# The Actual Data from PREMiSe Do Not Support the Highly Publicized, Anti-CCSVI Claims and Warnings of the University of Buffalo Researchers

Ashton Embry, DIRECT-MS, April, 2013

## Quick Summary

The actual data from the PREMiSe Trial do not support the highly publicized claim that CCSVI correction by angioplasty is not of value for MS and may worsen disease activity. In sharp contrast, the data suggest that CCSVI correction may well be of substantial value for MS. The misleading claims made by University of Buffalo researchers are based on irrelevant data from the failed Phase 2 portion of the trial in which no one had their CCSVI corrected. The anti-CCSVI bias and baseless claims may be explained by the conflicts of interest.

## Executive Summary

University of Buffalo (UB) MS researchers put out a press release and Youtube video with claims that the Phase 2 portion (controlled, randomized and double blind) of their PREMiSe clinical trial demonstrated that CCSVI correction (restoration of >75% venous blood flow from the brain) by means of venous angioplasty, was not of value for MS and was possibly harmful.

An inspection of the PREMiSe data on the poster presented by UB researchers at the recent AAN convention in San Diego reveals the following

1) All the subjects in the open label, Phase 1 portion of the PREMiSe trial had their CCSVI was corrected (>75% blood flow restored by venous angioplasty). They had very good clinical results over the 6 months with no relapses and only 2 new lesions among the ten subjects.
2) The controlled and blinded Phase 2 portion of the PREMiSe trial was a failure because those receiving angioplasty did not have their CCSVI corrected (i.e. they did not have their blood flow restored to >75%).

3) Among the nineteen, Phase 2 subjects, all of whom did not have their CCSVI corrected, there were a total of 4 relapses and 20 new lesions.
4) The reason for the failure of the angioplasty procedure to correct CCSVI in any of the Phase 2 subjects is unknown and is of concern because there was 100% success in Phase 1.
5) The failure of angioplasty to correct CCSVI in the Phase 2 patients means any comparison between the clinical outcomes of the angioplasty patients and sham ones has no scientific significance. Any detected differences between the clinical outcomes of the two groups are purely random and a consequence of the very small trial size and the acceptance of only persons with active MS into the trial.
6) The excellent clinical results of Phase 1 subjects, all of whom experienced CCSVI correction, compared to the adverse clinical results of Phase 2 subjects, none of whom experienced CCSVI correction, suggest CCSVI treatment may be of substantial value for MS.

An added complicating factor is that some of the researchers involved with PREMiSe are in a major conflict of interest in that they receive large sums of money from MS drug companies. Because CCSVI treatment has the potential to replace drug therapy in some cases, the compromised researchers and their drug company benefactors would potentially financially gain from a bogus claim that CCSVI treatment was of no value and might even be harmful.

The PREMiSe researchers launched a major media campaign a) to claim their data showed that CCSVI treatment was of no value and may be of harm, b) to dissuade persons with MS from getting CCSVI treatment outside of trials, and c) to dissuade practitioners from doing CCSVI treatment. These claims and warnings are entirely baseless because of the lack of significance of the results from Phase 2 in which no one had their CCSVI corrected. They may have been motivated by the major conflicts of interest referred to above.

The University of Buffalo should retract the currently available press release and Youtube video and replace them with ones that contain the real story told by the data of the PREMiSe trial.

# The Actual Data from PREMiSe Do Not Support the Highly Publicized, Anti-CCSVI Claims and Warnings of the University of Buffalo Researchers

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## Introduction

**Press release and Video** - On March 15, I received a flurry of emails letting me know about a very recent press release from the University of Buffalo (UB). The release (http://www.buffalo.edu/news/releases/2013/03/021.html ) boldly announced that University of Buffalo researchers led by Adnan Siddiqui and Robert Zivadinov had found that **correcting CCSVI with venous angioplasty was of no value for treating MS**. It included statements such as "The study showed that endovascular treatment of stenosed veins had no effect in MS patients" and "these findings lead us **to caution strongly against the general acceptance of this invasive procedure for MS patients**."

Accompanying the press release was a Youtube "video release" (a new innovation to spread the word) by the same principal investigators. It can be viewed at http://youtu.be/94gLM4QlU_A. This contained even more ominous information with a solemn Dr Siddiqui announcing that the randomized, blinded, controlled study found that, instead of providing benefit, **CCSVI treatment potentially was harmful**. He then continued to say that, based on these results, patients and practitioners should stop getting/doing CCSVI treatments outside of clinical trials.

**Problems with the Press Release -** Obviously, if their actual data supported such dire findings, then indeed these results were very newsworthy and Siddiqui's warning about CCSVI treatment might be justified. However, there were three problems:

1) There were no data publicly available to see if their findings actually supported their sensational claims and grim warnings.

2) In the past, some of the same UB MS researchers have spun either good or innocuous data with a strong, very anti-CCSVI bias. I documented this in 2011 (see Appendix 2 of this report).

3) A number of the UB researchers have major financial ties, both personal and scientific, with the MS drug companies and are thus in a major conflict of interest when it comes to objectively testing the efficacy of a non-drug treatment that might supplant drug treatment and negatively affect the drug companies.

Common sense tells us that anytime a major conflict of interest is present, one has to be very wary of any claims or warnings which would potentially benefit those in conflict.

**Negative Results Predicted in 2011 -** In my April 2011 essay which documented in detail the strong anti-CCSVI bias of the UB researchers (Appendix 2), I noted that **"One can imagine the monumental efforts that will be made by some anti-CCSVI factions to try to ensure that any CCSVI clinical trial that gets off the ground will have a negative result."** So here we are in 2013 and indeed the predicted negative result for a CCSVI trial run by established, anti-CCSVI researchers from UB has seemingly appeared.

Finally, it should be mentioned that the UB researchers' extraordinary efforts to get their major, anti-CCSVI findings out to the world were very successful and all the news and TV outlets, not to mention many bloggers, trumpeted the story of the failure of CCSVI treatment and its potential for harm. **And all this before a single shred of scientific data had been made publicly available!**

## PREMiSe Data and Why the Phase 2 Portion of the Trial Was in Reality a Failure

**The PREMiSe Data Become Available** - Two weeks after the UB researchers dropped their anti-CCSVI bombshell on the world but provided no data whatsoever to back up their claims, I received a copy of the UB poster. It contained a good summary of their work accompanied by clear and comprehensive tables and graphs of their results. **The poster comprises Appendix 1 of this report**.

The poster was presented at the recent, annual meeting of the American Academy of Neurology, a major event which is hugely subsidized by the pharmaceutical industry. Notably, their poster was presented on March 20, almost a week after their press release and YouTube video were made available, which is certainly not the normal way of doing things. Press releases are always issued on the day of presentation at the earliest, that is, simultaneous with the information being publicly presented. Issuing a press release, not to mention a video, nearly a week before the actual presentation may be unprecedented.

The good news was the results from the PREMiSe trial were now in my hands and **I could see if the UB researchers really had hard data to back up their anti-CCSVI claims and cautions or if they were still bashing CCSVI and its treatment with no real supporting data.**

**The PREMiSe Clinical Trial –** As clearly stated on the poster, the PREMiSe trial was designed "**To investigate the safety and efficacy of**

**percutaneous transluminal venous angioplasty (PTVA) for correcting CCSVI in MS in the setting of a prospective, double-blind, sham-controlled, randomized pilot trial".** I would note that "correcting CCSVI" means restoring reasonably normal blood flow from the brain and conservatively this can be defined as greater than 75% of normal flow. Achieving modest reductions of CCSVI (e.g. improving blood flow from 45% to 60%) can in no way be construed as actually correcting CCSVI.

The PREMiSe trial consisted of two phases:
Phase 1 - an open label study with 10 individuals who tested positive for CCSVI receiving venous angioplasty.
Phase 2 - a sham-controlled, randomized, double-blind, study which involved 19 people with MS who had tested positive for CCSVI. 10 persons had the sham treatment and 9 were given angioplasty.
The claims and warnings issued by the UB researchers in their press release and video were based on the Phase 2 results.

I would emphasize that a clinical trial which tests the safety and efficacy of a surgical procedure is somewhat different from that of a drug trial because the surgical procedure trial has the **major added factor of surgical competence**. In a drug trial one can be sure everyone is getting the same prescribed treatment. In a surgical trial**, if the surgeon is incompetent or inexperienced, some or all of the subjects may not get the prescribed treatment which in this case would mean they would not have their CCSVI corrected by way of venous angioplasty**.

**Blood Flow Data Are Critical -** Given the importance of surgical competence, some of the most critical data are the blood flow data of the subjects at the start and during the trial. Such data tell us if those who received angioplasty in Phase 1 and Phase 2 actually received the prescribed treatment (CCSVI correction) or not (CCSVI not corrected).

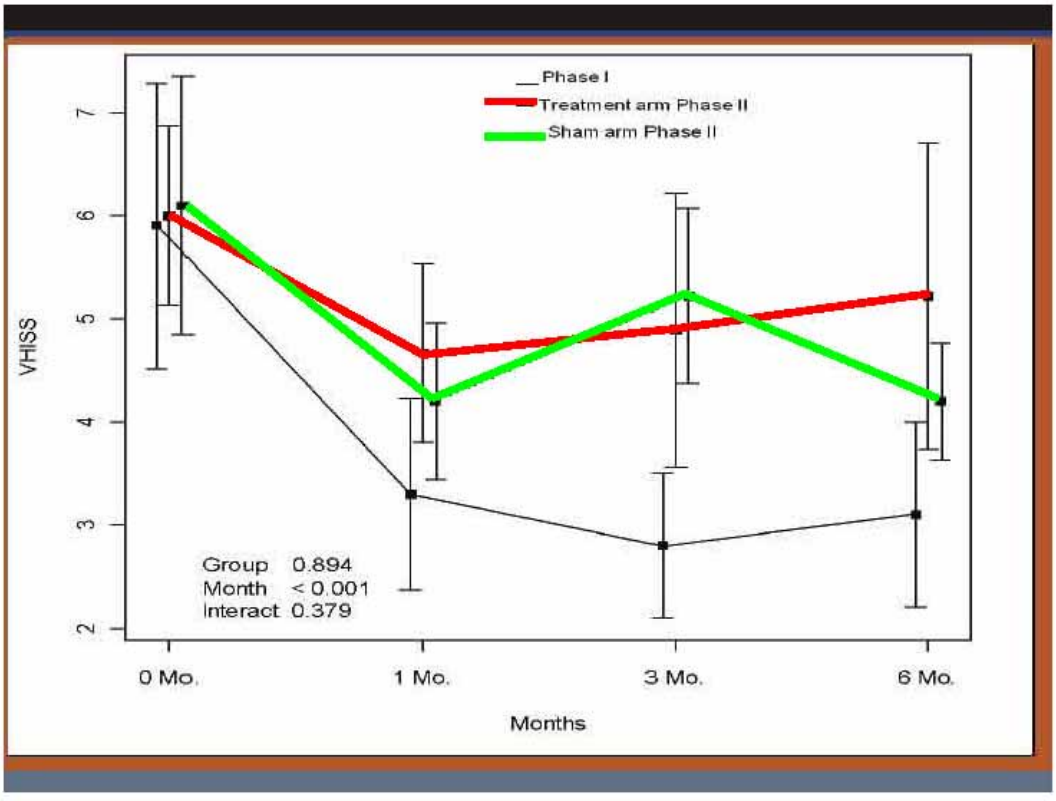
This is most important for the Phase 2 portion. **Clearly, if the treatment was not done adequately and CCSVI was not corrected in all or most of the treated subjects, then all the comparative data between the sham and angioplasty groups are scientifically irrelevant and the trial must be considered an abject failure.** On the other hand, if all, or at least most, of the angioplasty patients in Phase 2 did indeed have their CCSVI corrected, then changes in the measured variables such as relapse number and new lesions might possibly have meaning if statistically significant differences are present between the two groups.

I was pleased to see that the UB researchers included the key blood flow data on their poster for both Phase 1 and Phase 2 so as to allow one to determine the basic validity of the trial, especially the Phase 2 portion.

**Blood flow was evaluated by calculating a venous hemodynamic insufficiency severity score (VHISS) which is an accepted way of doing this. The lower the VHISS score, the better the flow and thus, if the angioplasty treatment was effectively done, the VHISS score of anyone who received angioplasty would significantly drop. In the Phase 2 portion, if the angioplasty was properly done, the VHISS scores of the angioplasty group (CCSVI corrected) would be significantly better than the sham group (CCSVI still present).**

**The Blood Flow Data from PREMiSe –** All the subjects in both phases of the trial had notable CCSVI and highly compromised blood flow at the start of the trial (VHISS score of ~ 6). This was reassuring.

Because the changes in VHISS scores are such important and critical results, the graph of the changes, which was in the poster, is reproduced below with some enhancement of the lines which follow the changes. The thin black line traces the major improvement of the VHISS scores of the subjects in the open label, Phase 1 trial. As can be seen, the subjects had a major improvement in VHISS scores (6 to 3) and all had their CCSVI corrected (>75% normal blood flow).




**The VHISS scores of the two groups from Phase 2 are coloured in red (angioplasty group) and green (sham group). Note that the VHISS score of**

**the angioplasty group was higher than sham group at both 1 month and 6 months after treatment and was almost the same at 3 months. These data reveal that, without a doubt, the subjects in the angioplasty group did not have their CCSVI corrected and that their blood flow remained as bad as that recorded for those in the sham group. The importance of this hard fact cannot be overstated.**

**Phase 2 of the PREMiSe Trial is a Dismal Failure -** The difference in VHISS scores between the angioplasty and sham groups as shown on the above graph is not statistically significant. However **the fact that both groups maintained the same highly compromised blood flow (CCSVI) throughout the trial says, without a doubt, that the angioplasty group failed to have their CCSVI corrected**. **This means, in reality, we have two similar groups with clear CCSVI both before and after either the sham or actual procedure.**

**There is no way to escape the obvious conclusion that Phase 2 of the PREMiSe trial was a dismal failure because no one in the angioplasty group received the necessary treatment of correcting CCSVI. This would be equivalent to a trial to test the efficacy of a drug and none of the subjects on the treatment side of the trial actually received the drug by error or by design. Who would question such a drug trial being called a dismal failure?**

**The bottom line is that, because the Phase 2 portion of the PREMiSe trial was a clear failure, a comparison of the clinical results (MRI changes, relapses) of the two groups in Phase 2 has absolutely no value or relevance for assessing the efficacy of correcting CCSVI by venous angioplasty.**

## Comparing Phase 1 and Phase 2 Results

**Introduction –** Just because the Phase 2 portion of the PREMiSe trial was a failure in terms of not being able to use the data to assess efficacy of correcting CCSVI for MS, does not mean the entire trial did not give us some insight into the potential of CCSVI correction for being of value for MS. As discussed earlier, all 10 subjects in the Phase 1 portion of the trial had their CCSVI corrected and all 19 subjects in the Phase 2 portion did not. Thus, if one wants to assess the value of CCSVI treatment for MS, the best way would be to compare the MRI and relapse data of the subjects from the two trial phases.

I would emphasize that, even though such a comparison is not blinded or randomized, it can be considered to be controlled and notably, the variables being compared cannot possibly be due to placebo effect.

**Comparing the Results –** The 10 Phase 1 subjects, who all had their CCSVI corrected (>75% blood flow restored), had very good clinical results over the 6 months with no relapses and only 2 new lesions among all ten subjects. On the other hand, the 19 Phase 2 subjects, none of whom had their CCSVI corrected during the course of the PREMiSe trial, had a total of 4 relapses and 20 new lesions. **These data strongly indicate that CCSVI correction may well be of substantial value for MS** although a much larger clinical trial will be required to provide a better statistical result.

It must be noted that the Buffalo researchers did not compare the results between the 10 subjects with corrected CCSVI (successful angioplasty) and the 19 subjects with uncorrected CCSVI due either to sham treatment or failed angioplasty. One has to wonder why such an obvious comparison (corrected CCSVI group versus uncorrected CCSVI group) was not made.

## UB Researchers Use the Irrelevant Phase 2 PREMiSe Results to Make Baseless Claims about the Efficacy of CCSVI Correction for MS

**Baseless Claims of the UB Researchers -** Despite the obvious and unequivocal failure of Phase 2 angioplasty to correct any subject's CCSVI and the consequent lack of value of any data or interpretations from this phase of the trial, the UB researchers publicly claimed, in no uncertain terms, that their research showed that correcting CCSVI by angioplasty was of no value and might even be harmful. They followed this with the ominous warning that such a result means that persons with MS should not get CCSVI treatment and that clinicians should not do CCSVI treatment outside of a clinical trial.

They based the above claims and warnings on the observations that the angioplasty group in Phase 2 had more MRI-detected lesions and more relapses than the sham group after six months. Of course, **such results have no relevance given no one who received angioplasty had their CCSVI actually corrected (>75% blood flow).** One might ask why angioplasty group ended up having more lesions and relapses given the irrelevancy of such findings.

**Why the Angioplasty Group Had a Worse Outcome –** One aspect of the PREMiSe trial is that the researchers only accepted persons with active MS into the trial (at least one relapse in the past year or at least one new enhancing lesion in the last three months). Notably, **it turned out that the angioplasty group by pure chance through randomization got subjects with more active disease** with an average of 1 previous relapse for the angioplasty subjects versus only .4 relapses for the sham group (i.e. more than twice as many relapses for the angioplasty group). **It is worth noting that one person**

**randomly assigned to the angioplasty group (50/50 chance) ended up with 8 new lesions which was almost as many as the total number of new lesions (12) developed by all other 18 people in Phase 2!**

**In summary, because no one in the angioplasty group of the Phase 2 trial had their CCSVI corrected, any MRI and relapse differences between the angioplasty and sham groups are purely random and have no absolutely no scientific relevance when it comes to assessing the efficacy of correcting CCSVI by angioplasty. Any attempt to attach clinical meaning to such random data is unequivocally unacceptable and unscientific and cannot be taken seriously**.

**To me, it is troublesome the UB researchers thought they could ignore the obvious failure of the Phase 2 portion of the trial and the consequent lack of any scientific meaning of the clinical changes between the angioplasty and sham groups. It is even more worrisome that they used their irrelevant and basically random results as proof that correcting CCSVI (which in reality did not happen) was of no benefit and that it may even be harmful.**

**Their possible motives for acting in such an unacceptable and unscientific manner – fabricating and widely publicizing baseless statements to influence the actions of others - are discussed below by posing two key questions:**

1) **Why did no one in the angioplasty group have their CCSVI corrected?**
2) **Why did the UB researchers recklessly use irrelevant clinical data from Phase 2 to make baseless claims that CCSVI correction is of no value for MS and is possibly harmful?**

## Why Did No One in the Angioplasty Group Have Their CCSVI Corrected?

**Dr Siddiqui's Failure –** Phase 2 of the PREMiSe trial failed simply because Dr Siddiqi, the interventional neurosurgeon who did the venous angioplasty, failed to properly open up the blockages in the veins of the MS patients and correct their CCSVI. After undergoing angioplasty performed by Dr Siddiqui and his team, not a single person in the treated group had >75% blood flow restored and thus still had CCSVI throughout the trial. One glaring question is why did Dr Siddiqui fail so miserably.

It is important to note that, in the Phase 1 open label portion of the PREMiSe, Dr Siddiqui was able to restore >75% venous blood flow in all 10 subjects (see data on previous graph and in Appendix 1). Thus, **it is clear Dr Siddiqui is quite capable of correcting CCSVI (100% success in Phase 1).** This proven capability suggests two main possibilities for Dr Siddiqui's complete failure to correct CCSVI in any of the Phase 2 subjects.

**Incompetence or Intentional -** There is a reasonable chance that Dr Siddiqui simply got very nervous during the key Phase 2 portion of the PREMiSe trial and botched each and every angioplasty such that blood flow remained poor for everyone. That is, Dr Siddiqui acted in an incompetent manner when it came to venous angioplasty for correcting CCSVI in the phase 2 subjects. I would emphasize I do not regard Dr Siddiqui as an incompetent interventional neurosurgeon because he was able to successfully correct CCSVI in all 10 Phase 1 subjects.

I am a little reluctant to bring up another possibility for Dr Siddiqui's 100% failure rate for correcting CCSVI in the Phase 2 subjects. However, as an objective scientist (skeptical empiricist and critical rationalist), I always try to look at all possible explanations for a phenomenon and then reject the ones for which there is little or no support.

Another possible explanation for the Phase 2 failure is that Dr Siddiqui purposely did a poor job so as to ensure those receiving angioplasty would not have normal blood flow restored and would not have a better result than the patients in the sham group. The current information which supports this explanation includes:
1) It appears that Dr Siddiqui is very capable of doing venous angioplasty properly when he wants to as demonstrated by the Phase 1 results (10 for 10 successes).
2) A number of the PREMiSe researchers have received and continue to receive large sums of money from the MS drug companies. These companies would be potentially adversely affected by the demonstrated success of the restoration of proper blood flow by angioplasty. Any adverse financial implications for the MS drug companies would translate into adverse financial implications for these PREMiSe researchers. Thus PREMiSe researchers would potentially financially benefit from the demonstration that CCSVI treatment is of no value or possibly harmful. The bottom line is that Dr Siddiqui possibly had a financial motivation for not doing proper angioplasty in Phase 2.
3) Despite the obvious failure of the Phase 2 portion of PREMiSe and the lack of any relevant data for assessing efficacy, Dr Siddiqui still made baseless claims and warnings about CCSVI treatment in an extraordinary public fashion (a Youtube video!). One has to ask why he would do this.

**In summary, we simply do not know why none of the subjects in the angioplasty group of Phase 2 did not have their CCSVI corrected with**

**angioplasty by Dr Siddiqui. I am confident there is a simple explanation for this stark fact that does not involve any unethical behavior. I look to the Buffalo researchers to provide such an explanation so that any thought of unethical behavior can be firmly put to rest.**

## Why Did the UB MS Researchers Use Irrelevant Clinical Data from Phase 2 to Make Baseless Claims that CCSVI Correction Is of No Value for MS and Is Possibly Harmful?

**Introduction –** There can be no serious doubt that the **Phase 2 clinical data have absolutely no relevance or value for assessing the efficacy of correcting CCSVI for MS.** The simple and most powerful reason for this simple statement is that no one in the angioplasty group had their CCSVI corrected. Thus a huge question is **why did the UB researchers purposely use data of no relevance to claim that CCSVI correction is of no value for MS** and may possibly increase disease activity. The answer to this question tells us a great deal about what is really going on in the murky world of MS treatment options, money and politics.

**Past Performance –** As mentioned earlier, some of the PREMiSe researchers (e.g. Zivadinov, Weinstock-Guttman) have a track record of strong, anti-CCSVI bias when it comes to interpreting and spinning scientific findings on CCSVI. Their past performance in this regard is detailed in Appendix 2. As I stated in this 2 year old essay **"There can be little doubt that the CCSVI researchers at the University of Buffalo have a significant, anti-CCSVI bias and want to discredit the concept." Thus it is not overly surprising that the UB researchers are repeating the same pattern of spinning their current, irrelevant data from Phase 2 of PREMiSe into anti-CCSVI claims and warnings about the possible problems associated with getting CCSVI treatment.**

**Motivation –** The question of what would motivate the UB researchers, who did not have any acceptable scientific data to support their claims and warnings, to discourage persons with MS from having CCSVI treatment naturally comes up. The obvious motivating factor is the financial implications for some of the UB researchers and the MS drug companies that generously support them when it comes to CCSVI treatment as discussed above.

**The huge and undeniable conflict of interest that exists when you have researchers who are heavily funded by MS drug companies in charge of testing a non-drug treatment which potentially may negatively affect the drug companies cannot be swept under the carpet. This conflict of interest is the elephant in the room which provides the simplest and thus best**

**explanation for the completely unsupported and baseless claims made by the UB researchers in regards to CCSVI treatment. I cannot think of any other factor which would motivate the UB researchers to act in such an unscientific and unacceptable manner.**

**The most impressive part of UB's scientifically unsupported and baseless campaign against CCSVI treatment was the fear mongering aspect which blatantly involved the suggestion in the Youtube video that not only is CCSVI correction by angioplasty of no value for MS but it may even increase disease activity. Undoubtedly, if a person was considering whether or not to have CCSVI treatment, even a hint that it might worsen MS symptoms would be enough to discourage them. A suggestion of possible harm is a classic way of persuading people against doing something you don't want them to do.**

**It would appear if the UB researchers added this element of unsupportable fear mongering to increase the likelihood that their claims would discourage both MS patients from getting CCSVI treatment and, perhaps more importantly, CCSVI treatment practitioners from continuing to treat CCSVI. Such reduced CCSVI treatment activity would certainly be welcomed by the MS drug companies and the neurological community in general.**

**The irony in all this is that the data collected in both Phase 1 and Phase 2 of PREMiSe actually indicate that angioplasty for CCSVI is safe (no serious adverse effects) and that CCSVI correction may well be of value for MS.**

## Summary

On the basis of the currently available data for the PREMiSe trial, it is clear that:

1. The data collected in both Phase 1 and 2 seem to be reliable.
2. The open label, Phase 1 portion was successful and every subject had their CCSVI corrected by venous angioplasty. Notably, the clinical results of no relapses and only 2 new lesions among all 10 subjects indicate that CCSVI correction may be of significant value.
3. The critical Phase 2 portion of the PREMiSe trial was a complete failure in that all nine subjects which had

angioplasty did not have their CCSVI corrected. Thus no one actually received the designed treatment which was being tested for its efficacy (angioplasty which corrects CCSVI as is clearly stated in the objective of the trial – Appendix 1).

4. The failure to correct CCSVI in any of the subjects of Phase 2 provides a control group of 19 subjects who had CCSVI throughout the trial period. These 19 subjects had 4 relapses and 20 new lesions. These data compared with the very positive data of the 10 Phase 1 subjects who did have their CCSVI corrected indicate CCSVI correction may well be of substantial value for MS.
5. The reason for the failure of the angioplasty procedure in Phase 2 subjects is unknown and this question needs to be clearly answered as soon as possible to put aside any question of unethical behavior.
6. Despite the complete lack of relevance of the results from Phase 2 for assessing the efficacy of CCSVI correction for MS, the PREMiSe researchers launched a major media campaign based on these irrelevant data. In this campaign they - a) falsely claimed their data showed that CCSVI correction by angioplasty was of no value and may be of harm, b) advised persons with MS to not have CCSVI treatment outside of trials, and c) admonished CCSVI practitioners about doing CCSVI treatment.
7. Some of the researchers involved with PREMiSe are in a major conflict of interest in that they would potentially financially gain from a demonstration that CCSVI treatment was of no value and might even be harmful. This may explain why they conducted an unaccetable, negative campaign against CCSVI with no scientific data to support their claims and warnings**.** Notably, this is not the first time that UB MS researchers have exhibited strong, anti-CCSVI bias.

## Recommendations for Action

Based on the above very troubling facts listed in the Summary, the following actions should be taken:

**1)** The University of Buffalo should retract the currently available press release and Youtube video and replace them with ones that contain the real story behind the PREMiSe trial (Phase 2 data cannot be used to assess CCSVI correction efficacy because no one had their CCSVI corrected; claims of no value and possible harm of CCSVI correction are baseless; comparison of Phase 1 and Phase 2 clinical results suggest CCSVI treatment may be of substantial value for MS. **An apology for the earlier release of false and potentially troubling information would be a nice added touch.**

**2)** The University should launch a major investigation into the PREMiSe trial to determine if there were any irregularities or fraudulent actions. Questions that need answering include **a) why did Dr Siddiqui have a 100% success rate for CCSVI correction in Phase 1 and a 0% success rate in the more critical Phase 2; b) were the blinding and randomization processes above reproach; c) what is the extent and magnitude of drug company money being received by various PREMiSe researchers?**

**3)** Drs Siddiqui and Zivadinov should be reprimanded for publicly issuing erroneous, scientifically unsupportable and highly biased statements regarding the value of CCSVI correction for MS.

**4)** The American Academy of Neurology (AAN) should sanction all the PREMiSe researchers and the University of Buffalo for putting out a very misleading press release which was based on irrelevant data and was coloured by a strong, anti-CCSVI bias.

5) The International Society for Neurovascular Disease (ISNVD) should sanction any member who was associated with the PREMiSe trial. This especially applies to Dr Robert Zivadinov who was one of the principle investigators, who has extensive financial ties to the MS drug companies (see poster disclosures), and whose strong, anti-CCSVI bias can no longer be doubted by anyone with a semblance of objectivity.

6) Anyone doing unbiased research on CCSVI should do some serious soul searching when considering working with any of the PREMiSe researchers in the future.

# Appendix 1

## Poster presented at the 2013 annual meeting of the American Academy of Neurology, March 20, 2013

# Appendix 2

## Buffaloed: The anti-CCSVI Bias of the University of Buffalo Researchers and their Unsupported Interpretations, April, 2011

**Comments and questions regarding this objective, in-depth appraisal of the PREMiSe Trial Results can be sent to info@direct-ms.org**

**Poster presented at the 2013 annual meeting of the American Academy of Neurology**

# Percutaneous Transluminal Venous Angioplasty (PTVA) is Ineffective in Correcting Chronic Cerebrospinal Venous Insufficiency (CCSVI) and May Increase Multiple Sclerosis (MS) Disease Activity in the Short Term: Safety and Efficacy Results of the 6-Month, Double-Blinded, Sham-Controlled, Prospective, Randomized Endovascular Therapy in MS (PREMiSe) trial

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## Background

• Multiple sclerosis (MS) is a disease of uncertain etiology characterized by demyelinating lesions affecting the central nervous system.

• In 2009, Zamboni et al. described an association between MS and extracranial venous outflow restrictive lesions detected by extracranial and intracranial venous duplex studies.1

• They named this venous outflow restriction chronic cerebrospinal venous insufficiency (CCSVI). In addition, they introduced endovascular treatment for CCSVI in an open-label study that included 65 MS patients with postprocedure followup of over 18 months.2

• Several subsequent prospective open-label, non-randomized studies investigated safety and efficacy of venous angioplasty in MS. 3-9 Findings from these studies have generated considerable controversy but remain unproven.

## Objective

• To investigate the safety and efficacy of percutaneous transluminal venous angioplasty (PTVA) for correcting CCSVI in MS in the setting of a prospective, double-blind, sham-controlled, randomized pilot trial.

## Methods

### Study Design and Patient Selection

• The study, Prospective Randomized Endovascular Therapy in Multiple Sclerosis (PREMiSe; ClinicalTrials.gov. NCT01450072), was planned in two phases. Phase 1 was an open-label safety study of endovascular venous angioplasty with an intended enrollment of 10 MS patients with CCSVI, whereas phase 2 was sham-controlled, randomized, double-blind, including up to 20 CCSVI-MS patients undergoing either angioplasty or sham procedure. Both phases were of 6 months' duration.

• The study was approved by the University at Buffalo Institutional Review Board and overseen by an independent datasafety monitoring committee. Written informed consent was obtained from all subjects.

• All screening, diagnostic, interventional, and follow-up procedures and visits were performed at no cost to the patients. Data were collected by the investigators and analyzed by an independent statistician.

• Inclusion criteria were as follows: age 18-65 years, Expanded Disability Status Scale (EDSS) score11 of 0-8.5 (0-5.5 for phase 2), active-relapsing MS (only for phase 2) or secondary progressive and/or progressive-relapsing MS,12 and fulfilling, at the time of screening, ≥2 CCSVI venous hemodynamic (VH) duplex criteria in phase 1 and ≥2 VH extracranial criteria in phase 2.13 Active-relapsing disease was defined as one relapse within the past 12 months or presence of contrast-enhancing (CE) lesion(s) on postcontrast magnetic resonance imaging (MRI) within the previous 3 months (only for phase 2) and concomitant treatment with disease-modifying treatments excluding natalizumab (only for phase 2).

• Patients were also required to fulfill screening criteria on catheter venography (CV) defined as azygous vein or internal jugular vein (IJV) luminal diameter reduction ≥50%. CV findings were confirmed by intravascular ultrasound (IVUS), and both studies were performed under conscious sedation with local anesthesia, preceding the endovascular venous angioplasty treatment or sham procedure.

• Randomization in phase 2 was performed by an independent statistician in 1:1 fashion, using sealed and numbered envelopes with predetermined treatments (10 angioplasty, 10 sham angioplasty). No preplanned replacement for subjects not fulfilling invasive screening criteria was included in the protocol. In phase 2, all study personnel, with the exception of the interventional neurosurgeons, were blind to the assigned procedure as were the patients.

**Sham and Venous Angioplasty**

• All endovascular procedures were performed under conscious sedation with local anesthesia. The goal of angioplasty was to restore venous outflow of the stenotic IJVs and azygous vein to <50% of normal proximal venous diameter at the time of intervention. Angioplasty was performed only in the treated, not in the sham arm.

**Endpoints and Follow-up Assessment**

• Primary endpoints of the study were safety at 24 hours and 1 month, venous outflow restoration of >75% at 1 month compared to baseline, as measured by changes in venous hemodynamic insufficiency severity score (VHISS), and effect of angioplasty on new lesion activity and relapse rate over 6 months. Secondary endpoints included changes in EDSS, brain volume, cognitive tests, and quality of life (QoL), including MS Functional Composite (MSFC) scores.

## Results

**Screening, randomization, and blinding:**

• In total, 15 patients signed informed consent in phase 1 and 30 in phase 2 after prescreening qualification procedures were completed. Of those, 5 in phase 1 and 10 in phase 2 did not fulfill noninvasive screening procedure requirements on duplex examination.

• As preplanned, 10 patients were enrolled in open-label phase 1 and 20 in sham-controlled, randomized, double-blind phase 2. Of those, 1 patient in phase 2 did not fulfill invasive screening criteria for endovascular intervention. Hence, 10 patients in the sham-treatment arm and 9 in the angioplasty-treated arm were randomized to phase 2.

**Demographic, hemodynamic, MRI, and clinical characteristics at baseline:**

• The sham and angioplasty treatment arms in phase 2 were well matched for various demographic, clinical, and duplex characteristics with no statistically significant between-group differences (Table 1).

**Safety and tolerability of treatment procedures:**

• All patients in phases 1 and 2 tolerated the endovascular procedure well, and no operative or postoperative complications (vessel rupture, thrombosis, or side effects to contrast media) were identified. No serious adverse events (AEs) weredetected at any time point in phase 1 (Table 2). Half of the patients in phase 1 reported a non-serious AE, but none were related to the treatment procedure (Table 2).

**Venous outflow restoration outcomes:**

• Venous angioplasty restored venous outflow to at least 50% of normal proximal venous diameter in all phase 1 and 2 patients at the time of intervention.

• In phase 1 (Figure 1), there was significant improvement of VHISS ($p<0.0001$) over 6-months that resulted in >75% restoration of the venous outflow compared to baseline.

• In phase 2, improvement was observed also in treatment ($p=0.02$) and sham ($p=0.04$) arms at month 1 but did not reach >75% restoration of the venous outflow compared to baseline. No differences in VHISS improvement were detected between phase 2 treated and sham groups ($p=0.894$).

**Changes in clinical outcomes:**

• No relapses occurred in phase 1. In phase 2, there were 4 relapses in the treated arm (among 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.

• In phase 2, no significant within- or between-group changes in EDSS, MSFC, or 6-minute walked distance were detected.

• No significant between-group changes in cognitive and QoL outcomes were detected in phase 2 patients.

**Changes in MRI outcomes:**

• Table 3 and Figure 2 show changes in MRI measures in the PREMiSe study over 6 months.

## Conclusions

• This is the first double-blind, sham-controlled, randomized trial evaluating PTVA to address CCSVI in patients with MS.

• We found that the procedure was not associated with any serious AEs.

• However, it failed to provide any sustained improvement in venous outflow as measured through duplex and/or clinical and MRI outcomes.

• To the contrary, more sizable change in venous outflow was associated with increased disease activity primarily noted on MRI.

• This study was a limited pilot trial, the results of which caution against widespread adoption of venous angioplasty in the management of patients with MS outside of rigorous clinical trials.

• It also provides validation for conduct of sham-controlled, double-blind trials in the evaluation of novel interventions in complex diseases.

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Study disclosure:

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Potential Conflict of Interest:

• Yuval Karmon, Yu Jinhee, Karen Marr, Vesela Valnarov, Cheryl Kennedy, Deepa P. Ramasamy, Kresimir Dolic, Ellen Carl, Michael G. Dwyer and Niels Bergsland have nothing to disclose.

• Adnan H. Siddiqui has received research grants from the National Institutes of Health and the University at Buffalo (Research Development Award); holds financial interests in Hotspur, Intratech Medical, StimSox, and Valor Medical; serves as a consultant to Codman & Shurtleff, Inc., Concentric Medical, ev3/Covidien Vascular Therapies, GuidePoint Global Consulting, and Penumbra; belongs to the speakers' bureaus of Codman & Shurtleff, Inc. and Genentech. He serves on an advisory board for Codman & Shurtleff; and has received honoraria from Abbott Vascular, American Association of Neurological Surgeons' courses, an emergency medicine conference, Genentech, Neocure Group LLC.

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• L. Nelson Hopkins received grant/research support from St. Jude Medical and Toshiba; serves as a consultant to Abbott, Boston Scientific,* Cordis, Micrus, and W. L. Gore; holds a financial interest in AccessClosure, Augmenix, Boston Scientific,* Claret Medical Inc., Micrus, and Valor Medical; has a board/trustee/officer position with AccessClosure and Claret Medical Inc.; belongs to the Abbott Vascular speakers' bureau; and receives honoraria from Boston Scientific,* Cleveland Clinic, Complete

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**Table 1. Baseline demographic, clinical, and duplex characteristics of patients enrolled in the PREMiSe study.**

| | Phase 1 (n=10) | Phase 2 Sham arm (n=10) | Phase 2 Treatment arm (n=9) | p-value* |
|---|---|---|---|---|
| Female gender, n (%) | 5 (50) | 8 (80) | 5 (55.6) | 0.350 |
| Age in years, mean (SD) median (min / max) | 46.5 (9.4) 47 (25 / 57) | 44.8 (10.5) 47 (20 / 56) | 43.3 (8.2) 44 (26 / 51) | 0.741 |
| Age (in years) at onset, mean (SD) median (min / max) | 34.9 (11.3) 31.5 (18 / 52) | 34 (10.2) 35 (12 / 46) | 32 (10.4) 35 (18 / 46) | 0.644 |
| Disease duration (in years), mean (SD) median (min / max) | 11.6 (7.7) 11 (2 / 22) | 10.8 (4.5) 10 (5 / 18) | 11.6 (9.7) 9 (2 / 31) | 0.827 |
| Disease course, n (%)<br>RR<br>RP<br>SP<br>PR | <br>6 (60)<br>0 (0)<br>3 (30)<br>1 (10) | <br>5 (50)<br>5 (50)<br>0 (0)<br>0 (0) | <br>7 (77.8)<br>2 (22.2)<br>0 (0)<br>0 (0) | 0.350 |
| Number of relapses in the year previous to study entry, mean (SD) median (min-max) | 0 (0) | 0.4 (0.7) 0 (0-2) | 1 (0.9) 1 (0-2) | 0.113 |
| EDSS, mean (SD) median (min / max) | 4.4 (2.2) 4.8 (1.0 / 8.5) | 4.0 (1.5) 4.0 (2.0 / 5.5) | 3.8 (1.5) 3.5 (1.5 / 5.5) | 0.720 |
| MSFC, mean (SD) median (min / max) | 0.06 (0.7) 0.08 (-1.6 / 0.8) | 0.04 (0.4) -0.02 (-0.5 / 0.7) | -0.4 (0.9) -0.3 (-0.2 / 0.7) | 0.198 |
| Distance (feet) walked in 6 min, mean (SD) median (min / max) | 1539.3 (727.6) 1245 (795 / 3215) | 1339.2 (505.5) 1092 (755 / 2130) | 1242.7 (725.5) 1626 (253 / 2050) | 0.738 |
| Type of DMT, n (%)<br>Interferon beta<br>Glatiramer acetate<br>Natalizumab<br>Rituximab<br>Mitoxantrone<br>Combination | <br>4 (40)<br>2 (20)<br>2 (20)<br>0 (0)<br>1 (10)<br>1 (10) | <br>7 (70)<br>2 (20)<br>0 (0)<br>1 (10)<br>0 (0)<br>0 (0) | <br>7 (77.8)<br>2 (22.8)<br>0 (0)<br>0 (0)<br>0 (0)<br>0 (0) | 0.638 |
| Months on DMT, mean (SD) median (min / max) | 37.7 (30.4) 32 (3 / 96) | 81.5 (52.6) 78 (6 / 156) | 47.4 (31.2) 43 (12 / 106) | 0.109 |
| VH CCSVI criterion, n (%)<br>VH1<br>VH2<br>VH3<br>VH4<br>VH5 | <br>10 (100)<br>9 (90)<br>8 (80)<br>2 (20)<br>6 (60) | <br>5 (50)<br>10 (100)<br>10 (100)<br>6 (60)<br>3 (30) | <br>3 (33)<br>8 (88.9)<br>9 (100)<br>7 (77.8)<br>1 (11.1) | 0.566 |
| ≥2 CCSVI VH criteria, n (%) | 10 (100) | 10 (100) | 9 (100) | 1.000 |
| ≥2 CCSVI VH extracranial criteria, n (%) | 10 (100) | 10 (100) | 9 (100) | 1.000 |
| VHISS, mean (SD) median (min / max) | 5.9 (2.2) 5.5 (2 / 10) | 6.1 (2) 5.5 (4 / 10) | 6 (1.3) 6 (5 / 9) | 0.842 |

Abbreviations: PREMiSe=Prospective Randomized Endovascular therapy in Multiple Sclerosis; SD=standard deviation; RR=relapsing-remitting; RP=relapsing-progressive. SP=secondary-progressive; PR=progressive relapsing; DMT=disease-modifying therapy, EDSS=Expanded Disability Status Scale; MSFC=Multiple Sclerosis Functional Composite; CCSVI=chronic cerebrospinal venous insufficiency; VH=venous hemodynamic; VHISS=venous hemodynamic insufficiency severity score

*p value represents statistical analysis between sham and treated arms of phase 2. Analysis between these groups was performed by using chi-square test, Student's t-test, and Mann-Whitney rank sum test, as appropriate.

**Table 1 Legend:**

Abbreviations: PREMiSe=Prospective Randomized Endovascular therapy in Multiple Sclerosis; SD=standard deviation; RR=relapsing-remitting; RP=relapsing-progressive.

SP=secondary-progressive; PR=progressive relapsing; DMT=disease-modifying therapy, EDSS=Expanded Disability Status Scale; MSFC=Multiple Sclerosis Functional Composite; CCSVI=chronic cerebrospinal venous insufficiency; VH=venous hemodynamic; VHISS=venous hemodynamic insufficiency severity score

*p value represents statistical analysis between sham and treated arms of phase 2. Analysis between these groups was performed by using chi-square test, Student's t-test, and Mann-Whitney rank sum test, as appropriate.

**Table 2. Adverse events in patients enrolled in PREMiSe over 6 months.**

| | Phase 1 (n=10) | Phase 2 Sham arm (n=10) | Phase 2 Treatment arm (n=9) |
|---|---|---|---|
| **Description of AE** | 1. Rash due to Doppler sonography at screening,<br>2. UTI treated with antibiotics for 10 days,<br>3. UTI treated with antibiotics for 5 days,<br>4. Intercourse pain (condom-related) that prompted hospitalization for 2 days,<br>5. Neck pain due to car accident, no hospitalization | 1. Immune thrombocytopenic purpura treated with 100mg prednisone once daily<br>2. Bladder infection treated with antibiotics over 10 days,<br>3. Diagnosis of shingles treated with Valtrex (GlaxoSmithKline) thrice daily for 7 days | 1. Cardiac event treated with pacemaker installation,<br>2. Swelling and soreness at left side of the neck; no treatment required,<br>3. Hospitalization for scheduled transobturator sling procedure |
| **Severity of AE** | 1. non-serious<br>2. non-serious<br>3. non-serious<br>4. non-serious<br>5. non-serious | 1. serious<br>2. non-serious<br>3. non-serious | 1. serious<br>2. non-serious<br>3. non-serious |
| **Time point of AE** | 1. baseline<br>2. 6 months<br>3. 6 months<br>4. 6 months<br>5. 6 months | 1. 6 months<br>2. 6 months<br>3. 6 months | 1. 24 months<br>2. 6 months<br>3. 6 months |
| **Relationship of AE to treatment or invasive diagnostic procedure** | 1. unrelated<br>2. unrelated<br>3. unrelated<br>4. unrelated<br>5. unrelated | 1. unrelated<br>2. unrelated<br>3. unrelated | 1. unrelated<br>2. related<br>3. unrelated |

Abbreviations: PREMiSe=Prospective Randomized Endovascular therapy in Multiple Sclerosis; AE=adverse events, UTI=urinary tract infection

AEs are listed in chronological order with individual AEs assigned an increasing number.

**Table 2 Legend:**

Abbreviations: PREMiSe=Prospective Randomized Endovascular therapy in Multiple Sclerosis; AE=adverse events, UTI=urinary tract infection

AEs are listed in chronological order with individual AEs assigned an increasing number.

**Table 3. Changes in MRI measures in the PREMiSe study over 6 months.**

| | Phase 1 (n=10) | Phase 2 Sham arm (n=10) | Phase 2 Treatment arm (n=9) | p-value* |
|---|---|---|---|---|
| Cumulative number of new T2 lesions, mean (SD) median (min / max) sum | 0.2 (0.4) 0 (0 / 1) 2 | 0.3 (0.7) 0 (0 / 2) 3 | 2.1 (2.9) 1 (0 / 8) 17 | 0.066 |
| T2-LV % change, mean (SD) median (min / max) | 1.3 (10.3) 0.6 (-15.9 / 23.4) | -4.7 (11) -1.5 (-21.4 / 12.2) | 13.9 (22.8) 2.9 (-10.6 / 45.8) | 0.04 |
| Cumulative number of T1 lesions, mean (SD) median (min / max) sum | 0 | 0.2 (0.6) 0 (0 / 2) 2 | 0.8 (0.9) 0.5 (0 / 2) 6 | 0.144 |
| T1-LV % change, mean (SD) median (min / max) | -2.9 (32.7) 2.5 (-73 / 28) | -14.6 (33.6) -5.3 (-100 / 14.1) | -10.2 (30.9) -8.3 (-50 / 32.9) | 0.811 |
| Cumulative number of CE lesions, mean (SD) median (min / max) sum | 0.1 (0.3) 0 (0 / 1) 1 | 0.3 (0.7) 0 (0 / 2) 3 | 2.4 (3.2) 1 (0 / 9) 19 | 0.062 |
| CE-LV % change mean (SD) median (min / max) | -100 (0) -100 (-100 / -100) | -94.1 (8.3) -94.1 (-100 / -88.3) | 34.4 (186.3) -44 (-100 / 247.1) | 0.262 |
| Active T2 lesion scan, n (%) | 2 (20) | 2 (20) | 4 (44.4) | 0.321 |
| Active T1 lesion scan, n (%) | 2 (20) | 0 | 4 (44.4) | 0.118 |
| Active CE lesion scan, n (%) | 2 (20) | 1 (10) | 5 (55.6) | 0.145 |
| PBVC, mean (SD) median (min / max) | -0.64 (0.66) -0.65 (-1.86 / 0.24) | -0.74 (0.93) -0.56 (-2.5 / 0.51) | -0.23 (0.84) -0.45 (-1.1 / 1.1) | 0.257 |
| GMVC, mean (SD) median (min / max) | -2.1 (1.2) 2 (-4.4 / -0.1) | -1.84 (3.1) -2.3 (-6.5 / 3.3) | -0.53 (1.6) -0.65 (-2.6 / 1.99) | 0.320 |
| WMVC, mean (SD) median (min / max) | 0.9 (1.5) 0.51 (-0.96 / 4.3) | 0.4 (2.9) 1.2 (-3.8 / 4.4) | 0.12 (2.6) 0.22 (-4 / 4) | 0.841 |

Abbreviations: MRI=magnetic resonance imaging, PREMiSe=Prospective Randomized Endovascular therapy in Multiple Sclerosis; SD=standard deviation; LV=lesion volume; CE=contrast-enhancing; sum=total number, PBVC=percentage brain volume change; GMVC=gray matter volume change; WMVC=white matter volume change

*p value represents statistical analysis between sham and treated arms of phase 2. The analysis between these groups was performed by using Student's t-test.

Statistical analyses between phase 2 sham and treated arms were also adjusted for age, sex, disease duration, relapse rate in the year prior to study entry, and number of CE lesions at baseline. No significant differences were found between these arms, except for T2-LV % change (p=0.05).

Of the 5 patients with active MS assigned to the treated arm in phase 2, cumulative numbers of CE lesions per patient over 6 months were as follows: 9, 5, 3, 1, and 1 (respectively. In the sham arm, one patient had 2 CE lesions and one had 1.

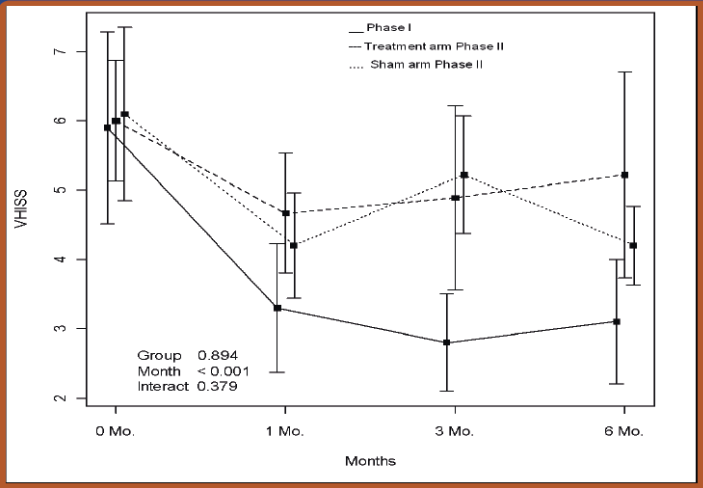


**Figure 1.**
**Changes in venous hemodynamic insufficiency severity score (VHISS) at 1, 3, and 6 months, compared to baseline, in phases 1 and 2 by using mixed-effect model analysis.**
**P-values in the plot are based on comparison between phase 2 groups.**
**Time effect p-values within groups are phase 1 (p<0.0001), phase 2 treated arm (p=0.02), and phase 2 sham arm (p=0.04), respectively.**

## Legend Table 3

- Abbreviations: MRI=magnetic resonance imaging, PREMiSe=Prospective Randomized Endovascular therapy in Multiple Sclerosis; SD=standard deviation; LV=lesion volume; CE=contrast-enhancing; sum=total number, PBVC=percentage brain volume change; GMVC=gray matter volume change; WMVC=white matter volume change

- *p value represents statistical analysis between sham and treated arms of phase 2. The analysis between these groups was performed by using Student's t-test.
- Statistical analyses between phase 2 sham and treated arms were also adjusted for age, sex, disease duration, relapse rate in the year prior to study entry, and number of CE lesions at baseline. No significant differences were found between these arms, except for T2-LV % change (p=0.05).
- Of the 5 patients with active MS assigned to the treated arm in phase 2, cumulative numbers of CE lesions per patient over 6 months were as follows: 9, 5, 3, 1, and 1 (respectively. In the sham arm, one patient had 2 CE lesions and one had 1.

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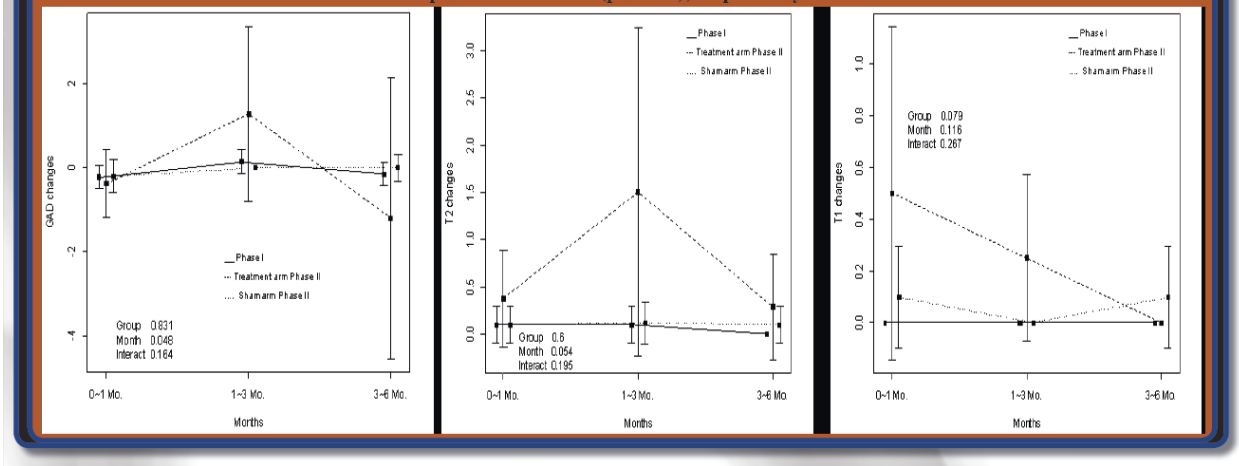
**Figure 2. Changes in accumulation of mean new contrast-enhancing (CE) lesions (left), mean new T2 lesions (middle) and mean T1 lesions (right), between 0-1, 1-3, and 3-6 months in phases 1 and 2, by using mixed-effect model analysis. Some means for new T2 and T1 lesions have standard error=0 since only values of 0 are presented. P-values in the plot are based on comparison between the phase 2 groups. Time effect p-values within these groups are for mean new CE lesions: phase 1 (p=0.198), phase 2 treated arm (p=0.593), and phase 2 sham arm (p=0.766), respectively; for mean new T2 lesions: phase 1 (p=0.617), phase 2 treated arm (p=0.254), and phase 2 sham arm (p=0.991), respectively; and for mean new T1 lesions: phase 2 treated arm (p=0.057) and phase 2 sham arm (p=0.776), respectively.**



# Buffaloed: The anti-CCSVI Bias of the University of Buffalo Researchers and their Unsupported Interpretations

**Ashton Embry, April 19th, 2011**

## Introduction

Last week researchers from the University of Buffalo published the results of their 2009 research on the prevalence of CCSVI in various groups of people including 289 persons with MS, 21 persons who had experienced a clinically isolated syndrome (CIS) (often a precursor to MS), 163 healthy controls and 26 subjects who were suffering from other neurological diseases. The paper was made available online on the website of the medical journal Neurology (http://www.neurology.org/content/early/2011/04/13/WNL.0b013e318212a901.abstract ) and the University also issued a press release (http://www.buffalo.edu/news/12469) summarizing the main points in the paper. These same results were made public 14 months ago in February, 2010.

In this essay I will demonstrate that in reporting and interpreting these results, the researchers have displayed a clear and strong anti-CCSVI bias. I find this very disturbing because in the past the researchers have portrayed themselves as a neutral group wanting to only determine the "truth". Because of this neutrality claim, the charity I am associated with (Direct-MS) has provided funding for CCSVI research at the University of Buffalo over the last 16 months. We would not have done so if we had known the researchers had a such a significant anti-CCSVI bias because such a bias cannot help but negatively affect their research effort and their publications as well as the public's perception of CCSVI.

Direct-MS is interested in funding only scientists who produce reliable results and who objectively interpret such results. Whether such results support or disprove CCSVI is not a concern. We want the real story not a desired one.

It is now painfully clear that the University of Buffalo CCSVI researchers are not capable of producing objective interpretations regarding CCSVI and MS and thus are not interested in the real story. The data they have produced are considered to be reliable but their interpretations of these data are so biased and unsupported that they are inconsequential and have to be ignored.

## Anti-CCSVI Bias in Data Reporting

The first obvious anti-CCSVI bias in the paper relates to how the percentage of persons having CCSVI was calculated for each group. For a diagnosis of CCSVI, two of five, blood flow parameters must be detected by Doppler technology. Unfortunately the Doppler technician had a problem with determining parameter 2 in a number of patients and, in 30 of these patients, one other parameter was positive. This created a problem of how to classify such patients (called

borderlines) who tested positive for one of four parameters and may well have gotten a diagnosis of CCSVI if the last parameter could have been evaluated.

An anti-CCSVI bias would assign all borderlines to the negative CCSVI category despite the fact that the chance of all 30 borderline subjects being negative for parameter 2 is very remote. An unbiased approach would be either to exclude such borderline subjects from the statistics or to assume half of the borderlines were positive for parameter 2, and thus had CCSVI, and half were not.

The authors offer CCSVI percentages based on both a fair approach (borderlines excluded from the calculations) and an anti-CCSVI bias approach (assumed all borderlines were CCSVI negative). However, in their reporting of CCSVI prevalence throughout their Discussion section, they used only the anti-CCSVI biased numbers. This allowed them to unfairly downgrade CCSVI association percentages. For example, with an unbiased approach, 62% of those with MS have CCSVI whereas with the anti-CCSVI approach only 56% have CCSVI.

Overall, this is a minor point because the key ratio of persons with MS and CCSVI versus healthy controls with CCSVI is essentially unaffected and remains at ~2.5. However, by frequently quoting the biased and unrealistic, lower percentage for CCSVI prevalence in MS, the authors make it seem CCSVI is not as common in MS as it really is. This statistical trick provides the first indication that we are not dealing with objective researchers.

**Anti-CCSVI Bias in Discussion of the Results**

The largest and most blatant anti-CCSVI biases in the paper are found in the Discussion section. First of all, the authors completely downplay their key finding that CCSVI is far more common in MS patients (62%) than in the general population (26%). The one mention of this major result is at the start of the section where they say “Our findings are consistent with increased prevalence of CCSVI in MS” and then they downplay it even more by adding a “but” statement - “but substantially lower than the originally reported sensitivity/specificity rates in MS”. Given that the main question the research was designed to solve was whether or not CCSVI was significantly more prevalent in those with MS than the general population, such a lack of discussion and trumpeting of a very important, positive finding demonstrates the significant anti-CCSVI bias of the authors..

In the next paragraph of the Discussion, the authors report the percentages of CCSVI in the various groups using the biased percentages (“**only** 56.1%”) and then claim “These findings point against CCSVI as having a primary causative role in MS”. Such a claim is completely unsupportable. The fact that CCSVI has a much higher association in MS says it may have a causative role but not necessarily. However, association data for other categories cannot possibly be used to argue against (or for) causation.

For a factor to be considered a probable cause, one needs higher association (which the Buffalo data clearly and indisputably demonstrate), the presence of the factor before disease onset (no data presented in paper) and plausible biological mechanisms which link the factor to the disease process (no data presented in paper). The association data for the other groups have absolutely no bearing on whether CCSVI is a causal factor or not for MS. The fact that the authors try to spin the data and claim it argues against causation indicates an incredible anti-CCSVI bias on their part as well as a lack of understanding of how a causal relationship between MS and a given factor can be reasonably determined

In the third paragraph, the authors claim that their association data argue against the published claim that lesions which cause CCSVI are congenital truncular venous malformations. This is false logic given the only way one can determine the origin of the lesions is to image the lesions with selective venography and intravascular ultrasound (IVUS). The association data have absolutely nothing to say about the nature of the lesions which are causing CCSVI in the various groups. Notably, selective venography and IVUS have clearly shown that many lesions causing CCSVI are indeed congenital malformations and the authors are well aware of this fact.

Given the above, the authors have exhibited both fervent anti-CCSVI bias and a tendency to ignore established data which do not fit their anti-CCSVI views. I assume the authors included their baseless attack on the existence of congenital lesions in CCSVI because, the established existence of such lesions which are formed before the MS disease process begins, in combination with the high association of CCSVI with MS (confirmed by the authors), and the well accepted, plausible biological mechanisms which link CCSVI to the MS disease process, leave little doubt that CCSVI is indeed a causal factor in many people with MS. It is not hard to understand why anyone with an anti-CCSVI bias wants to try to discredit a key aspect (e.g. lesions are congenital) of the well supported interpretation that CCSVI is very likely a causal factor for MS in many cases.

In paragraph four of the Discussion, the authors try to claim, on the basis of their data, that CCSVI is “a consequence of rather than cause of MS”. They do this on the basis of the data which show CCSVI prevalence becomes higher in more progressive forms. On the basis of these data alone one could say either MS causes CCSVI or that the presence of CCSVI causes more severe MS. The clear anti-CCSVI bias of the authors is unmistakable given the fact they only mentioned the first possibility (argues against CCSVI) and not the second one (argues for CCSVI). Researchers with even a semblance of objectivity would have mentioned both obvious possibilities and perhaps indicated what observations might decide the question of which explanation is more likely.

Notably, available research on the nature of the some lesions involved in CCSVI demonstrates beyond a reasonable doubt that CCSVI is not caused by MS. Such

lesions include webs, septa, inverted valves, malformed valves and external pressure from a bone or artery. It is impossible that such lesion types are caused by the MS disease process and thus any claim that the MS disease process is causing CCSVI has absolutely no support or validity. The fact that the authors completely ignore this obvious fact, which they are well aware of, is of great concern and leaves no doubt as to their complete lack of objectivity.

**Press Release**

The title and content of the press release which accompanied the publication of the paper were incredibly biased. This is an even more serious problem than the pervasive anti-CCSVI biases in the scientific paper because most public reporting of the research relies solely on the information in the press release.

The title of the press release is “Higher CCSVI Prevalence Confirmed in MS, but Meaning of Findings Remains Unclear”. An unbiased and honest title would have been “Higher CCSVI Prevalence Confirmed in MS”. The solid and indisputable confirmation of significantly increased prevalence of CCSVI in persons with MS is scientifically very important and is the big story.

The best they could say about the significantly increased prevalence of CCSVI in persons with MS is “While this may suggest an association between the MS and CCSVI”. Such a complete downplaying of their most important and uncontestable finding, and one which helps to establish CCSVI as a causal factor in MS, again indicates that the authors have a strong anti-CCSVI bias. An objective researcher would have said the results solidly confirm that CCSVI is associated with MS beyond a reasonable doubt and emphasized that this was by far the most important result of their research.

The authors also made sure they included in the press release the completely unsupported statements that “that chronic cerebral venous insufficiency may be the result of multiple sclerosis, not a cause” and that “These findings indicate that CCSVI does not have a primary role in causing MS". It was these inflammatory and entirely false, anti-CCSVI statements that made headlines in papers and on TV news channels in North America and Europe, thus completing a smear job on the concept that CCSVI may well play a key role in MS.

**Discussion**

There can be little doubt that the CCSVI researchers at the University of Buffalo have a significant, anti-CCSVI bias and want to discredit the concept. The entire neurological community shares the same anti-CCSVI bias. The simplest explanation for such a bias is the fact that if CCSVI treatment replaces drug therapy for MS, the neurologists stand to lose huge sums of money. Notably, the neurologists involved in the University of Buffalo research reported very extensive financial ties to pharmaceutical companies in the disclosure portion of the published article. Thus it is quite understandable that neurologists, including those at the University of Buffalo, are doing what they can to discredit the

concept of CCSVI. Very few people would not fight against a concept that has the potential to greatly decrease their earning power.

So why would the University of Buffalo workers undertake such research in the first place. The most obvious and simplest answer to this question is that they were sure that the CCSVI concept had no merit and they wanted to be the researchers which proved there was no association of CCSVI with MS. There is nothing wrong with this motive and science progresses on the desire to falsify concepts. I would have liked to have been there when they realized their research effort clearly showed there was an undeniable association between MS and CCSVI. They must have been very surprised and dismayed that they did not achieve their goal of dispatching CCSVI to the garbage heap.

Notably, after the Buffalo researchers announced the positive results of their research in February, 2010, other research teams lead by neurologists immediately started to do research to prove CCSVI was not associated with MS. The University of Buffalo researchers had failed to get the job done so it was now up to others to save the neurological community from the potential devastation CCSVI might cause. Because of the urgency to discredit CCSVI as a factor in MS, these new studies were quick and dirty and a number of them were published in less than 6 months after the research was started, an unprecedented turnaround. This fact alone suggests a lack of scientific integrity of these studies which predictably found no association of CCSVI and MS. Few people outside of the neurological community have taken these studies seriously.

The University of Buffalo researchers had spent over a year and a great deal of money on their MS/CCSVI association study so they had to publish it. This put them in the dilemma of how to publish a study which was positive in terms of CCSVI and MS when their main goal was to falsify CCSVI. We now know how they solved that problem. In their formal publication and in the all-important press release which accompanied it, they greatly downplayed their main finding that CCSVI was indeed associated with MS.  On top of this, they concocted completely unsupportable claims that their data suggested that CCSVI has no causal role in MS and CCSVI is likely an effect rather than a cause of MS.

The bottom line is that their data clearly show that CCSVI is indeed highly associated with MS and their data in no way indicate either that CCSVI is not a cause of MS or that it is an effect of MS. This is the real message their research has delivered.

**Reconciling the Buffalo findings with CCSVI testing and treatment findings**

About 20,000 persons with MS have been tested for the presence of venous blockages with selective venography and about 90% of them have been found to have significant blockages which required angioplasty to restore normal flow. Furthermore, MRV flow studies (very different from the MRV structural studies done at the University of Buffalo) of thousands of MS patients also indicate that about 90% have abnormal venous flow. Thus any question that CCSVI is not highly associated with MS has been put to rest.

An obvious question becomes why did the Buffalo researchers find only 62% of persons with MS have CCSVI whereas selective venography and MRV studies are finding venous blockages and flow problems in about 90% of persons with MS. I think the answer to this lies in the Buffalo data that are in the published paper. It was found that about 90% of persons with MS who were tested for all five parameters had at least one abnormal blood flow parameter. I suspect a single abnormal parameter as measured by Doppler may well indicate a significant blockage and associated flow problems which are imaged by MRV and selective venography.

**The Future**

It is now well established by large, well controlled association studies such as that of the University of Buffalo and by thousands of selective venographies and MRVs that CCSVI is highly associated with MS. We don't need any more small, poorly done, association studies using non-invasive techniques administered by inexperienced technicians and supervised by anti-CCSVI neurologists. However, we will continue to see such studies as the neurologists continue to try to discredit CCSVI. I suspect that the seven association studies currently being funded by the MS societies and supervised by neurologists will be negative in regards to CCSVI. There are 10 billion reasons why this will happen.

Of course, the research that needs urgently to be done is an objective and comprehensive clinical trial which tests the effectiveness of venous angioplasty for MS. The thousands of reliable and well documented (video) reports of significant symptom improvement following venous angioplasty suggest such a trial will yield a positive result. Thus such a trial presents a huge threat to future cash flows of neurologists so I expect it will be quite a fight to get one funded and completed in a rigorous and objective manner. One can imagine the monumental efforts that will be made by some anti-CCSVI factions to try to ensure that any CCSVI clinical trial that gets off the ground will have a negative result.