
Chronic cerebrospinal vascular insufficiency (CCSVI) – An update

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CCSVI – The hypothesis

- CCSVI is a reduction in drainage and/or a reversal in blood flow in the veins coming from the central nervous system.
 - This leads to the damage seen in MS.
 - Repair of the blood vessels reverses this damage
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CCSVI – Four key questions

- Does CCSVI exist?
 - How is CCSVI defined?
- Is CCSVI associated with MS?
 - What is the incidence in the broader population?
- Does CCSVI cause MS?
 - Correlation vs. causation
- Is treating CCSVI effective in treating MS?
 - Comparison to existing therapies
 - Cost-benefit analysis



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Five criteria defined for CCSVI

- CCSVI is defined as evidence of any **two** of the following **five** specific features:
 - Reflux in the internal jugular and vertebral veins
 - Reflux in the deep cerebral veins
 - Stenosis (narrowing) of the internal jugular vein,
 - Absence of flow in the internal jugular or vertebral veins
 - Reverted postural control of the main cerebral venous outflow pathways.
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Transcranial Doppler Sonography

- This specific technique is highly operator dependant. A positive (or negative) identification of CCSVI in one clinical setting may get the opposite result in a different setting.
 - CCSVI studies thus far have not been blinded. Therefore, they are open to the possibility of bias.
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Associations between CCSVI and MS

- Original Zamboni study showed unprecedented levels of association (100% sensitivity, 100% specificity, 100% positive and 100% negative predictive value)
 - If true, it will be possible to independently verify this.
 - A variety of sources of information are available
 - Press releases, marketing material, blogs, personal anecdotes, etc.
 - Published, peer reviewed studies are the best available evidence.
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Independent verification of CCSVI in MS

A screenshot of the PubMed website showing a search for 'ccsvi'. The search bar contains 'ccsvi' and the results are 19. The text 'Results: 19' is circled in red. The URL in the browser is http://www.ncbi.nlm.nih.gov/pubmed.

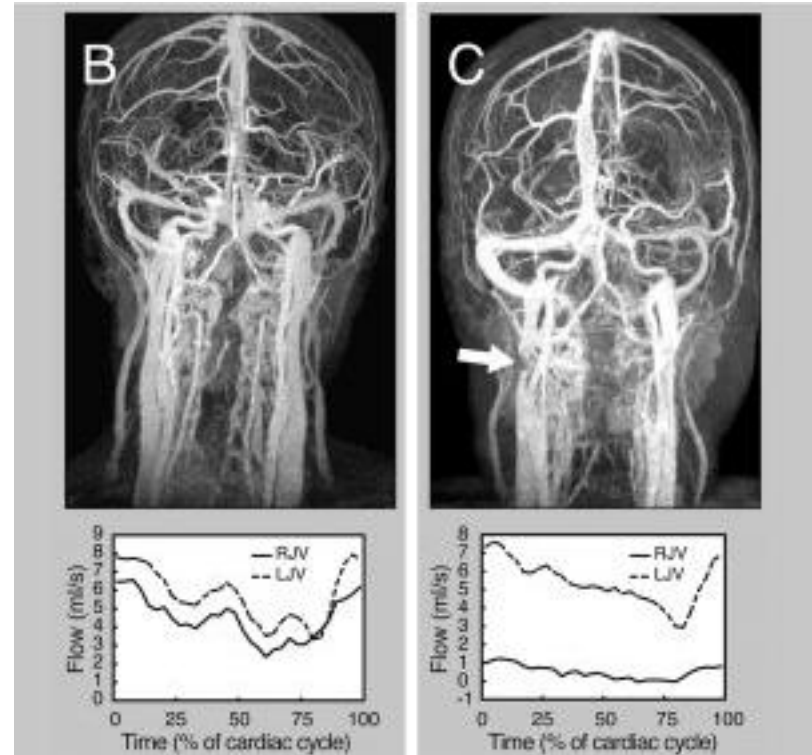
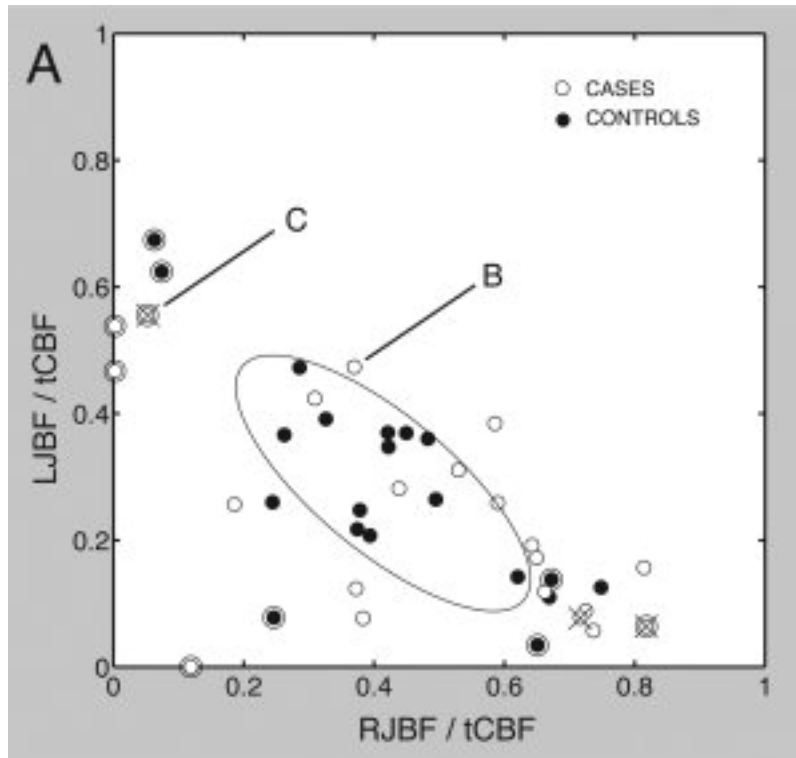
A screenshot of the PubMed website showing a search for 'ccsvi zamboni'. The search bar contains 'ccsvi zamboni' and the results are 14. The text 'Results: 14' is circled in red. The URL in the browser is http://www.ncbi.nlm.nih.gov/pubmed?Db=pubmed&term=ccsvi%20zamboni.

- This leaves very few non-Zamboni publications
- 1 editorial (Embry, International Angiology 2010)
- 2 reviews (Lee *et al*, International Angiology 2010 ; Khan et al, Annals of Neurology 2010)

Independent verification of CCSVI in MS

- 4 peer reviewed, published independent studies published thus far
 - Given the CCSVI hypothesis is so new, independent evidence will be limited
 - **Jordan:** Al-Omari and Rousan (International Angiology, 2010)
 - 25 patients, 25 controls, assessed by ultrasound
 - 84% of patients had evidence of CCSVI, versus 24% of controls
 - **Germany:** Krogias *et al* (Nervernarzt, 2010)
 - 20% of patients fulfilled criteria for CCSVI
 - Concluded that there was no justification for invasive treatments
 - **Germany:** Doepp *et al* (Annals of Neurology, 2010)
 - 56 patients, 20 controls, assessed by ultrasound
 - No evidence for CCSVI in any subjects.
 - **Sweden:** Sundström *et al* (Annals of Neurology, 2010)
 - 21 patients, 20 controls, assessed by MRI
 - No evidence for CCSVI in any subjects.
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Increased CCSVI in MS?



Note the overlap between cases and controls. This suggests you can't tell them apart based on the vascular measurements

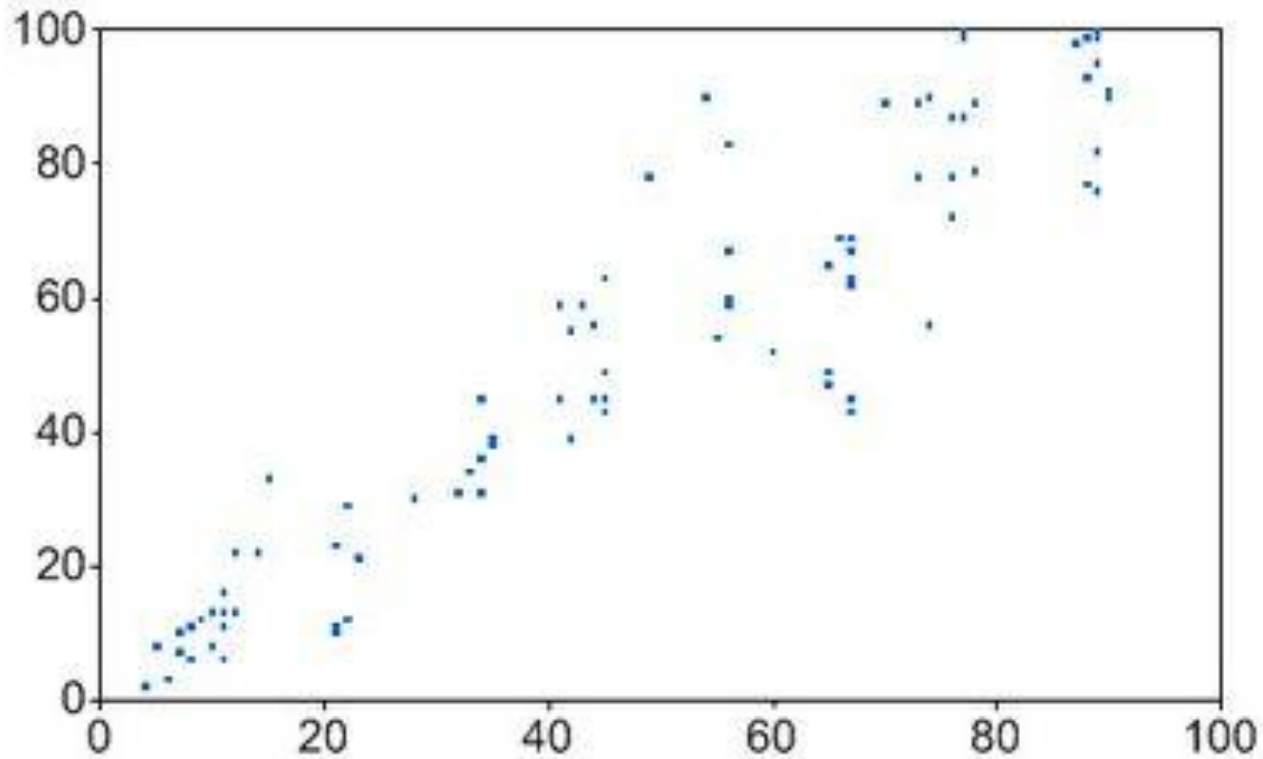
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Correlation and causation

of ice creams sold



Murder Rate

Does CCSVI cause MS?

PROOF



Correlation

Order in
time

Plausible
mechanism

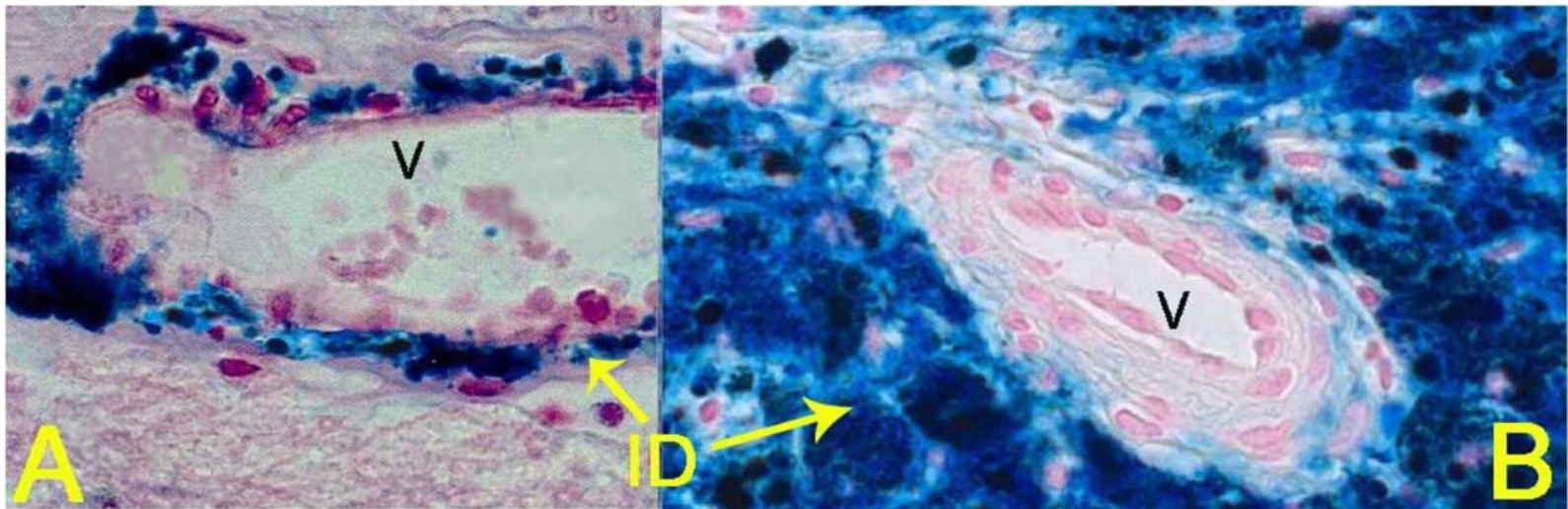
How is CCSVI proposed to cause damage?

- Several mechanisms have been proposed
 - Increased pressure across veins
 - Reduced blood flow leads to hypoxia (lack of oxygen)
 - Accumulation of cytokines and toxic metabolites
 - Iron deposition leading to inflammation/autoimmune response
-

Iron deposition, blood flow and inflammation

MS

CVD (chronic venous disease)
(e.g. varicose veins)

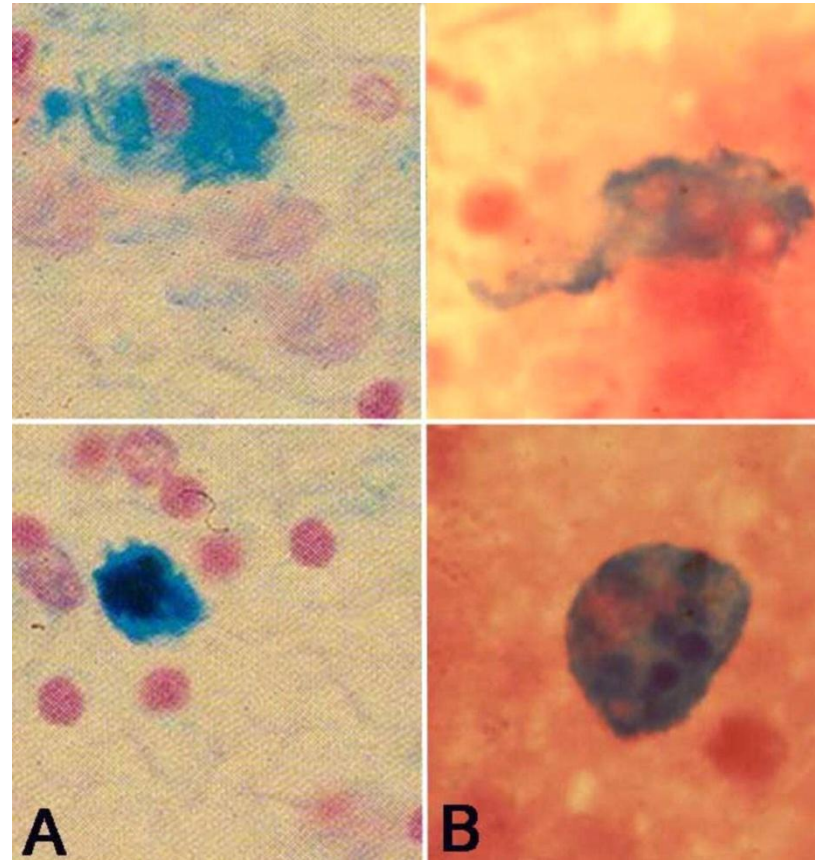


Iron deposition, blood flow and inflammation

- Blue – Iron in macrophages (immune cells)
- Iron deposits also seen in other neurological diseases (e.g. Alzheimers)

MS

CVD



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No direct evidence exists showing how CCSVI leads to the demyelination and damage underlying MS.

Does CCSVI cause MS?

PROOF



Correlation



Order in
time



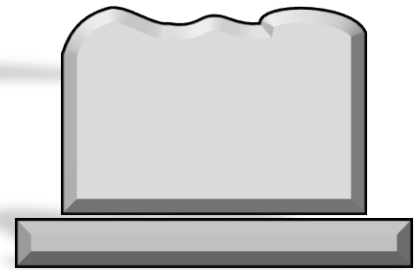
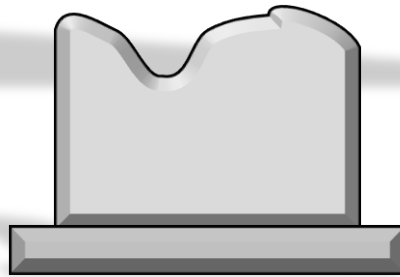
Plausible
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Does CCSVI cause MS?

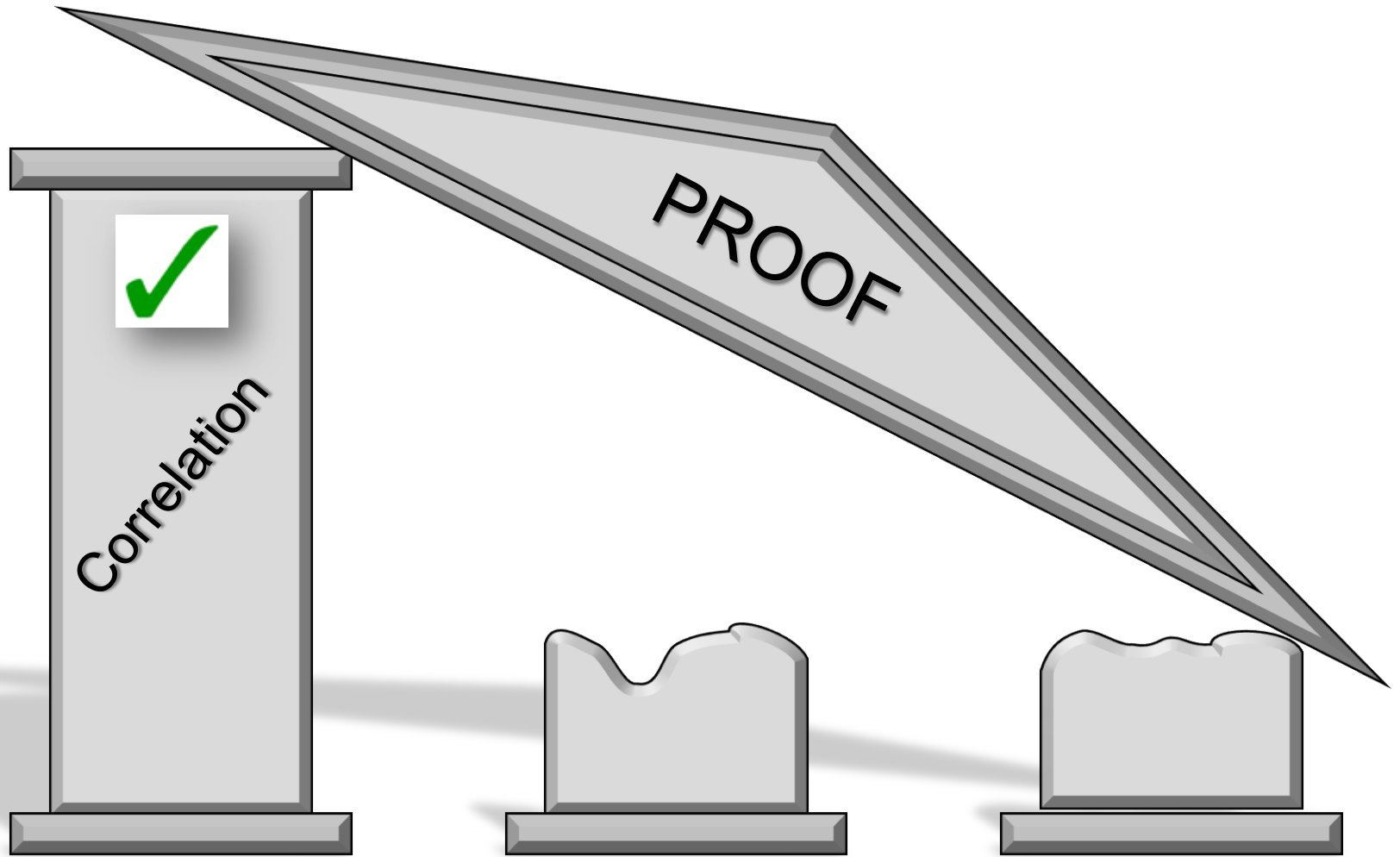
PROOF



Correlation



Does CCSVI cause MS?



Another possibility...

- It is possible that CCSVI exists, and **correlates** strongly with MS, but is in no way the **cause** of MS.
 - CCSVI, or other vascular conditions, may be **secondary** effects of demyelination and/or inflammatory damage, i.e. caused by MS, as opposed to being the cause of MS.
 - If this were true, vascular problems could hypothetically contribute to the severity of symptoms.
 - There is also no direct evidence for this association. However, this explanation requires less assumptions than the claim that CCSVI causes MS.
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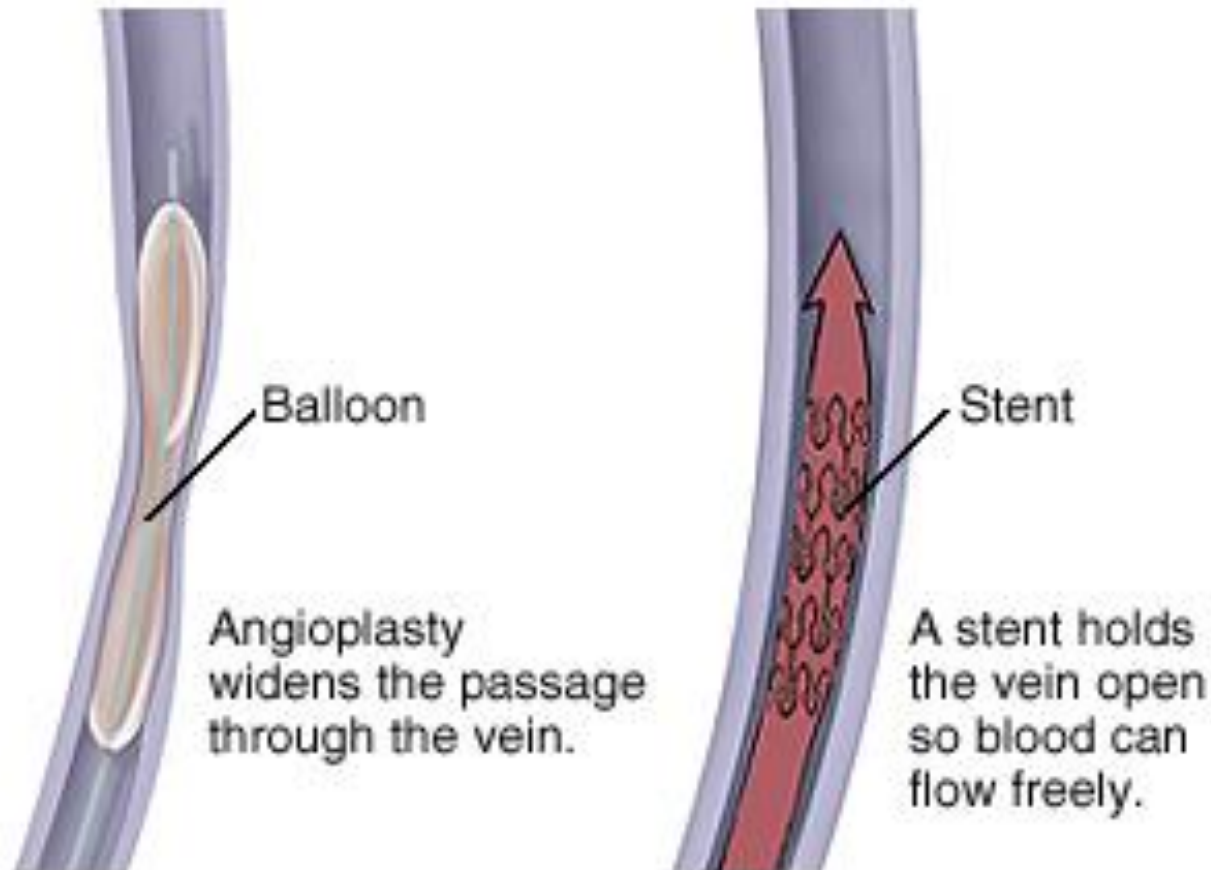
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Treating CCSVI

- Two interventions for reducing CCSVI have been proposed: balloon angioplasty and stenting.



Treating CCSVI

- Two interventions for reducing CCSVI have been proposed: balloon angioplasty and stenting.
 - Balloon angioplasty. Small pilot study (Zamboni et al, 2009) reported high levels of restenosis. As a result, angioplasty would have to be repeated at regular intervals.
 - The second approach, stents are used to support the veins. While theoretically a longer term solution, this has been associated with several severe side effects, and treatments at Stanford University were halted.
 - Published trial showed some positive results, but have not been well controlled and blinded. Proper assessment of CCSVI intervention needs well controlled, blinded trials with long term follow up.
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Many of the most important questions have not yet been answered

What happens next – an example

- Special CCSVI research scheme: NMSS and MSSC
- Results announced 11th June, 2010
- 7 projects funded; total awarded \$2.4 million
- Broad range of well designed studies:
 - MRI, ultrasound, twin studies, tissue studies, comparison to other neurological conditions etc.
- No studies involving treatments approved

"Any procedure where you inject a catheter in a vein, where you compress the vein, where you risk damage to the internal sheath of the vein, is not without risk."

***Dr. Alain Beaudet
President, Canadian Institutes of Health Research***
