, which made it difficult to draw direct comparisons across studies. In addition, the length follow-up was limited to 12-18 months, and as such it was not possible to assess the long-term efficacy of the intervention. The reestablishment of a normal cerebrospinal venous return through percutaneous venoplasty significantly reduced chronic fatigue perception at 12 months follow-up, and improved the rate of relapse-free patients, quality of life, and neurological function at 18 months follow-up, in MS patients diagnosed with CCSVI. RRMS patients appeared to benefit the most from endovascular intervention. Percutaneous venoplasty appears to be a safe treatment for CCSVI in MS patients, with no major adverse events reported in this cohort of patients.

## **HEALTHPACT ASSESSMENT**

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 randomised controlled trials become available.

## **NUMBER OF STUDIES INCLUDED**

Total number of studies	3
Total number of Level IV studies	3

## **REFERENCES**

- Access Economics (AE) 2005. *Acting Positively: Strategic implications of the economic costs of multiple sclerosis in Australia*, Access Economics Pty Ltd for Multiple Sclerosis Australia. Winter 2005.
- Australian Institute of Health and Welfare (AIHW) 2001. *Morbidity of Vietnam veterans. Multiple sclerosis and motor neurone disease in Vietnam veterans: Supplementary report no. 3*. AIHW Cat. no. PHE 31. Canberra: AIHW.
- Duddy M, Haghikia A, Cocco E et al. Managing MS in a changing treatment landscape. *Journal of Neurology* 2011; 258: 728-739.
- Laupacis A, Lillie E, Dueck A et al. Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a meta-analysis. *Canadian Medical Association Journal* 2011 Oct 3 Epub ahead of print.

Lublin FD and Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology* 1996; 46: 907-911.

Malagoni AM, Galeotti R, Menegatti E et al. Is chronic fatigue the symptom of venous insufficiency associated with multiple sclerosis? A longitudinal pilot study. *International Angiology* 2010; 29: 176-182.

MS Australia 2011. <http://www.msaustralia.org.au/> [Accessed October 2011]

Multiple Sclerosis Network of Care 2011.

<http://www.msnetwork.org/advocacy/national%20CCSVI%20strategy.htm> [Accessed October 2011]

Petrov I, Grozdinski L, Kaninski G et al. Safety profile of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *Journal of Endovascular Therapy* 2011; 18: 314-323.

Taylor B, McDonald E, Fantino B et al. The cost of multiple sclerosis in Australia. *Journal of Clinical Neuroscience* 2007; 14: 532-539.

Vedantham S, Benenati JF, Kundu S et al. Society of Interventional Radiology; Canadian Interventional Radiology Association. Interventional endovascular management of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: a position statement by the Society of Interventional Radiology, endorsed by the Canadian Interventional Radiology Association. *Journal of Vascular and Interventional Radiology* 2010; 21: 1335-1337.

Zamboni P, Galeotti R, Menegatti E et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. *Journal of Vascular Surgery* 2009; 50: 1348-1358.

#### **SEARCH CRITERIA TO BE USED**

Percutaneous venoplasty OR Balloon angioplasty OR Percutaneous transluminal angioplasty OR PTA; Multiple sclerosis OR MS; chronic cerebrospinal venous insufficiency OR CCSVI