

Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Safety and efficacy of venoplasty in MS: A randomized, double-blind, sham-controlled phase II trial

In the article "Safety and efficacy of venoplasty in MS: A randomized, double-blind, sham-controlled phase II trial", Traboulsee et al. compared balloon or sham venoplasty of extracranial jugular and/or azygous venous narrowing (>50% by venography) in 104 participants with relapsing or progressive MS followed for 48 weeks. They concluded that their data did not support the continued use of venoplasty to improve patient-reported outcomes, chronic symptoms, or disease course of MS. In response, Juurlink et al. note that no venous flow data were presented, positing that there may be therapeutic benefits in those patients who achieve better flow after venoplasty. They also highlight a discrepancy between numbers of new MRI-detectable lesions reported in the Results section vs table 3 of the article. Replying to these comments, Drs. Traboulsee et al. note that vessel patency and venous flow through the narrowing were confirmed with postprocedural venography, but caution that quantitative measures of venous flow may be confounded by multiple factors. They argue that post hoc analysis of small subgroups (as in a previous study by Drs. Zamboni et al.) will have insufficient power and is prone to erroneous interpretation. They clarify that the numbers in table 3 are correct. In another response, Dr. Rasman perceives a lack of MRI data in the article and contrasts the study's mixing of relapsing and progressive MS with the inclusion of only relapsing-remitting MS in the Brave Dreams trial. Dr. Rasman also contends that the relatively older population with longer disease duration in this study is unsuitable for venous percutaneous transluminal angioplasty (PTA) and argues that gastrointestinal symptoms and anxiety should not have been attributed to PTA. Finally, Dr. Bruno reports a lower rate of adverse events from PTA of the internal jugular and azygous veins in their own practice. The authors did not respond to these additional comments.

Aravind Ganesh, MD, and Steven Galetta, MD
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Reader response: Safety and efficacy of venoplasty in MS: A randomized, double-blind, sham-controlled phase II trial

Bernhard H.J. Juurlink (Saskatoon, Saskatchewan, Canada), Ashton F. Embry (Calgary, Alberta, Canada), and Pietro M. Bavera (Milan, Italy)
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The objective of venoplasty is to improve venous return from the CNS, yet no flow data were presented in the Traboulsee et al.¹ article examining the safety and efficacy of venoplasty in MS. The venoplasty trial by Zamboni et al.² showed that only 54% of the venoplasty patients had improved venous flow. There were no significant differences in the development of new MRI-detectable lesions between the venoplasty and sham groups²; however, when the venoplasty group was divided into those with improved blood flow and those with no improved blood flow, the data showed that there were significantly fewer new lesions ($p < 0.07$ at 6 months; $p < 0.05$ at 12 months) in the venoplasty subgroup with improved venous flow.³ Are the greater SDs seen in figure 2 of the Traboulsee et al.¹ article due to better outcomes in a small subset of the venoplasty group with improved blood flow?

Author disclosures are available upon request (journal@neurology.org).

There is also a major discrepancy in the Traboulsee et al.¹ article between the text in the Results section and table 3 with respect to numbers of new MRI-detectable lesions in the venoplasty and sham groups. Which is correct?

1. Traboulsee AL, Machan L, Girard JM, et al. Safety and efficacy of venoplasty in MS: a randomized, double-blind, sham-controlled, phase II trial. *Neurology* 2018;91:e1660–e1668.
2. Zamboni P, Tesio L, Galimberti S, et al. Efficacy and safety of extracranial vein angioplasty in multiple sclerosis: a randomized clinical trial. *JAMA Neurol* 2018;75:35–43.
3. Zamboni P, Zivadinov R. Extracranial veins in multiple sclerosis: is there a role for vascular surgery? *Eur J Vasc Endovasc Surg* 2018;56:618–621.

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Author response: Safety and efficacy of venoplasty in MS: A randomized, double-blind, sham-controlled phase II trial

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On behalf of all coauthors, we thank Juurlink et al. for the comment on our article.¹

Regarding flow: The preplanned experimental procedure was dilation of extracranial venous narrowing as proposed by Zamboni et al.² Up to 3 dilation attempts were permitted to ensure optimal expansion of the narrowing. Vessel patency and venous flow through the narrowing were confirmed with venography after dilation. In contrast to arterial studies, quantitative measures of venous flow can be affected by catheter position, injection rate and pressure, and physiologic factors. Interpretation of quantitative venous flow data from any study would require technical standardization with independent reproducibility studies to ensure reasonable validity.

Regarding MRI lesion subgroup post hoc analysis: MRI lesion activity counts are highly variable between individuals. Post hoc analysis of small subgroups of patients will not have sufficient power to demonstrate benefit and is prone to type 1 error, especially when covariables are not taken into account.

Regarding figure 21: The standard errors are similar. There was no significant difference seen.

Regarding table 31: The numbers in the table are correct. There was no significant difference between the 2 cohorts.

1. Traboulsee AL, Machan L, Girard JM, et al. Safety and efficacy of venoplasty in MS: a randomized, double-blind, sham-controlled, phase II trial. *Neurology* 2018;91:e1660–e1668.
2. Zamboni P, Galeotti R, Menegatti E, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. *J Vasc Surg* 2009;50:1348–1358.

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Reader response: Safety and efficacy of venoplasty in MS: A randomized, double-blind, sham-controlled phase II trial

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It is very strange that Traboulsee et al.¹ did not publish any MRI data; this does not allow a meta-analysis comparison with other trials. The Brave Dreams trial² examined patients with relapsing-

remitting MS (RRMS) undergoing percutaneous transluminal angioplasty (PTA) for chronic cerebrospinal venous insufficiency, and this Canadian study contains a mixed population of RRMS and secondary-progressive MS.¹ Furthermore, a population with a mean age of 50 years and a disease duration of 17 years is not an acceptable study group for PTA. Adverse event nausea and gastrointestinal symptoms are in no way attributable to PTA. Why did the authors attribute a symptom of understandable anxiety (agreement to a double-blind surgery) to the PTA?

1. Traboulsee AL, Machan L, Girard JM, et al. Safety and efficacy of venoplasty in MS: a randomized, double-blind, sham-controlled, phase II trial. *Neurology* 2018;91:e1660–e1668.
2. Zamboni P, Tesio L, Galimberti S, et al. Efficacy and safety of extracranial vein angioplasty in multiple sclerosis: a randomized clinical trial. *JAMA Neurol* 2018;75:35–43.

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Reader response: Safety and efficacy of venoplasty in MS: A randomized, double-blind, sham-controlled phase II trial

Aldo Bruno (Telese Terme, Italy)

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My experience was not promoted through social media, but my papers and presentations at international conferences received an international diffusion: International Society for NeuroVascular Disease conference, Italian Society of Otorhinolaryngology, Society of Interventional Radiology meeting, and International Conference on Meniere's Disease.

The results of my experience were evaluated only by ear, nose, and throat evaluation before and after percutaneous transluminal angioplasty (PTA) with a committee on hearing and equilibrium guidelines during and after a 24-month follow-up. The patients underwent ultrasonography, magnetic resonance venography, and phlebography; the diagnosis was confirmed in all. The patients who underwent PTA did not have any benefits from any other therapies.

About Traboulsee et al.'s¹ procedures, I have some questions: What was the material the radiologists used? The criteria to determine the stenosis were very reductive so to affirm the presence of stenosis: only when you observe a >50% narrowing of any of the 3 veins. However, as the *Journal of Vascular and Interventional Radiology* guideline described,² that I followed for my patients, it is also necessary to evaluate the empty time and the reflux of the blood in the internal jugular veins and azygos vein (the presence of intrinsic lesions and the presence of collateral veins with empty time). I have not found the diameter of balloons used and inflation time too brief. I inflated the balloon for 120 seconds and sometimes repeated venoplasty after persistent narrowing.^{2,3} I had no major adverse events in all patients and only minor adverse events in 5 patients treated with conservative therapy.³ Therefore, I can affirm that PTA of the internal jugular veins and azygos vein is sure, and the risk of adverse events is low.

1. Traboulsee AL, Machan L, Girard JM, et al. Safety and efficacy of venoplasty in MS: a randomized, double-blind, sham-controlled, phase II trial. *Neurology* 2018;91:e1660–e1668.
2. Zivadinov R, Bastianello S, Dake MD, et al. Recommendations for multimodal noninvasive and invasive screening for detection of extracranial venous abnormalities indicative of chronic cerebrospinal venous insufficiency: a position statement of the International Society for Neurovascular Disease. *J Vasc Interv Radiol* 2014;25:1785–1794.e17.
3. Bruno A, Napolitano M, Califano L, et al. The prevalence of chronic cerebrospinal venous insufficiency in Meniere disease: 24-month follow-up after angioplasty. *J Vasc Interv Radiol* 2017;28:388–391.

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Risks and benefits of clopidogrel–aspirin in minor stroke or TIA

Time course analysis of CHANCE

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In the article "Risks and benefits of clopidogrel–aspirin in minor stroke or TIA: Time course analysis of CHANCE" by Y. Pan et al.,¹ there are errors in table 1 for "Moderate to severe bleeding" events in both the ASA and CLP + ASA treatment groups. The corrected table 1 is posted below with changes in bold type. Accordingly, the passage on page 1908 should read "A total of 6 moderate to severe bleedings occurred within the first month in the clopidogrel-aspirin group with 3 during the first week... Only 2 moderate to severe bleedings occurred during the first week of the first month in the aspirin alone group" rather than "A total of 4 moderate to severe bleedings occurred within the first month in the clopidogrel-aspirin group with 1 during the first week... No moderate to severe bleeding occurring within the first month in the aspirin alone group" as originally published. The authors regret the errors.

Reference

1. Pan Y, Jing J, Chen W, et al. Risks and benefits of clopidogrel–aspirin in minor stroke or TIA: time course analysis of CHANCE. *Neurology* 2017;88:1906–1911.

Table 1 Time course distribution of ischemic stroke and bleeding by treatment assignment

Outcome	Group	Total	No. of events					
			1st week	2nd week	3rd week	4th week	5th week	6th week-day 90
Ischemic stroke	ASA (n = 2,586)	295	223 (75.59)	19 (6.44)	8 (2.71)	6 (2.03)	2 (0.68)	37 (12.54)
	CLP + ASA (n = 2,584)	204	145 (71.08)	13 (6.37)	12 (5.88)	6 (2.94)	3 (1.47)	25 (12.25)
Any bleeding	ASA (n = 2,586)	41	15 (36.59)	8 (19.51)	3 (7.32)	2 (4.88)	2 (4.88)	11 (26.83)
	CLP + ASA (n = 2,584)	60	23 (38.33)	15 (25.00)	9 (15.00)	3 (5.00)	1 (1.67)	9 (15.00)
Moderate to severe bleeding	ASA (n = 2,586)	8	2 (25.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (12.50)	5 (62.50)
	CLP + ASA (n = 2,584)	7	3 (42.86)	2 (28.57)	1 (14.29)	0 (0.00)	0 (0.00)	1 (14.29)
Mild bleeding	ASA (n = 2,586)	19	3 (15.79)	7 (36.84)	2 (10.53)	1 (5.26)	1 (5.26)	5 (26.32)
	CLP + ASA (n = 2,584)	30	8 (26.67)	9 (30.00)	8 (26.67)	1 (3.33)	0 (0.00)	4 (13.33)

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Risks and benefits of clopidogrel–aspirin in minor stroke or TIA: Time course analysis of CHANCE

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