

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



### Transcript of live Web forum: CCSVI and what it could mean to people living with multiple sclerosis

Broadcast live from Toronto, Canada on Wednesday, April 14, 2010 at 12:00pm EST

Panelists: Dr. Paolo Zamboni, Dr. Robert Zivadinov, Dr. Andrew Common, and Dr. Aaron Miller.

[ Start ]

>> Hello and welcome everyone. My name is Jay McBride and I'll be moderating today's webcast focusing on chronic cerebrospinal venous insufficiency also known as CCSVI, and what it could mean to the future of people living with multiple sclerosis. Our program today is co-sponsored by the National Multiple Sclerosis Society and the American Academy of Neurology.

I'd like to welcome the journalists on site and our international online audience and thank them for joining us for this educational forum. Before I introduce our distinguished group of panelists, I just wanted to address the fact that this forum was established to address the most prominent questions that the media and the general public have about CCSVI. The panelists will try and answer as many questions as time permits over the next 90 minutes.

We will alternate questions from our on-site audience and our online participants. And because we have almost 4200 people from around the world registered to participate in today's web forum, the questions that we'll be answering are those that could apply to the greatest number of viewers. So we regret that we cannot answer any personal medical questions.

Now, I like you to meet our panelists, each of which will speak briefly about CCSVI, after which we'll open up the floor and the lines to questions. Down there on the end, we have Dr. Paolo Zamboni, Director of the Vascular and Diseases Center at the University of Ferrara, Italy. Next to him is Dr. Robert Zivadinov, Associate Professor of Neurology at the University of Buffalo at the State University of New York. Next to him is Dr. Andrew Common, Radiologist-in-Chief at Saint Michael's Hospital at the University of Toronto. And finally on my right I have Dr. Aaron Miller, Professor of Neurology and Director of the MS Center at Mount Sinai New York. Dr. Miller is also a member of the AAN Board of Directors and Chief Medical Officer of the National Multiple Sclerosis

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



Society. Dr. Miller, let's begin with you, if you could please just give us a short overview about MS and the disease process.

[ Pause ]

>>Thank you, thank you, Jay. First of all, I'd like to reiterate Jay McBride's welcome to all of you who are here live at the American Academy of Neurology Annual Meeting, including some of my esteemed colleagues from the world of MS who share my passion and concern for every person with MS, and also my greetings to those of you who have joined us from around the world. Multiple sclerosis is an autoimmune inflammatory disease. It primarily affects the young adults. It has an extremely variable and unpredictable course. We are very fortunate that we have a number of medications that have been proved by vigorous scientific investigation to have a significant impact on the course of multiple sclerosis in many people. However, we're left with many questions about MS. What causes the disease? What triggers the inflammation? Why do some people go on to have a progressive course of deterioration and others don't?

As someone who has spent most of his adult life in the research and care of people with multiple sclerosis having shared in the heartbreaking challenges that persons with MS face, I'm greatly encouraged by the diversity and potential of new treatments that are on the horizon. Still, I know that people with MS want answers now. I can tell you that good things are happening in the world of MS.

[ Pause ]

>> The first drug to improve walking in multiple sclerosis was approved in the United States and marketed just a month ago. The first oral therapy that modifies the disease will be reviewed by an FDA advisory panel on June the 10th, and we're making strides in beginning to be able to find ways to repair the nervous system. And with the newer medications that are in advanced stages of testing, we've seen extremely encouraging results, with some drugs appearing to reduce the rate of relapses to perhaps as little as one attack in 20 years.

When a new discovery is made that impacts the MS community, it sparks many questions and it should stimulate rigorous discussion and debate. Right now, people around the world with MS are engaged in these discussions about what CCSVI might mean for them. Investigators and scientists in the MS research community need to engage in those same rigorous discussions as they plan the proper ways to conduct

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



scientific investigation of this new lead. I'm pleased to be here today to explore with my colleagues an interesting avenue of potential research in multiple sclerosis that has prompted a lot of interest over the last few months, chronic cerebrospinal venous insufficiency or CCSVI. We're going to hear directly in a few moments from Professor Zamboni and Dr. Zivadinov about their work in this area, and my job here is to set the stage for the next couple of hours.

Recent preliminary studies reported by Professor Zamboni have suggested an association between CCSVI and multiple sclerosis. CCSVI is an abnormality in the blood drainage from the brain and the spinal cord. Based on Dr. Zamboni's initial work, larger studies have already been initiated to investigate this further. Dr. Zivadinov will discuss some of his work on that subject in a little while. In addition, Dr. Zamboni's pilot work is leading to large scale studies to investigate whether correcting CCSVI through endovascular surgery which involves inserting balloons or in some cases stents into blocked veins in order to improve the blood flow out of the brain and spinal cord has any effect on the MS disease process.

But in order for the MS world to understand the long-term benefits and the risks of procedures related to CCSVI, it's very important to balance the need for due speed with the importance of understanding that we must apply rigorous scientific investigation which can only come about through the conduct of properly controlled trials to understand this phenomena. We want to make sure that we provide the best information for all people with MS so that they can make informed decisions about their future.

Because of the many years that I've worked with the National MS Society, I know that they share the public's sense of urgency in advancing any lead that may help us to understand the cause, provide the cure, or improve the course of multiple sclerosis. Accordingly, the National MS Society and the Canadian MS Society have responded dramatically to this new lead. In December, they sought applications through requests for proposals for new research to study this phenomenon. By February, a number of research proposals came forth from seven different countries throughout the world. In May, an international panel consisting of both neurologists and vascular experts will conduct an expedited review of all applications received through this process. In June, the funding decisions will be announced. In July, it is expected that the work will begin.

As you will hear, the early findings about CCSVI are surprising and intriguing, but a number of questions remain about how, when, and indeed whether CCSVI has any role

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



in the nervous system damage seen in multiple sclerosis. Only through scientific, rigorously controlled investigations will we be able to answer those questions. Some of the questions raised in the preliminary CCSVI research that we need to address, and some of which will be discussed today, include the question of whether or not other investigators in larger scale trials can confirm the initial results reported by Professor Zamboni and his colleagues. And if CCSVI does occur in MS, how common is the problem actually?

>> It's interesting to note already that the results of Dr. Zivadinov as reported are very substantially different quantitatively from the results that Professor Zamboni reported. If indeed CCSVI does occur in patients with multiple sclerosis, what does it have to do with the course or the severity of the disease and how would we go about determining whether people who have CCSVI and multiple sclerosis might benefit from surgical approaches to relieve that problem. And if they do achieve any benefit, are those benefits temporary or longstanding? Why have the preliminary results been associated with such a high percentage of recurrence of these abnormalities in the jugular venous system? And how can we address the known risks of endovascular surgery?

By acknowledging these questions, we will be better able to design the proper research necessary to secure the needed answers. While this research work is underway, we recognize that people with MS have many questions. Should I be tested for CCSVI? If I have signs of CCSVI, should I have surgical treatment? A very important question for people with MS -- How can I get involved in research in CCSVI? And patients ask, does CCSVI mean the standard treatments for MS are meaningless? To that, I can take the liberty of answering an empathic no. The drugs that we currently have available for multiple sclerosis have been demonstrated by replicated scientific work to having impact in reducing the relapse rate in the most common form of MS.

At this point, I'd like to turn the floor back to Jay McBride so we can hear from my colleagues, Dr. Zamboni and Dr. Zivadinov and then Dr. Common on what the current CCSVI research indicates and what they believe the next steps should be in building on and determining the implications of this research for people who are living with MS. Thank you.

[ Pause ]

>> Thank you very much, Dr. Miller for that overview. And now I'd like Dr. Zamboni to come up and maybe, Dr. Zamboni if you could talk about your research up to date on

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



CCSVI and what you think we understand so far and what needs to be determined for further research.

>> Thank you. Good morning to everybody. And thanks to the Society for the opportunity to be here and to clarify points. CCSVI is a combination of a narrowing in the main outflow route from the brain or from the spinal cord especially our azygous vein and internal jugular vein with opening of collaterals and insufficient drainage proven by MRI perfusion study that are--actually presented at the American Academy this year. In addition, venous pressure in the blocked vein was measured and shown to be significantly increased in CCSVI.

After the first publication, Dr. Zivadinov in the other group investigated people with color Doppler examination. We found the 100 percent association and zero percent in control by using combination of venography and color Doppler. This is substantially different methodology with respect to the other group. Dr. Zivadinov presents here in the American Academy a poster showing a rate in MS prevalence between 56 and 62 with borderline and 22 percent in the normal controls . Mamoon recently published 84 percent prevalence and zero percent in control. This is for middle orient. Simka from Poland found 90 percent of MS, no data about control. So this means that this CCSVI is present, is found in different latitude and in different people with genetic background from the Italian initial group. Thoracic pump aspiration with a motor energy of venous blood return, and we may measure very high flow velocity close to the chest. And this velocity reduce the lateral pressure and create a normal emptying from the deep cerebral veins to the sinuses, and from the sinuses to the main inflow route. When you have a block, you have a flow velocity reduction, increases left lateral pressure and activation of collateral circles that try to bypass the obstacles which reduces the risk of venous hypertension but create an insufficiency of drainage of the central nervous system. The vascular community agreed to put the stenosis found in the jugular and the azygos vein among truncular venous malformation that have congenital malformation developing between the third and the fifth months of pregnancy and is well known. You may see in panel a comparison between the external iliac vein congenital developmental malformation with left internal jugular vein. You may compare the inferior vena cava creating a [inaudible] in the liver with the membranous obstruction of the internal jugular vein. So the vascular community published this in a consensus document called diagnosis and treatment of venous malformations, a consensus

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



document of the IUP [International Union of Phlebology], which is the largest scientific society involved within venous disease in the world. Catheter venography is the gold standard. You may see easily what is a normal jugular vein in aortic control and what means CCSVI. This is the ruin of the jugular vein. You may see stenosis and collateral circulation as showed in the caption in the movie. What we may see now the diagnosis. Catheter venography, no doubt, is the gold standard in medicine. MRV was use to try to demonstrate CCSVI, but MRV are very low diagnostic accuracy. This has been demonstrated recently in a paper published in 2010 in International Angiology. Because MRV with a good accuracy in measuring the cross-sectional area but is not capable to detect intraluminal sector valve malformation, the membranous obstruction, that have a majority of [inaudible] obstruction. Azygous cannot be studied due to the movement of the heart. Color Doppler is a fast diagnostic step in venous truncular malformation. It is a level A recommendation of the IUP consensus document published last December. Color Doppler gives indirect information of the azygous system as well morphological and hemodynamic information on the outflow through the internal jugular veins. In trained operators, color Doppler show that the satisfactory reproducibility 0.88. You may see by high resolution venography and normal valve above that can be easily seen opening and closing. And you may see a valve malformation, a septum that cannot be crossed by the blood flow. So this is very clear as a noninvasive screening by using our methodology.

Regarding treatment, percutaneous transluminal angioplasty, PTA, was the only published technique. And please, refer just to what is published, not the blog of patient. PTA was demonstrated to be safe. Stenting was never used in consequence of the high risk of migration, we do not have currently-knowledge of the fate of metallic stent implanted at long-term in the venous wall in people with life long expectancy, like young people affected by MS, and for the lack of dedicated material.

>> So, we do not recommend to use stenting procedure. PTA in the jugular vein showed high rate of restenosis from 29 to 47 percent, but in the azygous did not. However, PTA can be safely repeated and they are recommended to use this instead of the stenting procedure. Influence on PTA on MS outcome in the internal vascular surgery studies cited by Dr. Miller. Significant reduction of relapses, significant reduction of active lesion, improved multiple sclerosis functional composite, improved quality of life also in secondary progressive and primary progressive people. Significant decrease

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



in chronic fatigue, and probably chronic fatigue is the symptom of CCSVI. This study is of course is a pilot study and presents shortcoming, absence of control group and of blinded assessment. This is certainly not rigorous study. We need of this in order to plan further controlled study is it on the results of this pilot study.

We also designed a pilot study together with the Buffalo group that is called endovascular treatment multiple sclerosis study. We divided our patient population in two groups. The first group underwent immediate treatment is immediate endovascular treatment group and the second group, delayed endovascular treatment group, was operated on 6 months later. So, for 6 months, you take the opportunity to measure clinical and MRI outcome with very rigorous protocol, and this is under the way of publication. We know just vascular outcome. Treatment also in this group with endovascular angioplasty was safe and well tolerated. Rate of restenosis was decreased with respect to the first study, 0 percent in the azygous, 29 percent in the internal jugular vein, and the vascular treatment MS study evaluated its clinical outcome measure, MRI conventional and non-conventional measure, including longitudinal data on iron deposition. Complete statistical analysis is under the way by an independent statistician and we plan to present this at the next ECTRIMS meeting.

Perspectives, these are some perspectives in our center. From the point of view of the basic sciences, we are creating a model of endothelial cells modification at the transcriptional level modulated by the known and measured hemodynamic stimuli. Through the point of view of epidemiology, we are planning together with Italian Society of MS the blinded studies on CCSVI prevalence in our country. Genetics, we investigated mutation in genes involved in venous apparatus development in the locus related to multiple sclerosis susceptibility. This pilot study is in press that is under embargo, and we reveal the results very interesting from my point of view next month. Pathology of venous malformation, including morphology and proteomics, and under the way of publication together with the genetic group. Pathophysiology included advanced MRI and non-conventional technique. Our working group, together with Robert Zivadinov in Buffalo, on treatment. We are planning together with the Italian MS Society a vigorous randomized controlled trial to compare treatment of CCSVI with and without the additional tool of angioplasty. Thank you for your attention.

[ Pause]

>> Dr. Zamboni, thank you very much for sharing that valuable information. Maybe you could just kind of summarize what you can conclude from the research that you've

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



completed so far, speaking to what you believe researchers could build on from your work and what more we need to learn in order to determine what the suggested relationship between CCSVI and the disease process in MS might be.

>> Yes, this is really work in progress. We proved the association, and this I think that's very important and we cannot think that it is so strong association that's not have a connection with the mechanism of the disease. We also have important data seen from the point of view of vascular pathology. If you look at the veins, the central vein in the active plaque by histology, you find that the vein is encircled by iron deposition and red blood cells travasation, and this is characteristic of chronic venous disease or impaired drainage, and this I think that may influence the immune system because of CCSVI associated to MS and I invite the experts in the immunology to look at this point. Also, we have the evidence of fibrin cuff that encircled the vein. This is very important because a vascular pathology fibrin cuff means venous hypertension, it's the marker of venous hypertension. And also, together with Robert Zivadinov, we've found reduction of that CSF flow, so reduction in CSF flow dynamics, and this suggest that you have a less reabsorption due to venous hypertension and probably you have an increased pressure of the level with superior sagittal signs and this need to be investigated. But also, the pathophysiology of CSF flow is deeply modified by this because CSF flow in the mirror of the disease because of the majority of data of immunology comes from the CSF flow examination and this is very important to know that CSF flow dynamics is deeply modified by the presence of CCSVI. From this point of view, you may easily understand that any opportunistic infection, virus, of a different course. And also, you have to understand that extravasation of red blood cells is a very important stimuli. For example, complement is activated by membrane of erythrocyte that slowly overload chronically from the third most of life, the central nervous system. I think that this is a new spectacular finding that needs investigation. I am not an immunologist, unfortunately, but I invite colleagues to investigate this point.

>> Thank you again, Dr. Zamboni, and now Dr. Zivadinov, if you could come up to the podium. Maybe you could speak to the research that you've presented here at the AAN Annual Meeting and what the next steps might be that better understand and build on that research.

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



>> Chairman, ladies and gentleman, thank you for the opportunity to present on the CCSVI and this research we are doing. Before I start, I would really like to acknowledge the elephant in the room. As you know, there is really enormous amount of attention and interest in this work, and clearly today, availability of connection brings tens of thousands if not millions of people together in what maybe couple of years or decades ago would just be a conversation between handful scientists about this problem . Clearly this is something different now. But because of all this attention, I think that we as researchers and medical caregivers, it would be irresponsible from us not to put even more attention on this.

>> When any new diagnostic test or new treatment standard of care is proposed, there is a classical ethical tension. And in this case, this ethical tension is even higher because of the urgency in this research. What usually is ethical might be challenging to determine because what is right might be really in conflict with something else that is right. And I think that in the case of the CCSVI, we should really balance the scientifically rigorous research with respect of the patients' needs and rights, needs to know the results and rights to really grapple with this devastating disease. Clearly, all this is so important I would say for the community of MS that MS work on CCSVI should proceed under the microscope of the public and scientific scrutiny. And allow me to just before I start with my scientific part, point to a couple of I think important points. First one is, I think that CCSVI as we heard might really expand the understanding of the MS disease process in patients with MS. Also, whether the CCSVI might not be applicable to every patient with MS according to our study that I will present to you in a second. probably it is important for a number of MS patients and the prevalence we found might be compared to the established risk factors for MS. I think that research on this point, which is as you heard one of the central sources from Dr. Miller's central points at this time at the first step into the CCSVI might proceed in a blinded studies under really traditional ways of how the research is done. I think that clearly it was already alluded that diagnosis and treatment are important point and I think that we are as researchers we do research. Our goal is 1700 people that we are going hopefully to recruit in the CTEVD study to demonstrate what is the real prevalence of this problem. But when it comes to diagnostic and treatment, I think this should remain in the domain of the providers. Diagnosis and treatment is not at this time the business of researchers like us

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



who are proceeding on the studies. We also have to take into account that to do research, clearly funding is needed and most of the funding at this time is remaining with the traditional understanding we welcome all new endeavors like from NMSS Society and others to provide a piece for this type of research. But at this time, clearly the funding is coming from the biggest stakeholders in this research, and these are patients themselves. I can speak probably for a long time about this point but I really think that you didn't come to hear a presentation about ethics on CCSVI but really about what we found in the CTEVD study.

So the CTEVD study was a blinded study in which we applied ultrasound Doppler according to Zamboni criteria and MRV on subpopulation of patients in order to understand what first is main in point in prevalence, differences between the study groups including MS patients, healthy controls, and patients with other neurologic diseases. We also planned to correlate the MRI, these findings with MRI, clinical, environment, infective and genetic outcomes. Originally, we plan to include 1700 subjects between clinically definite MS, more rare types of disease like pediatric patients, patients experiencing their first clinical attack and with uncertain diagnosis called radiological isolated syndrome. We also had about 600 controls divided between the healthy controls and patients with other neurologic disease divided in three different groups, people with inflammatory disorders, vascular disorders, and neurodegenerative disorders. With respect to the progress of the study on blinding, it was originally planned in three phases. After 500 of 1,700 subjects were collected, we took the privilege at that time to rationalize that we should continue with thousand or 1700 subject collection after the first 500 data. The first 500 patients were collected by the end of 2000--sorry, subjects, by the end of 2009, and the results will be presented just in a minute by me and tomorrow as part of the normal session. The CTEVD phase 2 studies waiting for funding. We have a lot of new ideas how to improve what we did on the first 500 subjects. Because of the enormous interest in this research, we extended the recruitment nationwide by the end of 2009. Of the 500 subjects included in the CTEVD study, there are 499 were eligible for statistical analysis. One secondary progressive patient was examined twice and on both exams he was positive for CCSVI and only one assessment was used. 374 subjects were assessed on the 5 CCSVI criteria --they're assessed on all five criteria but there are 125 were not assessed on criteria number 2, Zamboni criteria number 2, which are deep cerebral veins because of the technical difficulty we had. So there are three terms that we use for the prevalence, those who have the CCSVI certainly, those who do not have CCSVI certainly, and those who are borderline. So, 42 subjects in the CTEVD study did not fit any of the four other criteria.

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



So even if they would fit that criteria number 2 which we were not able to assess, they would not have according to the Zamboni criteria CCSVI. Thirty-one subjects had already two or more criteria and so one missing criteria clearly would not change their diagnosis and the rest of the 52 subjects had only one criteria fulfilled and they were called borderline. This is a prevalence table showing the prevalence according to the specific of five criteria between the five groups and there were 163 normal controls, 21 CIS, 26 ONDs, and 289 MS patients. As I told you, the prevalence was done by using the borderline cases as positive or negative, and that's creating two different types of prevalences going from 62, in the MS patients 45 OND, 42 CIS, and 25 percent controls. In--when the borderline cases there included as negative, this was 56, 42, 38, and 22. We also looked at one criteria, any of the five criteria positive and that was 55, 76 in CIS patients, 81 in MS patients, and 65 in ONDs. If you look where the highest prevalence was, it was in the criteria number 3 in MS patients which are intraluminal abnormalities like membranes, [inaudible], and flaps. We looked at the differences by age comparing pediatric and MS adult patients and we found no difference. There were 10 pediatric MS patients in the study and the both prevalence is they're equal 56 percent in the borderline cases that included as negative. In terms of the disease progression and different disease subtypes, there was a clear cut difference going from relapsing-remitting to secondary progressive cases. The highest prevalence was in relapsing secondary progressive patients, it was almost 90 percent. And this was significantly different in primary progressive was approaching 70 percent, and clearly in relapsing-remitting is in the low 60's.

>> We also looked at 163 normal controls. We had 115 nonfamilial healthy controls and 48 had familial connection, which means genetic connection, there were sister, brother, mother, or daughter and there was no significant relationship, and we will look more into this--in the CTEVD phase 2. One of the most important things that comes clearly from specificity, and this is a table again showing sensitivity, specificity, positive, negative, predictive value and odds ratio, you can see that the borderline excluded or included gave very similar specificity that there was only one criteria had very low specificity. I think this is very in line what Professor Zamboni said originally. I would also like to have your attention on specificity of criteria 1, 2, 3, and 4, because when they have been present, they were highly predictive of the CCSVI. The odds ratio was very similar between 4 and 6. In this meeting, we are presenting a number of other studies looking more into correlation with MRI at 2:30. There is a platform on impairment of drainage in

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



the brain parenchyma in MS patients, the case control study. As Professor Zamboni mentioned, we are presenting a number of studies on the cerebrospinal fluid flow. This morning, we presented a study on iron deposition and on hypoperfusion of the brain parenchyma.

Let me finish by saying that as the CCSVI proceeds, I think that we should proceed under the ethical caution as guide of research. And just to point couple of, I think, important things to consider. We have to, continuing this research, balance the patient's rights and needs with the prudence and scientific rigor. And I applaud Dr. Miller for already pointing that out. I think that in such type of research, we need to invite and search for ethical oversight. Because I don't think that the local IRB approvals made this sufficient to ensure that what we are doing is proper and right. In that sense, our team made a decision to contact officially National Multiple Sclerosis Society and to ask for creation of so called observational data monitoring task force which will look at our research and say that they are ethically approved as right or not right. I don't think either one of us is smart enough to make a right decision for the future. I think another critical point is to ensure that no medical risk occurs to the study participants. In this sense, I think that our research on prevalence of this disease is without risk, but others can comment. We are proceeding with the safety pilot treatment studies. We did one with Zamboni and we are, as we speak, start another one, placebo controlled one. I think that the steps should be respected of scientific research and thus we need to first find whether something is safe then but there might be effective. And in this sense clearly I need to call in question all those people around the world who are providing the open-label treatment without the IRB approved studies to immediately do so. I think that we need to insist on transparency of the funding, wherever according to the American College of Physician Guidelines, whatever the--wherever the funding is coming from, but there is from funding agency's patients or the payment fees themselves. I think, focus should remain on the research leaving the treatment to the providers accustomed to evaluating these new approaches, and maybe later Professor Zamboni will comment on this because we need to look on the history and what happens in some other diseases when similar problems have been observed in the past. I welcome a dialogue to bring together researchers to look at this question. Finally, I think that this forum is really a first important step in putting together, and probably not enough, scientists to really begin to openly discuss about these issues and I really thank American Academy of Neurology and NMSS Society for the opportunity again. Thank you very much.

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



>> Dr. Zivadinov, thank you very much for bringing some new insight to the initial research done by Dr. Zamboni. And for sharing a great deal of information with the group as its whole, I'm wondering, we're running a little short of time but maybe you could just very briefly summarize what you believe we know or can conclude from the research that you've done so far and what you believe that other researchers who build off your work need to learn in order to determine what the suggested relationship between CCSVI and the process NMS.

>> I think there are, you know, three fundamental steps that have to be in phases undertaken regarding this research. The first one is to determine how this phenomenon or association or condition is real. In order to do that, we need to determine what's the best diagnostic tool to investigate this condition? Is it Doppler as Professor Zamboni is suggesting? I think the Doppler clearly has advantages in respect to the other static techniques because it's dynamic in its nature. You can move the patient between the supine and upright very quickly and get a lot of answers that you can't do with a more static examination like this MRI and others. We are proceeding also with some more advanced techniques probably only at experimental basis. These are intraluminal ultrasounds and [inaudible] that we will perform in our pilot studies. Second, we will clearly based on that, determine whether selective angiography is gold standard or really a noninvasive exam which we just published recently was very, very, very predictive of what has been found on selective angiography. Second point will be that many other groups in the world will be able to reproduce these results. If these results are really present in patients with MS, and then the question is what is prevalence others will find. What we found was the best of our abilities in the best blinded study we could have organized at University of Buffalo. And the other researchers will tell clearly their point. The second step is to determine whether there is some correlation between the CCSVI and MRI and clinical outcomes so important for this disease. We have started a pilot work. We are extending this work in the CTEVD study on almost 500 subjects. And I think that from our work, important data will come as well as from the other research groups in the world. We need to understand, is it just an epiphenomenon or if there is a difference between 38 percent in CIS patients and 90 percent in secondary progressive patients, thus the CCSVI happen as a collateral of the disease or there is some more important connection. The third step is clearly once we determine the first two steps is to determine whether pilot safety approaches may show to be beneficial, and I think that based on what is known from the patient case reports as well

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



as some more rigorous studies that have been done of it clearly [inaudible] not being blinded and controlled, we--I see two different ways how this research will go. One, we clearly need to use well established MRI and clinical outcomes like we are doing in the phase 2, phase 1 and phase 3 clinical trials in a blinded control fashion whether we can show that this is useful as a disease modifying approach.

>> Number 2, we can't ignore the symptomatology effect that there is a placebo or it's something more. I think that symptomatology studies also have to be taken into account and show whether this might be useful because we really care about the quality of life of patients and the--I can say just for patients we send to treatment to Dr. Zamboni that most of them said that they can dream again, and really dream again literally, dream again after the procedure. The night after the procedure, people who had no dream for so long many years had dreams, didn't have headache, had much less fatigue. So clearly, within design even now we study to measure these points because that was really not the point that we wanted to assess in this pilot study but clearly, the signs will go here. In terms of the design of the trials, I think that along will be the debate at what was the best and what has to be done and I will limit my self to these three important points.

>> Okay. Thank you. Thank you so much. And now I would like to call Dr. Common up to the podium and I'm wondering if, Dr. Common, if you could speak to what's currently known about interventional radiology and what steps that need to be taken to determine any possible relationship between CCSVI and MS.

[ Pause ]

>> Thank you very much for the opportunity to speak. My impression of my role here was to present an interventional radiologist perspective on venous lesions in general. So, most of you will ask what is an interventional radiologist? So I'm a radiologist. I do procedural work throughout the body with image guidance, that might be ultrasound or CT or fluoroscopy x-ray guidance. I've had a long experience in this field and lots of experience in particular treating venous disease, venous lesions in many different forms. So, quite familiar with venous angioplasty, with venous stenting, with embolization of veins, meaning plugging veins up, thrombolysis of veins, dissolving

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



blood clot in veins, sampling of veins for various hormonal irregularities and also shunting creating abnormal or unusual connections between different venous systems in the body. Here is my disclosure. I have not performed any CCSVI related venous procedures personally. Although, I've had a lot of patient contact requesting that I embark on this therapy, but I certainly followed the research of Dr. Zamboni and others and Dr. Dake in particular at Stanford who is an interventional radiologist who's actually done a fair amount of this work.

So what do we know about the venous system. In general, it's a low pressure system. It is a highly redundant system, multiple variable channels throughout the body, it's very adaptive to changes in pressure and to changes in blood volume. Veins in general are very thin walled, that is compared to arteries which contain a lot of muscle. They are non-muscular vessels. There are multiple levels of communication between intracranial veins and extracranial veins as we've seen between intraspinal and extraspinal veins, paravertebral, retroperitoneal, thoracic, throughout the body. So, it's a very redundant and very forgiving system.

This picture basically is a schema of the venous system extracranially. Jugular veins plug in at the top of the first image and you can see the azygous vein. Well, I don't operate this. Oops. Backwards, backwards. So, azygous vein, we can see coming off the side of the superior vena cava on the second image there. You can see it's a very, very redundant system. So if you were to block one channel, blood has multiple other routes to find its way back to the heart. And again if you look more closely at the venous system in relation to the spine here, again a very redundant system with multiple channels through which blood can flow in the face of a blockage in one or two or other segments, so again a very forgiving system.

What do we know about stenosis in the venous system? They can be caused by many things, trauma of some sort, either blunt or penetrating or compression of veins by overlying bones for instance. They can be caused as a consequence of inflammation, thrombophlebitis, with or without clot. And they can be caused by tumor and by sheer stresses when flow in the venous system becomes turbulent or higher than normal.

Venous blockages tend to develop very slowly and they tend to be very well tolerated by the body in general. They're not plaque. They're different from what we treat on the arterial side of the body. They're not lipid, they're not cholesterol. They're basically fibrotic and somewhat elastic lesions.

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



Imaging venous blockages as you've seen, ultrasound, magnetic resonance, venography, CT venography and conventional catheter based venography which is the gold standard. Each technique of course has advantages and disadvantages. I would say a few words. Duplex ultrasound is non invasive. That's the ideal part of the study and it tends to be rather time consuming and clearly you need well defined protocols in terms of what you measure, where you're measuring and what you're looking for and those need to be shared. It certainly gives you direction and velocity of flow but is somewhat limited by bone, by gas filled structures and by the depth of the vein you're interrogating. MR venography, time consuming, expensive, certainly a lot of interesting work going forward in this area. At the moment, it's not really ideal for small moving vessels and it may be used to indicate both direction and velocity of flow. CT venography suffers again from requiring contrast or dye administration which may damage kidneys and from a significant radiation dose, and it also suffers from only basically providing new static imaging without sort of direction of flow. Conventional venography, an invasive procedure requiring a needle entry into the venous system at the groin or in the neck, or in the arm, then catheter and wire insertion, again, radiation and contrast is used. In terms of venography, technique is crucial. So you have to take into account where you were injecting your dye, the volume of dye you are injecting, how the patient is positioned and how the patient is moving or breathing and the timing of your imaging. But it does provide the greatest anatomic detail and the greatest information about patterns of flow. There is potential for damage to the venous system, perforation with catheter or wire dissection, venous spasm which may be unremitting. But there is also the potential to intervene.

In the cardiology world, we talk about an oculostenotic reflex. So if you identify narrowing in a coronary artery, there is a tendency to want to open it up. The same thing may be at play here. So we see lesions, we really need to consider whether or not weighing risk and benefit to the individual patient these lesions should be opened. The risks of venous intervention are generally very small. Certainly, it is a safer territory to work in than the arterial system, and basically what can we do in the case of venous narrowings, we can angioplasty or venoplasty them using a balloon. Venous lesions tend to show a lot of recoil. So even though they may open with the balloon, as soon as the balloon is removed, they tend to come back down to their original narrow state. There is also a very high restenosis, right? So over the course of months, the stenosis may recur. There is a risk of rupture if you over dilate venous stenosis leading to bleeding. And once you dilated them, they may actually thrombose and close off completely.

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



So, that has brought around the use of stents which are simply metallic mesh work tubes if you want to hold this elastic structure open. But stents have their own risk, in particular, they require anticoagulation, antiplatelet therapy with risks of bleeding to the patient. Stents tend to be expensive,, and again there are risks of thrombosis, of stent migration in the venous system, and they do not prevent restenosis, so you can get re-narrowing through the stent.

So before treating CCSVI, we need to address a lot of questions. Are the stenoses causally related to MS or simply a secondary association? Are there benefits to relieving stenosis? What we have heard of are general constitutional benefits, so patients who find that their fatigue is less, their brain fog has cleared up, they have a lot more energy. But we haven't heard a lot about benefit in symptoms related to specific plaques within the central nervous system such as symptoms of ataxia or leg weakness. What are the short-term versus the long-term benefits and what is the risk benefit to an individual patient. So the recommendation from me is for patients considering endovascular therapy, we should really only be doing this in a clinical trial setting and in institutions where there are experienced interventional radiologists or other specialists who can do this work and where the interventionalist and the neurologist are working closely together and cooperatively. Thank you.

[ Pause ]

>> Thank you very much, Dr. Common for that valuable perspective. I want to allow some time for some questions, so let's take some questions from our on-site audience. We have a runner with a microphone. If you could just see this person here and we'll get started. Oh, and please identify yourself.

>> Robert Lisak, Wayne State University in Detroit. For Dr. Zamboni, I would point out that extravasation of red cells is not a hallmark of the MS lesion at all, not at all. I would also point out that you can get fibrin in an autoimmune model, goes back to the '60s, Phil Paterson and other work by [inaudible] and simply the inflammatory mediators released by inflammatory cells are quite capable of up regulating factors like VGF [phonetic], thrombo--corresponding thrombo and other related things that can cause local fibrin deposition. So I think one of your biggest problems is the pathology doesn't match this. And the iron deposition is, as you know, nonspecific as seen in Parkinson's, Alzheimer's, and is actually normal since they age and most often in the deep grey

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



structures where you've seen it. So, I think you got a major disconnect with the pathology if you're counting on red cells and fibrin and showing that this is a vascular disease. Just a comment, not a question.

>> Okay, I want to give him a chance to respond.

>> Oh, thank you. I thank you because your comment may permit me to explain some things. What's the origin of fibrin? In the blood. If you have venous hypertension, you have the tight junction in several models, especially in models of pulmonary hypertension made by West that indicate that you have tight junction enlarged and macromolecules, including fibrin, that pass through endothelial cells. This is very important because our data show that we have hypertension and so tight junction dilator and you have extravasation of macromolecules. Additionally, when you have no venous hypertension, but simply in [inaudible] venous [inaudible] in the main outflow route, you have diapedesis at the level of microcirculation. And this is particularly evident in the paper on MS in which the pathologist investigated to take the opportunity to investigate a recent plaque, an active plaque, not an old plaque with remodeling in which we lose the trace of the branches. There are papers from Adams and Langdon [phonetic] that clearly demonstrate these in a fantastic collection of people who died from car accident or something like this, in which if you look at the active lesion, you find strong extravasation. And if you use now SWI facility, you may easily see that despite a difference in iron deposition in Alzheimer disease or in Parkinson disease, the iron encircle the vein but in Parkinson, you do not find this finding, and also in Alzheimer, because you have amyloid deposition in the media of [inaudible]. There's a completely different branches. And also the origin of that iron is completely different.

>> But my point was that you can produce a mature autoimmune process with fibrin with absolutely no evidence of venous hypertension and that the fiber is left to describe any lesions where there was no evidence of red cell, no involvement of the blood-brain barrier, and indeed molecules that are macro [inaudible]. We get diapedesis without anything [inaudible] hypertension to the reaction of leukocytes and things like [inaudible], so your evidence is not as strong.

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



>> Sure. Oh yes.

>> We have a lot of questions to get through, so I want to make sure the dialogue is available for everyone including the public, so I'd like to take a question now from the press.

>> Yes, hi. Avis Favaro from CTV, I wonder if it's possible for either Dr. Zivadinov or Dr. Zamboni to summarize the findings presented today in lay language when you were looking at iron deposits and the cerebral spinal flow. What do those studies presented today add to the understanding, and then I have followup if I'm allowed after.

>> I mean, I can comment on the SWI study and Dr. Zamboni can comment on his hyperperfusion study. So clearly, our attempt was very simple in a very small pilot study to look whether there is a correlation between amount of iron we see in the certain structures of the brain that we believe are important for iron deposition and maybe somebody, I think, Dr. Miller mentioned before, iron is storing not just in MS patient but in Alzheimer, in Parkinson, and in normal people. My personal interest in this new type of research is really beyond MS because I would like to understand the venous function of the central nervous system in relation to aging, in relation to number of neurodegenerative diseases, and my research on iron might be very helpful. Now, the reason, one of the principal reasons why the iron is building in certain structures, nobody knows really the answer but it seems to be that the highest concentration of the ferritin receptors is physiologically present in those structures, and so well, there is excessive iron, that there it's a primary secondary phenomenon or result of, you know, just mitochondria dysfunction and oxidative stress. The iron is building in those structures. So what we show this morning is that there are certain pathways actually where the iron is building, and there are--one important pathway is in the thalamus and in particular in a region called pulvinar nucleus of thalamus that until now really was not investigated in MS by the pure reason that you can't see the pulvinar nucleus of thalamus, very hardly you can see, if not on the SWI sequence which is like hundred times more sensitive for seeing iron than other techniques. And our region number 1 to

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



be investigated in the future studies will be pulvinar nucleus of thalamus. I have now several data sets that are pretty much showing very similar thing as in this first pilot study. And we need to understand what is the connection of this buildup in the thalamus with disability lesions and start of the disease. To make a parallelism to what is going in a conventional MRI research if you have been yesterday on MRI imaging 1--number 1 presentation of I think 9 papers, 6 or 7, have been on the thalamic and deep gray matter atrophy in MS, so we need to understand whether the deep gray matter atrophy in MS is a result of the iron deposition concentration and toxic effects.

>> May I just ask a followup? It has to do with the 500. You mentioned testing difficulties, what did that mean and could that affect the prevalence rates that you've discovered as opposed to some of the other subjects?

>> Thank you for the opportunity for us in this and answering this question because this is something that clearly we did not speak about until now and will be in our clearly peer reviewed paper when we will be published. But we believe strongly that the type of the machine you are using is very important for determining certain structures. The deep cerebral structures are very difficult to determine, if not, with some specific technology that Dr. Zamboni actually developed and is now commercializing through a commercial company. And we believe that this is one of the reasons why our prevalence in certain--in this criteria was definitely lower than in Dr. Zamboni work. We have some experience by using this new technology that has been developed in the meantime and we see substantially different results. I also want to point out that the training and the reproducibility of scanner, scan tests in Doppler will be essential because you know that definitely may alter the prevalence of the disease, and that's why I strongly believe that only multitest will be able to show whether there is, you know, confident--certain confidence that the diagnosis is met.

>> Thank you, Dr. Zivadinov. Dr. Miller, do you have a comment?

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



>> Yes, there is a lot of the information that Dr. Zivadinov has been talking about that I think is highly technical and difficult for many of you who are listening in the audience to understand. The preliminary work particularly about iron deposition is giving us lots of things to explore, but I think for the audience the most important thing to understand is that when you see a new finding in biology there are many, many potential explanations, and the critical point about iron deposition which does seem to be increased in some people with MS, is again, there is a big difference between finding an association and knowing that it has some implications in cause and effect. It's just as plausible that the iron that is there is a consequence of the disease process rather than having anything to do with either causing or making the disease process worse.

>> Thank you very much, Dr. Miller. We have a lot of questions from people online, so I wanted to take our next question from Johanna on Facebook who asks, if we're able to have this procedure done as a possible cure, would we still need to stay on our drugs to help keep the disease from progressing too fast? Some research says we should and other states we should not. And I'm wondering maybe, Dr. Miller, you could start again.

>> Yes, Johanna and others, as I said in my preliminary comments, there is absolutely no reason that a person who was contemplating a surgical procedure for CCSVI, and I echo what Dr. Zivadinov and Dr. Zamboni have said that if one is contemplating that surgery, it should be only done in the context of a properly controlled trial by people who have participated with other investigators who can understand this process. But even if one--those entered in a trial or had the procedure, there is absolutely no reason to discontinue the disease modifying therapies. And I believe in Professor Zamboni's cohort of patients, they were all continuing on their treatments.

>> And let me add, and I think Professor Zamboni will do the same that this thing has to--maybe repeated 3 times at this press conference. There is no reason that patients stop their therapy. As Doctor Miller said, clinical trials over the last 25 years clearly showed the advantages of those therapies in the most rigorous studies that have been done. Until something else is determined, we should continue in that way and there is no reason to stop the therapies.

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



>> Yes, I agree completely with these positions, especially I recommend to people that are ours--under treatment with well stabilized disease, I have [inaudible] to continue and to wait for new evidences. There is some concern regarding people not responding to any treatment with very rapid decline. In this kind of people, I understand that the publication of our people generate--thus provide need to try this kind of treatment. And it is very important that her or his neurologist aware of the patient not responding to treatment, may [inaudible] offer angioplasty for this particular kind of people on compassionate ground. Otherwise, the danger is that people come outside where business is organized for performing angioplasty with technique that are not controlled without any ethical issue, any IRB, any ethical protection in terms of neurological control will be outcome and also with the MRI conventional and non-conventional measurement. So, I think that in this particular people with very aggressive, very progressive rapid decline not responding to any treatment or often to treatment, I think that based on the safety of the study that we presented, I invite the neurologist to consider the opportunity to offer [inaudible] this kind treatment on compassionate grounds with the help of very good interventional radiologists that can cooperate with the neurological team.

>> Thank you very much. I'd like to take a question from the press, but just remind everyone that we're really, really running short of time and we want to make sure that we have ability to answer questions from the public as well as the press here in attendance. So let's take another question from someone here in the press. If you just identify yourself.

>> Hi, it's Kelly Crowe from CBC. I'd like to ask Dr. Zivadinov, what do you say to patients who are right now traveling around getting this done without a clinical trial or any research or any standards having been established? Oh, I have one other question.

>> I can answer you very shortly or with the longer answer? I think they should not do it until we have data that this is helpful. That is my very short answer. I think that we don't have data at this moment to determine whether this is useful. I think that we should--I support initiation of more safety studies and hopefully more efficacy studies. But at the

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



end, I will also have this. As I said in my presentation, we should respect the individual patient needs and rights, and it's really a business of a caregiver for that individual patient to determine with the patient himself what is to be done. I think that at the moment, this question is completely out of the research arena. But as I said, my position is that I do not recommend open-label treatment without proper studies.

>> Okay, I wanna take an opportunity to take another question from online. Maybe, Dr. Common, if you could speak to this. Sheryl from New York is asking, is there anything besides surgery that might be effective in addressing the problem of the constricted vein so that surgery would not be necessary?

>> I am not aware of anything other than what you're calling surgery, but what I would call interventional--procedural surgery, yes.

>> Nonsurgical interventional procedures. I am not aware of anything other than that which would help with the venous narrowings. From my perspective, you know, the intervention that has been carried out is a relatively straightforward one, so it is not something that is difficult to do but we would certainly, I think, not undertake it or not advise it without the recommendations of a clinical neurologist who knows the patient and is willing to follow them and objectively assess their improvement. So, if there is no clinical trial that we can participate in, the minimum is a registry with the support of the neurologist following the patients and documenting outcomes.

>> Okay. Thank you, thank you very much. We'll take another question from the press.

>> Hi, Pauline Dakin from CBC Radio. There has been a suggestion from some researchers that the placebo effect in MS can be as high as 50 percent. I'm just interested in hearing reaction to that both from either Dr. Zamboni or Dr. Zivadinov, and also Dr. Miller.

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



>> Maybe I'll tackle it first. There is a high placebo response in almost any condition in which there are subjective symptoms that the patient has. Many of the symptoms that MS patients have are undoubtedly real such as fatigue and pain but we can't measure them readily at the bedside. It's those kinds of symptoms that tend to be most responsive to any, any intervention, be it a medication or a procedure or an exercise regimen or anything. The placebo response is much lower in the objectively measured neurological changes such as strength, spasticity, and coordination. Even there, there may be a minor placebo response but it's usually not persistent and it's not very--it's not very strong. In addition, we also have the benefit in MS that MR is a very sensitive indicator, particularly in relapsing-remitting disease to the effects of therapy. We do see in almost every trial that is conducted with medications that there is a decline in both the placebo and the treated groups in MR activity which probably reflects entrance criteria of more active patients going into the trials who have a natural tendency to decline. So, I applaud Dr. Zivadinov and Dr. Zamboni for encouraging the need for properly controlled trials. And that's very difficult when you have an intervention. Because to do an ideal controlled trial with an intervention, you really need a sham control, patients need to not realize that they're actually getting or not getting the intervention.

>> Thank you, Dr. Miller. We have another question online from Kim. She wants to know, are there certain symptoms that we who have MS can recognize if we have CCSVI so that we can go on to further diagnostic testing? So, I'll just leave that as an open question in case someone wants to--

>> I mean in terms of the epidemiology, we are looking at many things at the moment. The CTEVD study was very rich from collecting the data that are really connected both with symptomatology and environmental risk factors from the vitamin D to the HLA to the, you know, smoking and everything that we--we had almost 300 question, long questionnaire that collecting everything what is connected with the risk to MS. In terms of certain symptomatology, that I think is a very relevant point because we need to know and we need to work on certain pathways that might be connected with the certain obstructions. You know, one pathway that comes immediately to my mind is the pathway between the jugular vein, optic nerve, and the pulvinar nucleus of thalamus

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



because it's the same pathway. And if you think one of the most frequent symptoms in this disease, at least in earliest phases is optic neuritis. So, I know that Professor Zamboni and we too are looking on those, let's say regional pathways.

>> Just--I wanted to ask, optic neuritis I think is the word you use. Is there something in lay terms, so--

>> Alteration of a lesion.

>> Okay, thank you. I will take another question from the press.

>> Hi, Amy Schonfeld from Clinical Neurology News. Can you give me extent of the scope of what's going on? How many patients are actually undergoing so called unauthorized procedures outside of the research studies and what specific procedures are they going for and where are they going for these procedures?

>> Feel free to jump in.

>> No, I don't think certainly from my perspective that we have any idea of the answer to that. We know that among the community of persons with MS, there is a lot of interest and inquiry, but there is no current requirement or registry as Dr. Common suggested established. So, we don't know how many are going, where are they going and who's doing them [inaudible].

>> Yeah, but just--this is a very important point, and that's why I said before that clearly we recommend to all those people who are doing those things to get their IRB approved, to create their registry and to really connect with the neurologist in, you know,

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



a team research based on this. I think that at this important forum, we need to make clear that those people who are doing that probably will not benefit this research in long the term if they don't follow certain, really--I mean fundamental ethical rules, how this research should be done.

>> Regarding registry, we are preparing a registry and this could be a good tool for knowing exactly the amount of the procedures done in off-label patients and probably to reduce phenomenon of malpractice that are related to this kind of procedure.

>> I would like to comment that a registry is very important for patients who are doing this outside of controlled clinical trials. There is absolutely no substitute for the rigor of a properly controlled trial where patients are examined under standard conditions, randomization to the procedure or a non-procedure.

>> Thank you. And speaking of procedures, we have a question from Dawn from the United States who asks, at what point can we expect the medical community to pursue this avenue, more specifically how many trials and tests must be completed before this may or may not become a mainstream? Dr. Miller, do you have a perspective on that?

>> Well, as I said in my first comments, the MS Society is about to review a number of proposals that have come through, so studies are going to begin imminently. Dr. Zivadinov and Dr. Zamboni have already alluded to a small prospective clinical trial. It's very hard to say when an answer is going to come because one doesn't--one can't prejudge what the results of the earliest studies are.

>> Okay, we'll take a question from the press here.

>> Hi, I am Susan Jeffrey from Medscape Neurology. I--Dr. Common, you mentioned Dr. Dake and recently the Wall Street Journal reported that Dr. Dake had stopped

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



interventions. I wondered if you could give your perspective on that, whether it caused you to rethink anything that you're doing or just what your perspective is on that? Dr. Zamboni and Zivadinov as well.

>> I've talked to Dr. Dake about his experience. He's done or had done at most recent count I think about 35 interventions for CCSVI. He had two complications, one related to a migrating stent that was dislodged from the jugular vein and ended up in the right heart and that didn't have to be but was surgically removed. And another complication related to antiplatelet therapy and anticoagulation for a patient with a stent. He, I think was asked to stop or told to stop by--I'm not sure on what grounds, whether it was ethical or the way his study was being conducted. I honestly don't know why he has stopped but I know that Dr. Zamboni has stated quite in black and white fashion we shouldn't be using stents in this treatment, so.

>> And I want to add that certainly stent may give the opportunity to treat the stenosis and probably to prevent restenosis. However, in this particular phase, we needed to assess by rigorous randomized control trial using angioplasty surgery, of course.

>> The real effect without confusing data regarding placebo effect, so we need to have no doubt about the effectiveness of correcting coherently venous narrowing in CCSVI. But we need to use the safer technique. We need to--For this reason for assessing this in this phase, we needed to be as safe as we can and so I recommend angioplasty. And the other thing is that there are guidelines regarding the treatment of venous malformation and the first step is angioplasty and the second step is, again, angioplasty. And when you have no response there, you have to balance between stenting and open surgery regarding the site of a stenosis. For example for this test, if you consider the internal jugular vein at the base of her neck, certainly open surgery is a safe option. For example, open patch angioplasties by autologous vein can be considered a not responder. We are lucky to say that azygous vein is a challenging territory for open surgeries, very difficult and very dangerous, respond very well to simple angioplasty because we have 100 percent of resolution. And so this is good because we have in the neck opportunity to perform open surgery and we do not have need of any stent in the

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



azygous vein, so this I think is the right direction to go--to have balancing between safety and effectiveness.

>> Okay, I'd like to take another question from our online audience. I quickly want to just let everyone know, we are going to extend the time until quarter to 2 because we have so much interest especially from online. This comes from Mark from New York, a.k.a. Wheelchair Kamikaze. It says, what about the things we know regarding MS that CCSVI doesn't explain, such as male-female ratios, the common comorbidity with other autoimmune disorders and the most certain link with EBV--that EBV has to MS.

>> I think I may take this question. This is really an excellent point and one of the really key points of our study that we are exploring the female to--I mean if you think in the venous disease in general, there is 2 to 1 female to male ratio, but we are looking on many different things in terms of the jugular diameter, how the jugular diameter is playing a role with the gender. We are clearly determining the Epstein-Barr Virus and trying to link that. So there will be a lot of research I think in that case, but at this point is really too preliminary to comment on that.

>> Okay, thank you very much. Let's take another question from the press.

>> I just like to ask Dr. Zivadinov, how do you account in your prevalent studies for the number of healthy people who have--or showing CCSVI?

>> You mean, why they are showing?

>> Yeah, how do you explain that?

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



>> That's why I said that my interest in this research is probably just bigger than is MS. I want to understand, you know, in the hopefully next decade a full research on this whether who presents because if you look my other neurological disease data, these are mostly people with inflammatory diseases, right, neurosarcoidosis, Hashimoto, anti-phospholipids syndrome, et cetera. We saw a clearly higher prevalence, although it's a very small sample size than in the normal healthy controls. Also, we have seen some tendency of the higher prevalence, approximately 6 percent in the familial healthy controls than in the unknown familial healthy controls. So, clearly we want to understand if you are born with one regular vein closed, what does that mean for you if you never--if you never developed MS, and is this just one point in the cascade of many things. And I have some nice slides on this that if you are, you know, living in Buffalo and there is not enough vitamin D and smoking, et cetera, we need to link that to the other risks factors and determine if this is just an epiphenomenon or maybe a risk factor.

>> I think this--this is an area that raises a lot of questions about why is there so much discrepancy between Professor Zamboni's work and Dr. Zivadinov's work. There was fully--approximately 45 percent of CCSVI identified in Dr. Zivadinov's group of other neurological disease controls, whereas Dr. Zamboni found 9, and admittedly these are small numbers. But when one sees any phenomenon in biology that occurs in so many different kinds of populations, one always has to have some concern about what its implications are. So I--I think this just points to fact that we need more data collected in a controlled way by a variety of other centers and preferably in multicenter studies.

>> Okay, we have time for one more question and we're gonna go online, that's from Edward from Oklahoma and he asks, what can the MS community do to accelerate CCSVI research?

>> I think you should clearly--I don't think we're appropriate people to ask that because we are doing the research, so maybe Dr. Miller and other talk leaders in the room could answer to that.

## April 14: A live Web forum on CCSVI and what it could mean to people living with MS



>> Well, it's--I'm not entirely clear what the question is referring to in terms of the MS community. I think the MS research community and the National MS Society, the Canadian MS Society, the Italian MS Society apparently are actively involved and engaged in exploring this interesting avenue of research. From the point of view of the community of MS persons, I would turn that back and make that a much more generic plea which is the community at large needs to get involved in pushing for more research dollars. National Institutes of Health's funding dollars are at all time lows. The National MS Society can't pick up the slack and they need to get out and make sure that the appropriate amounts of money are allocated for MS research, be it for CCSVI or other interesting avenues of the course.

>> Thank you, Dr. Miller. I really want to thank everyone for an informative discussion on CCSVI and how it might change the lives of people living with MS. I wanna let the press in attendance know that we do have accessibility to everyone. Please stay seated, I'm not done. Thank you. We aim to answers as many questions as possible for especially people at home who are--have a lot of questions and weren't unfortunately able to answer them all. I think we had more than 1,000 questions sent to us and we're very grateful for all of those. Thank you. For more information on CCSVI and putting updates on research and clinical trial opportunities, please visit the [nationalmssociety.org/ccsvi](http://nationalmssociety.org/ccsvi). Thank you again to our panelists, Dr. Zamboni, Dr. Zivadinov, Dr. Common, Dr. Miller, especially for all the help in better informing people about CCSVI and what it could mean for people living with multiple sclerosis. This session will be posted shortly online with a transcript on the National MS Society website shortly. Okay, now you can go. Thank you everyone. Thanks guys.

[ Music ]

[ End ]