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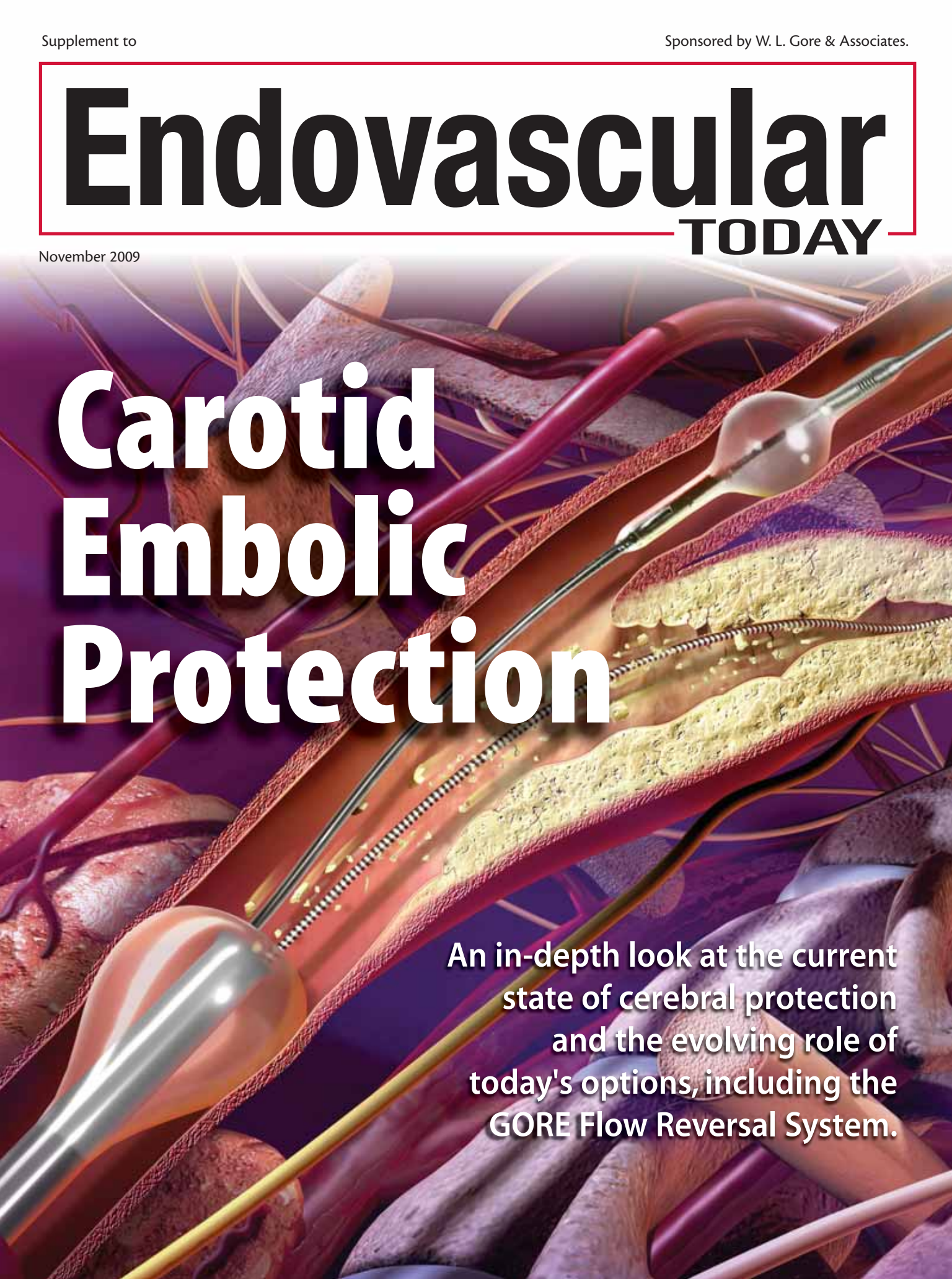
Carotid Embolic Protection



An in-depth look at the current state of cerebral protection and the evolving role of today's options, including the GORE Flow Reversal System.

Carotid Embolic Protection

This supplement to *Endovascular Today*, sponsored by W. L. Gore & Associates, highlights not only advances in embolic protection technologies, but also some of the larger trends in the ever-changing field of carotid artery stenting. First, a roundtable featuring an esteemed and experienced multidisciplinary panel engages in a candid discussion of everything from past data, FDA regulation, CMS reimbursement issues, and the role of Flow Reversal—patient selection, optimal device use, and what the future may hold for this technology.

After the roundtable, several authors from both sides of the Atlantic collaborate to present current data and practical information regarding the incidence of microembolization in stenting procedures. Next, experiences from the two largest single-center Flow Reversal datasets are discussed in detail. The supplement concludes with a brief interview regarding the current state of neuroprotection in carotid stenting procedures.

Our sincere thanks to the authors and panelists who contributed their valued experiences to this unique collection of articles.

Contents

INDICATIONS FOR USE: The GORE Flow Reversal System is intended to provide embolic protection during carotid artery angioplasty and stenting for the patients diagnosed with carotid artery stenosis and who have appropriate anatomy as described in the Instructions for Use. Refer to the Instructions for Use at goremedical.com for contraindications, warnings and precautions. $R_{x\ Only}$

The State of Carotid Embolic Protection and the Role of Flow Reversal

A panel of carotid stenting experts engages in a candid discussion of data, devices, decisions, and the future of embolic protection in carotid stenting procedures.

PANEL

Daniel G. Clair, MD

Dr. Clair is Chairman, Department of Vascular Surgery, The Cleveland Clinic Foundation, in Cleveland, Ohio.

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Dr. Gray is Director of Endovascular Services, Center for Interventional Vascular Therapy, New York-Presbyterian Hospital/Columbia University Medical Center in New York.

L. Nelson Hopkins, MD, FACS

Dr. Hopkins is Professor and Chairman of Neurosurgery, Professor of Radiology, and Director of the Toshiba Stroke Research Center, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York in Buffalo, New York; and Chairman, Department of Neurosurgery, Millard Fillmore Gates Hospital, Kaleida Health in Buffalo, New York.

DATA AND DEVICES: WHAT HAVE WE LEARNED?

***Endovascular Today*:** Based on your experiences and the data so far, what are some of your broader observations regarding the various types of embolic protection devices—both occlusion and filters?

Dr. Clair: As the field has progressed, there has been a significant decrease in the profile of filtration devices, making them easier to use. There has also been improvement and experience on the part of the operators after using filter devices over a period of time, and these devices continue to be the primary method of protection in treating patients with carotid disease.

I think distal occlusion is much less frequently used now than it was before. It offered a profile advantage and potentially an embolic protection advantage because it stopped the flow completely. Flow reversal does that, but it also provides the ability to treat almost any kind of anatomy distally that you may encounter. This is one critical area in which flow reversal in particular adds something to the procedure.

Dr. Gray: I agree. On the whole, filters have significantly come down in size and profile as well as ease of use. Some of the newer technologies in filters have been alterations in approaches—nets, etc.—but even the original filters that we started with have generally seen tweaks that improved their usability. In spite of that, there are still patients for whom filters are not the ideal option, so proximal occlusive protection is reasonable in those patients.

I have not frequently used distal occlusive protection, so I don't speak about it very often. We have used proximal protection though, and from a clinical standpoint,

it has been a lifesaver with occasional patients in whom there is just no way to do the procedure otherwise.

This instills a comfort level because we do not have to perform the procedure unprotected, which was the only other option before if the patient absolutely couldn't have surgery. Proximal protection has really allowed us to access a lot of patients who were otherwise considerably difficult or for whom placing a filter could be more problematic and dangerous than completing the procedure without protection.

Dr. Hopkins: If you perform 100 carotid stenting procedures, you're going to see debris in a significant number. I don't know whether it's 20%, 30%, or 40%, but you're going to see it. You take the filter out, look into it, and there's debris. So you have to ask yourself, do I want that in this patient's brain? The answer is of course not. If I can keep that out of the brain safely, to me the only argument against it now is that of safety. If operators can't use embolic protection safely, then they shouldn't do the procedure at all.

I've been working with the brain for 35 years, and there are still huge areas of this organ that aren't fully understood; they don't function at a level that we can detect clinically, and that leads to one of the other issues about embolic protection. There hasn't been enough attention paid to mental status changes associated with carotid artery disease, and the guys at Columbia did some great studies with endarterectomy.

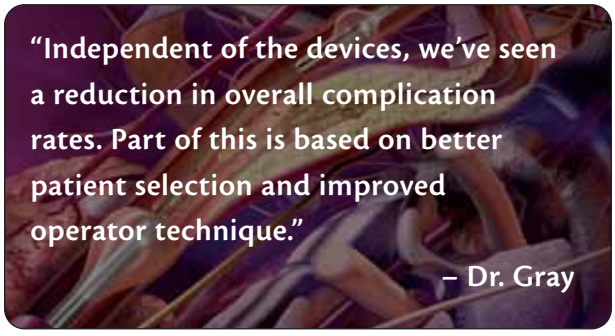
What they showed with endarterectomy is pretty conclusive, including that you can expect to see a dip in mental status function for a period of 30-plus days after endarterectomy in a significant number of patients. It usually returns to baseline within 3 to 6 months. What we really need are more data on stent patients with mental status changes pre and post.

Dr. Clair: And you're just talking about visible material, not microscopically visible material, which is much more frequently present. It doesn't matter whether I can see it or not. If it's present, even under a microscope, I still don't want it in someone's circulation. I want it out of the patient, not in their brain somewhere.

***Endovascular Today*:** Based on the data available, can comparisons be made between specific embolic protection devices or types of devices?

Dr. Gray: I'm not aware of any direct data that compares these devices in a prospective, randomized study with sufficient numbers to really make a differential decision between specific devices in terms of embolic protection. All we really have are the data that were developed for the IDE trials, which are probably the most rigorous data available on each individual filter or embolic protection device.

We've seen a pattern of reduced stroke and death at 30 days over the course of the last 7 or 8 years, since the beginning of these trials having been reported, with SAPPHIRE and ARCHeR being granddaddy trials. More recently, EPIC and EMPiRE are more robust. The data have gone from about 7% or 8% complication rates to about a 3% complication rate, which is a significant reduction. The question really is, is it something inherent in the newer devices, or is the field itself improving?



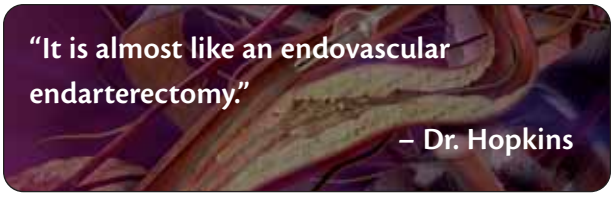
Independent of the devices, we've seen a reduction in overall complication rates. Part of this is based on better patient selection and improved operator technique.

Now, having said all that, there are data that suggest that if you take a look at some of the secondary, nonclassic endpoints of stroke and death, such as TCD or DWI, Flow Reversal may show a differential compared to distal embolic protection. The challenge here is to determine whether the results will translate into a clinical outcome, and we all just talked about the fact that we think it's important. Intuitively, it makes sense; it feels better not to have any embolic material in somebody's brain.

Dr. Clair: I completely agree. It is pretty clear, though, that Flow Reversal in particular, at least in any study that's looked at it, has had an advantage in soft markers of what are potentially cerebral events, meaning fewer DWI infarcts on early postoperative scans and fewer microembolic HITS or signals during the performance of the procedure.

Dr. Hopkins: There's a clear trend of improvement in terms of morbidity and mortality as more and more experience has been achieved and newer devices are coming along. How do you look at the most recent

data where you have the EMPiRE data, which are superb, and you have the EPIC data, which are also superb. They're all getting better. We are learning—as each trial gets published and the data get scrutinized, we learn something new. I mean, what Bill did with the CAPTURE data is phenomenal. You learn so much from just really scouring that entire database and finding things like, 18% of the strokes occur in the contralateral hemisphere—how about that? And, only one-third of the ischemic events occur during the procedure. What are we doing about that?



We learn from each dataset. We now know that symptomatic patients are problematic when it comes to filters, for whatever reason. For Dan and me, having spent a number of years doing endarterectomies, it doesn't surprise me at all, now that the data have hit me in the face. Because when you operate on symptomatic patients, very often you see the ugliest plaques. So it's no surprise to me that filters are overwhelmed by the amount of thrombus and plaque debris that you see when a plaque ruptures and the patient becomes symptomatic from carotid artery stenosis.

The evolution toward something to do a better job, toward proximal protection, is a natural evolution. Whether or not proximal protection will be the answer for all symptomatic patients, I have no idea, but it certainly seems to be a step forward in terms of our ability to clean up the plaque debris. It's almost like an endovascular endarterectomy.

You're shutting everything down, cleaning everything out, and then the only thing that's left behind is that debris that's attached to the stent or that herniates through the struts of the stents. Now we need to figure out something to eliminate that, and then we'll have made another big step forward.

Dr. Gray: We have also learned from the people who have more experience than we do in some of these fields. The European Flow Reversal trialists won't do a symptomatic patient with anything but Flow Reversal because they feel like they've already lived this experience, they don't need to go back and relearn the filter experience.

There are some tantalizing data from EMPiRE looking at the outcomes between symptomatic and asymptomatic patients, and there really wasn't much of a difference. That is unique because if you look at most trial data, there is a difference in outcomes between symptomatic and asymptomatic patients.

Dr. Clair: I've had a couple of patients with very tight lesions that we have treated with the GORE Flow Reversal System, such that when we initially inject, there is no flow reversal because the lesion is tight enough that it can't generate a pressure head. When we dilate those individuals, and even in pre-dilatation, it reverses and goes out through the filter. I have to admit, as an interventionist, it makes me feel a lot more comfortable than what I would have to do in this situation if I were using simply flow stagnation. And, for those individuals, when I put a stent in, again, I get that same situation where I'm watching the flow I've injected just come right back through the sheath and through the filtration system. From my standpoint, you're not going to get a better protection situation than that. Those are the patients in whom filters or simply flow interruption won't offer the same kind of protection.

Patients with lesions so tight that I don't think I can get a filter through them without predilating are ideally suited for Flow Reversal because as you do that predilation, you want everything to start being filtered. You obviously can't do that with a distal protection device, and I don't think you can do it easily with flow stagnation either.

Dr. Hopkins: Dr. Clair is showing the thought process of a vascular surgeon. He was thinking about how to reproduce the experience that we have when we perform a carotid endarterectomy. We are meticulous in making sure we've stopped all flow when we do an endarterectomy, and we always ligate the superior thyroidal temporarily. We don't leave anything going besides that, with a clamp distally. There's no doubt that Flow Reversal comes closer to that than flow stagnation because you are not actually reproducing the endarterectomy ligation, but you're overcoming that one branch that can provide some antegrade flow. You're overcoming that by reversing the flow. I would imagine that most vascular surgeons will feel a little more comfortable when they've shut everything down because that's what they're used to. And, for symptomatic patients, my hope is that proximal occlusion will achieve better outcomes to the point where we can clearly say it's equivalent or better than endarterectomy.

Dr. Clair: Really, it's almost any patient with a complex lesion, such as one so tight you don't think you're

going to be able to get a filter through it or at best you're going to struggle to get through it, or distal tortuosity, or there is symptomatic or ulcerated plaque present, especially if you can see it on the angiography—I think those patients in particular are ideally suited for a Flow Reversal protection system.

Dr. Hopkins: And it may be that the elderly patients fit into that category, as long as they don't have a very difficult arch. Any patient with difficult perilesional anatomy is clearly a potential problem for a filter, particularly if there's a major kink in the artery at the lesion or just distal to it. The cases where we've had the most trouble are severe kinks in which we place open-cell stents; even though you need an open-cell stent for a kink, those are some of the cases when you'll sometimes have trouble retrieving your filter device. If you have proximal occlusion, you don't have to worry about all that. You just perform the procedure and go home. So, as Dan says, difficult anatomy is another great indication.

These procedures—stenting and surgery—are quite complementary. I keep saying that, but everyone keeps wanting to push comparing one to the other. We should no longer be looking at randomized, prospective trials comparing the two. Previous trials have taught us enough that we now can select very well between the two procedures and decide which is best for the patient. We're now accumulating more data on which type of protection is probably best, and eventually we'll get to the point where we're very comfortable in determining which procedure overall is going to be best for the patient.

Dr. Clair: I think what you said is really important, that there are clearly patients we know ahead of time are high risk for surgery or are high risk for stenting, and the concept of randomizing those patients just seems crazy.

Dr. Gray: As a cardiologist, I have listened to you say that, and only in the last few years have I really come to understand the true place of these procedures relative to each other. I look at it like coronary angiography. I do a coronary angiogram, and I know I can place a stent in just about anybody, but that doesn't mean I should. There are patients with coronary artery disease for whom bypass surgery is the appropriate procedure; carotid disease should be approached with a similar mindset to get the best outcomes for our patients.

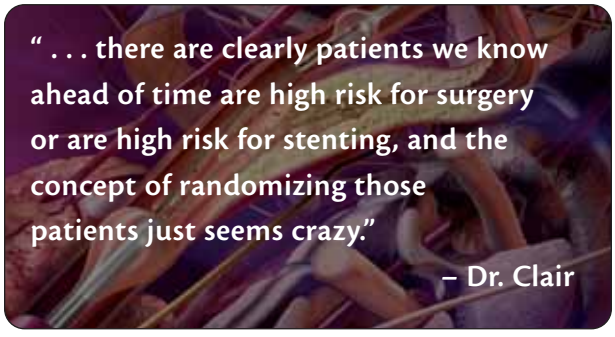
Dr. Hopkins: That's such an important point because back in the days of CREST lead-in, our attitude was we can stent anything.

Dr. Gray: That's my concern about CREST—that we did not have that selection pressure, that we felt we had something to prove, and we did, and we didn't have the data that suggested that we couldn't stent everybody.

A CRITICAL LOOK AT THE CLINICAL DATA

***Endovascular Today*:** Have EVA-3S and SPACE had a long-term impact on your practice?

Dr. Clair: Patients are told by their physicians not to let us put a stent in because the data argue against it or the data show that it has higher stroke risk. It's turned people who are potentially very good candidates for stenting away from seeking that therapy or from even accepting it at times, and it's made it extremely difficult to randomize patients who really should be included in trials like CREST to look at carotid stenting versus surgery in asymptomatic individuals who are good candidates for both procedures. We have seen an overall decrease in the number of patients we've stented since that data came out.



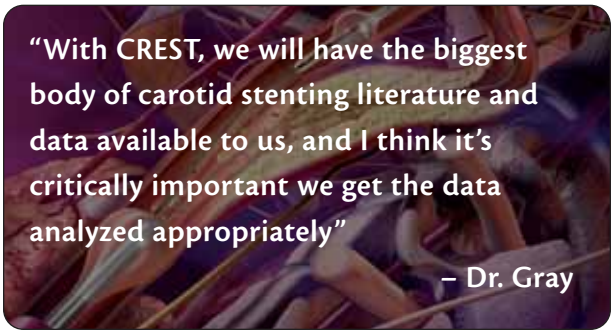
Dr. Gray: I agree. EVA-3S was the one that hurt most. I look at SPACE as a positive study for stenting—1,200 patients, no difference. It's hard to make a negative out of that. The conclusion that SPACE reached was that they failed to show non-inferiority. That's the wrong conclusion. They failed to complete the trial, and that's an important difference. It was never powered properly.

Dr. Hopkins: They didn't have the funding to complete it, and then they didn't have the data to say that there was anything other than equivalence.

Dr. Gray: And, only 25% of the patients were stented with embolic protection. Those studies were published in the *New England Journal of Medicine* and *Lancet*—well-respected journals—but if we thought in this community and the US, or in England for that matter, that those trials were well done and gave us a specific

answer that we could rely on, then we would have shut down ICSS, we would have shut down CREST, and we would have shut down ACT I. We didn't do that because we didn't believe those trials were well conducted or gave us the answers that we needed, specifically about symptomatic patients.

Dr. Clair: Despite the fact that SPACE has not really shown the same problem really that EVA-3S did, the challenging aspect is that the conclusion is the headline of the study. I've presented the SPACE data a number of times as part of a talk and always reached the same conclusion—that the ipsilateral stroke and death rates were similar. You're talking about four events in 1,200 patients. There really is no difference.



Dr. Gray: Lost in SPACE and EVA-3S to some extent is that both looked at long-term stroke outcomes between stenting and surgery; EVA-3S was four years and SPACE was two years. If you take away the procedural 30-day outcomes and you just do a landmark analysis, which basically sensors all the events before 30 days and just looks at the events after 30 days, you see that there's no difference in stroke prevention between stenting and surgery. Both had very low event rates. It's all about the 30-day data, because in the end, the stroke prevention efficacy is very good for stenting, as good as it is for surgery, and better than the natural history at least as we have it now for medical therapy in many of these patients.

The other thing that wasn't really highlighted in SPACE that came out in subsequent publication, which was, again, prespecified, so it's not just data dredging, was an analysis looking at age as predictor of outcomes. If you look at these data published last January, almost two years ago now, patients under the age of 68 do better with stenting, statistically better with stenting than surgery. Ridiculously low rates of 2.8% stroke and death at 30 days, compared to surgery, which had a relatively flat by-age stroke and death rate of about 5% or 6%. Over the age of 68, surgery looked better than stenting, but not statistically different.

So what that tells us is, we've been attacking the most difficult patients with stenting, the ones who are the elderly, who are older and sicker, and what I'd hate to see is a therapy that is just tuned beautifully for the youngest patient, even potentially better than surgery, wiped out by a lack of appropriate analysis.

***Endovascular Today*:** Next on the radar is CREST.

Dr. Gray: With CREST, we will have the biggest body of carotid stenting prospective randomized data available to us, and I think it's critically important we get the data analyzed appropriately by time from symptoms to treatment, age, symptomatic status, operator specialty, and any number of different things. If we don't do that, then we've done the entire field a disservice and potentially our patients, denying them access to what could be for certain patient subsets a very useful and safe alternative.

Dr. Hopkins: We'll never get a more complete, comprehensive study than CREST. But we have to stop talking about which is better and start talking about what we can learn about each subset of patients from these trials as we go forward. CREST will teach us something about symptomatic patients, and it may be that surgery in that group with that protection device is better. However, that is a first-generation device, and nobody would use it anymore.

Dr. Clair: The other problem is that when CREST was designed, we didn't understand completely what the differences were between subpopulations of patients getting carotid stenting. In order to move forward with CREST, you have to believe there is clinical equipoise between the two procedures. The fact is that there isn't clinical equipoise in certain groups of patients, and we know that now, and any trial that would be done from this point forward should clearly take advantage of the data that have already been generated about risk related to, number one, natural history. We know that patients with different comorbidities have different natural histories of their lesions.

Dr. Gray: If, in the early era of coronary angioplasty, in the '80s, coronary angioplasty had been forced to compete in a randomized trial versus coronary bypass, we would not have coronary intervention today. Period, end of discussion. We would have only really been able to address a small subset of the simplest lesions in such a trial, and without stenting would have had excessive acute and late failures. The point I'm trying to make is

that you can't kill CAS before it's been fleshed out. The problem is that CREST was conducted in a revolutionary time with carotid stenting, beginning at a time when it wasn't a stable platform. And, it has the potential to be the last word.

We haven't talked about ACT-I, which I think is a very important trial because it is a randomized trial including asymptomatic patients, 3:1, hopefully in a more modern context of carotid stenting with better patient selection. We hope there'll be a second shot on goal for the asymptomatic population. We're halfway done with that trial now, at 900 give or take, and until we see the results of CREST, especially for the asymptomatic cohort, which is the majority of patients undergoing procedures in this country, I think that trial is very important to continue.

Dr. Hopkins: Medicare is sitting on maybe the greatest opportunity it has ever had to shoot itself in the foot. Stroke is the most expensive disease that we treat, hands down, and if Medicare figures out a way to distort the data to a point that allows them to, in their own mind, rationalize shutting down carotid stenting, it's just a tragedy.

Another frustrating aspect is that many companies have invested considerable money, time, and effort into this technology, which is clearly valuable. The biggest tragedy would be if Medicare figures out a way to make it so it's not worth industry's time to continue to go after this market, not only for the companies, but for the population at large. Sadly, it's happened in some ways already.

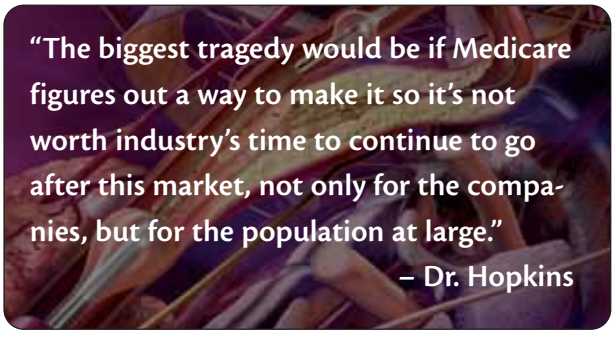
CMS CONSTRAINTS AND FDA MANDATES ON EMBOLIC PROTECTION CHOICE

***Endovascular Today*:** As we have discussed, some of the limitations regarding CAS procedures and technologies have little to do with the the details of the procedures themselves, and more to do with their regulation and reimbursement. How does the current CMS coverage decision impact the use of specific embolic protection devices, such as distal filters versus Flow Reversal?

Dr. Gray: Both devices are approved by the FDA for symptomatic and asymptomatic patients who are at high risk for surgery as defined by a list of fairly standard high-risk criteria. CMS, again, as I understand it, reimburses the use of those devices only in the symptomatic population at high risk. So the asymptomatic population would not have access.

Dr. Clair: And, unless there were registries involving those devices, there currently is no way to treat asymptomatic individuals with these devices and get reimbursed for it.

***Endovascular Today*:** So, absent a change in CMS's position, as soon as these post-market surveillance studies and registries are concluded, these devices will all be in the same situation as far as reimbursement is concerned—limited to the high-risk symptomatic patient.



Dr. Gray: We treat them in one of two ways: They get treated and the hospital takes a loss, or the patient gets a bill. For some patients, it's one of those options, or not get treated at all. That seems fundamentally unfair to patients who can't afford to pay or to hospitals who shouldn't have to pay for approved devices.

Dr. Hopkins: There's a lot more we could learn about Flow Reversal in a postmarket surveillance setting.

Dr. Clair: True, and we already have information from Gore's submission for approval indicating that there are differences between Flow Reversal and what's recorded in previous filter registries. That makes it even more interesting in terms of gathering additional information about how beneficial this might be in certain populations of patients undergoing carotid stenting. It makes it even more imperative in my mind that we have this option available. We may not have enough data to say it for sure, I think there clearly are advantages for this in certain subpopulations, but we really need to have the ability to use it to define those better.

ADVANTAGES OF THE GORE FLOW REVERSAL SYSTEM

***Endovascular Today*:** What are some of the primary advantages of the GORE Flow Reversal System?

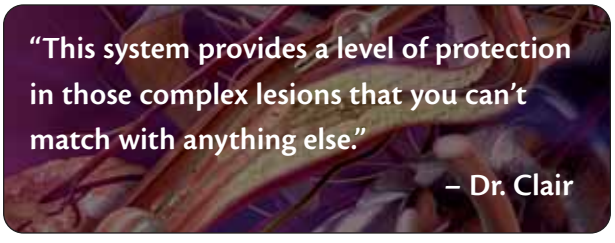
Dr. Clair: One of the major advantages is in complex lesions, which would include ulcerative lesions. In a

patient who has thrombus, I think it's hard to justify not using this system when treating them. Severe stenosis, such that you think placing a filter through the lesion is going to be difficult, mandates the use of this type of protection. And, obviously, I think tortuosity in the vessel makes this an outstanding option.

Another advantage is that you get to choose the wire that's going to be best to cross the lesion, and you have protection beforehand. In fact, we have had situations, some of the patients enrolled in the EMPiRE trial, where I had trouble getting a .014-inch inch wire to cross the lesion and needed to actually put a micro catheter in with the wire in order to get across the lesion. I would never have tried that with a filter device. I believe it's just completely impossible to do that with a filter device.

This system provides a level of protection in those complex lesions that you can't match with anything else.

Dr. Hopkins: You can break it down into categories; the anatomical issues for which a proximal device is clearly a better choice with difficult perilesional anatomy, and then the symptomatic patients for whom we know there's a higher risk of a lesion having a large plaque burden that may be fractured, therefore posing a greater risk of embolization and a greater risk for overcoming a filter. Those are some of the patients for whom we think there may be an advantage to embolic protection proximally with the Gore device.



As Dr. Clair mentioned, any complex anatomy in which you don't feel comfortable or you know there's a greater risk using a filter is the kind of patient where the Gore device is a much better choice.

The downside, of course, is just that there is a real or perceived difference in terms of the ability to get a larger device that is used for proximal protection around a more difficult arch. I say "real or perceived" because I think that it's a lot easier to use than most people think it is. It is a 9-F device, so it's bigger, and it can be more difficult to navigate. It's a little more bulky at the tip, but I'm impressed with how flexible the distal end is.

A difficult arch comes with its own set of challenges, and there are a lot of people who, in my own shop, were using the Concentric balloon catheter for any situation in which we wanted to occlude the common carotid until Gore came along. Now that we have the Gore device, it's taken a lot of encouragement to get the guys away from the Concentric device even though it is not nearly as good a device, and it doesn't have anywhere near the stability that the Gore device has. Most of the difference is perception rather than reality. It's a pretty easy device to use, but we have to first get past people's natural concern about the fact that it's a bigger device and it has more paraphernalia on the end of it, and, therefore, it may be more of a challenge to get it around a difficult arch.

Dr. Gray: I don't think it's more difficult to place the sheath itself. I like the sheath design. I think the sheath is among the best I have used. Although a bit larger in terms of French size, it has a nicely graduated taper of the stiffness, such that the durometer of plastic is very nicely segmented and matches its placement in the aorta and common carotid anatomy. I find that it goes places I didn't think it would go, so I've been favorably impressed with that.

The only real challenge to the device is getting the external carotid balloon into place, when occasionally there are external lesions or a very proximal superior thyroidal artery, as well as hooking up everything in the back end to make sure it's all flushed and ready to go. Once it's established, it's a very quick procedure, and it doesn't require the release and recapture of filters. Also, a wire specific to the patient's anatomy can be used. It's very helpful in those aspects.

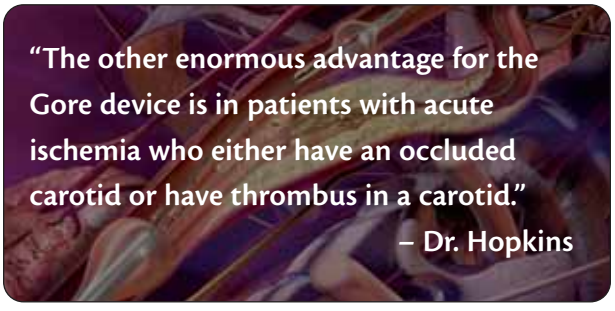
I think we've gone over the lesion sets, but the other thing that I'd say about that is, although we do use the device for certain lesion sets—either symptomatic or difficult tortuosity or so on—I also think it's probably important to use beyond that, because if you're only pulling it out for the most difficult lesions, it's going to be tough to maintain an expertise. So the last thing you want to do is pull out a complicated device in a difficult lesion that you don't have a familiarity with or the last time you did it was a year ago.

I would encourage people who are getting this device into their labs to use it randomly on a few patients just to maintain their level of expertise so that they don't just have it during the most difficult cases. I think that's probably good advice. We're trying to follow it in our lab too.

Dr. Hopkins: The other enormous advantage for the Gore device is in patients with acute ischemia who

either have an occluded carotid or have thrombus in a carotid. We use that device, or something like it, all the time. So in acute stroke, it's enormously valuable if you have an occluded carotid because you can put that device up, go through the clot, open the carotid artery, aspirate the debris, and then go on upstairs if you need to. But for patients with acute occlusions, this is a wonderful device. Because if you have an acute occlusion and you don't use this type of device, you invariably run a high risk of having distal embolization into the intracranial circulation when you open the carotid. So this is a great device for that.

***Endovascular Today*:** How would you summarize the importance of tailored stenting—choosing which stent and embolic protection device to use?



Dr. Hopkins: We're way behind our European colleagues because we cannot tailor our choice of devices to the patient the way they can in Europe. We're entering patients in registries, and the FDA mandates that we put a system in rather than tailor them. So I think we're at a significant disadvantage because we don't have that freedom. It's clear that there are differences between the various types of devices. Navigability of a device, appropriateness in a curved lesion versus a straight lesion. There are all kinds of variables. There's still a big a debate as to whether open cell is better than closed cell. All these things may have a role, but for now, we're stuck with what we have.

That's why the Gore EMPiRE clinical study was wonderful—because you could choose the stent you wanted.

Dr. Gray: We'd have much more creativity. Also, without tailored stenting, we'll reach a plateau in our outcomes at some point. We haven't had any integral changes in the devices, stents, or anything else because of the marketplace we talked about before; we're forced to use systems rather than mixing and matching what we might think is the best thing for the patient. Now I recognize there are compatibility issues there, and I'm not suggesting that we shouldn't take those into account. However, it does limit our ability to do what we think might be best for the patient.

***Endovascular Today*:** What issues are there with regard to access when using the GORE Flow Reversal System?

Dr. Clair: I think there are cases in which it could be an issue, but the fact is it's never precluded us from being able to use the device, and in any patient in whom we're choosing to do carotid stenting, we haven't had an issue with accessing the carotid with this device. It's probably just about as easy as any of the other sheaths that you're going to place into a carotid.

Within the trial, I think we had one patient with a high-grade iliac stenosis that we simply angioplastied and then proceeded to use the device. And, honestly, this is the equivalent of a 7-F shuttle sheath, which is very similar. It currently has to go in through a 9-F sheath, but the fact is the device itself is like what we were using 6 or 7 years ago to treat carotid disease anyway, only it's more flexible and I would say easier to get where you want to, and to Bill's point, with the balloon up, it's more stable once you get it to where you want it to be anyway.

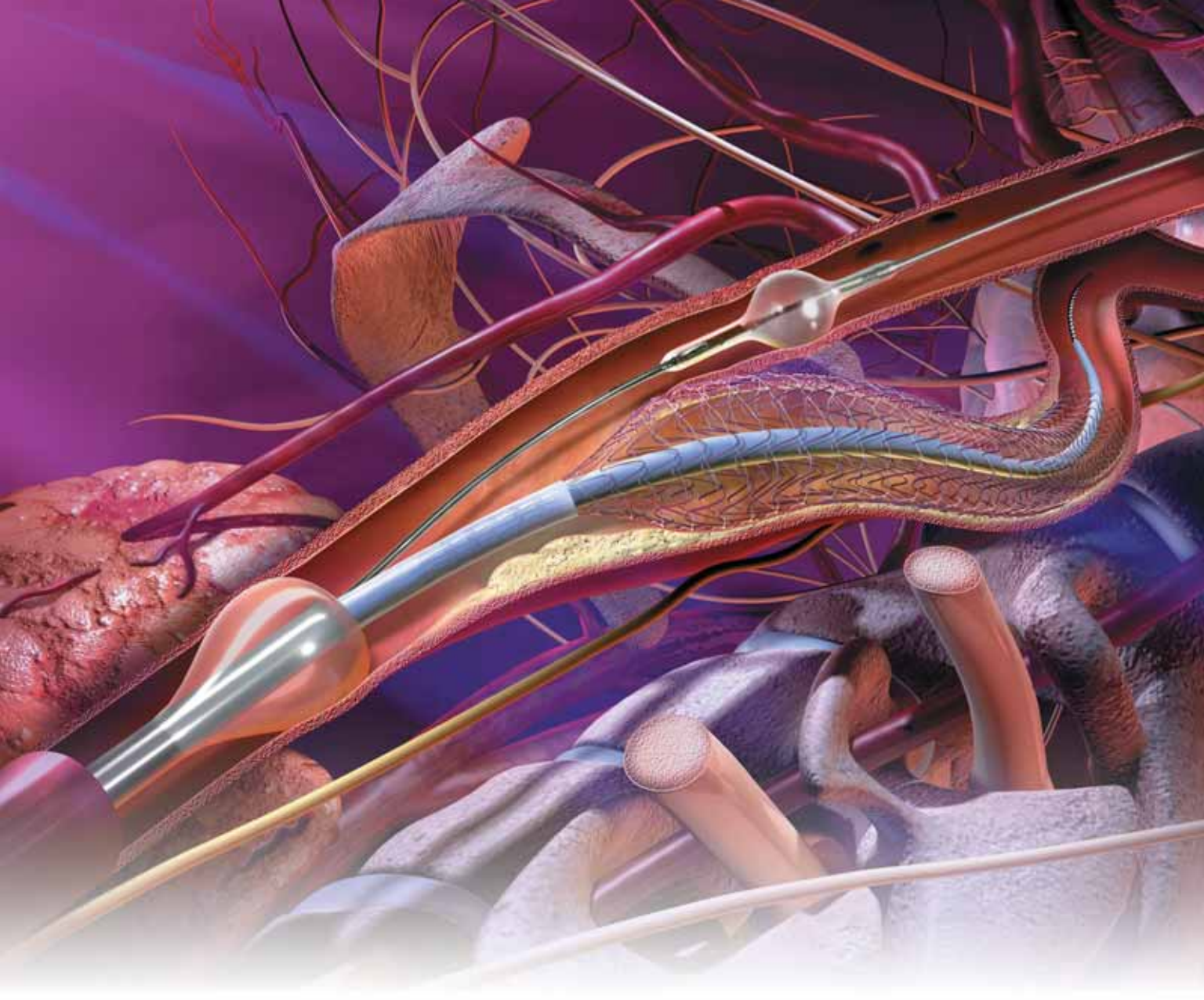
You don't have the ability to catheterize the vessel like some of the systems, where you can catheterize it and then take the sheath in over the catheter. That would be a nice thing to see with this device, but right now, I don't see getting access as an issue with this device.

Dr. Gray: We've actually done that with the 125 Cook Shuttle—we've been able to do that using this device over that system. So it can be done. And we haven't had a patient in whom we weren't able to deliver the device due to difficult anatomy.

Dr. Clair: And, like you said, the distal tip of that is extremely flexible.

***Endovascular Today*:** Are incidences of access-site hematoma an issue?

Dr. Clair: One impressive element in the EMPiRE trial was that the access complication rates were very low, particularly from what we'd expect to see with 6-F sheath access sites. I think that's a function of physicians learning how to deal with larger access sites, and closure devices have dramatically reduced the issues with this. Physicians have learned how to use closure devices well in this situation, such as in methods where the closure system is delivered initially, and then the working sheath is inserted.



It's impressive that the groin access complication rates are very low, and despite the fact that we're using a 9-F sheath, physicians are obviously very comfortable dealing with sheaths of this size. Because these patients are aggressively anticoagulated with antiplatelet therapy, we're all very careful in dealing with the access site.

There are pretty good data that access-site complications worsen outcomes, so if you have one, you're at much higher risk regardless of the interventional procedure. In carotid intervention in particular, that recognition has led to a lot of attention being paid to the groin access site in minimizing those complications, and I think this is a good example of it.

Dr. Gray: I agree. We use a 10-F sheath so we can watch our pressure—and some of the 9-F sheaths can do that too—but we just go to the 10-F sheath anyway because it's either a ProGlide or a Prostar.

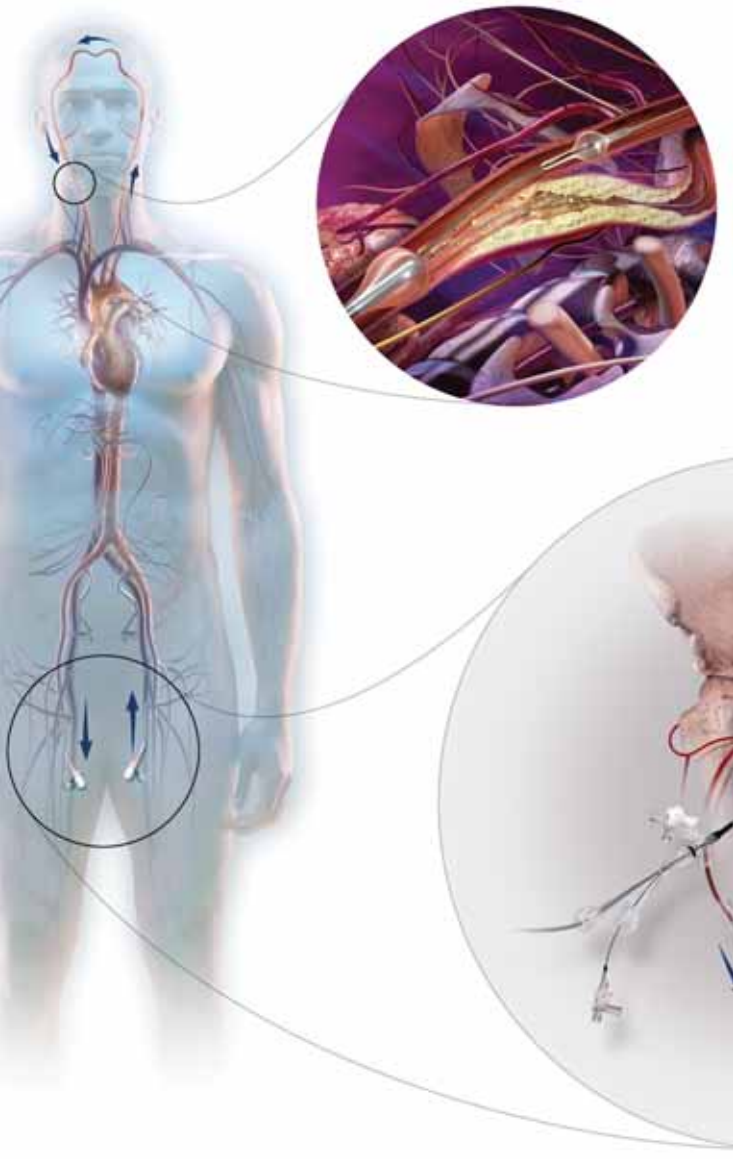
And the fact that the sheath is in for about 30 minutes, I think the duration of dwell is a very important part of hematoma management. We pull the sheath right after the procedure, tie it, and we're done. That really limits complications to a large extent as well. If you don't have a dwelling sheath in for 6, 8, or 10 hours, that makes a big difference. We learned that a long time ago in our coronary experience.

POSSIBLE LIMITATIONS OF THE GORE FLOW REVERSAL SYSTEM

LEARNING CURVE

***Endovascular Today*:** What would you say about the learning curve associated with the GORE Flow Reversal System?

Dr. Hopkins: I think there's a learning curve with anything. With this though, there's a mental block because everybody's used to a 6-F Cook Shuttle, and you see a 9-F and say, "Wow." There's a psychological barrier that has to be overcome, but once you get past that, the



reality is that it's really not any more difficult to use. It's just a matter of getting over it as a psychological hump.

Dr. Gray: I agree. The learning curve issues are not in the placement so much, although there's some learning there. It's not really "learning," it's just experiential. Putting a balloon in the external is not a big deal, and working with the balloon, making sure you have stump pressure—that kind of assessment. It's not a big deal.

The bigger technical issue is the back end of the device, making sure that the entire device is flushed adequately, the Thouy ports are closed, that Flow Reversal is established, and that you manage the procedure in a systematic way—that you aspirate after critical parts of the procedure, and when you actively aspirate, that you don't aspirate during an open Thouy, and so on. Those kinds of things take a procedure or two. It really doesn't take more than that to get a sense of how to manage everything, and you get your own stylistic way of doing it. But once that's established, the rest of it is very easy.

With the technical parts of using the device, there's actually not much learning curve there at all.

DEVICE INTOLERANCE AND ISOLATED HEMISPHERE

***Endovascular Today*:** What can you tell us about patients in whom there is intolerance for Flow Reversal?

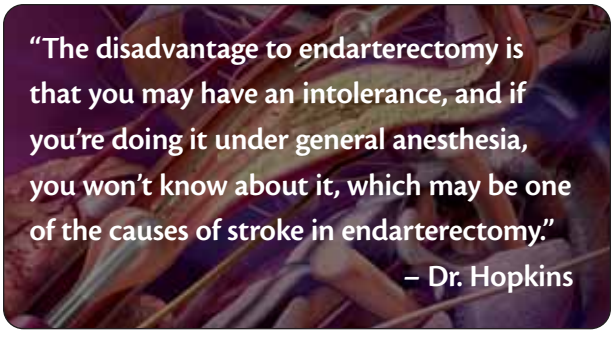
Dr. Clair: We had three patients in the trial who had intolerance in one way or another, and in each one of those situations, we were able to complete the procedure by performing it in steps. We predilated and stented, then released the Flow Reversal, and postdilated. After each point before opening it up, we did active aspiration, and then were able to reperfuse the patient. The total time for the procedure itself, once you have the sheath in place and initiate Flow Reversal, is normally no more than about 10 minutes. It's usually not a large portion of the population of patients who can't tolerate flow reversal for 10 minutes.

There is also a group of patients, and we didn't see this in the trial, but it's been published before, in which adaptation occurs—if you occlude a patient initially and they have intolerance, the next time you occlude them, there tends to be a smaller number of patients who are affected.

For some physicians this is one of the things they are initially concerned about, but the fact is, if you're treating any patient who has carotid disease, you will have periods of time where you're doing inflation and a patient has an ischemic event while you're occluding that ipsilateral carotid. It's a small number of patients. I personally think it's pretty easy to deal with if you're used to dealing with this process. If you've done carotid endarterectomy with a patient awake, it's pretty easy to deal with this sort of thing, you put a shunt in.

Functionally, you're doing the same thing here; if you have a problem while the patient's awake, you just open up the carotid after you've done some active aspiration and those steps of the procedure that you've completed to that point.

Dr. Gray: The trial data Dan is reflecting on is pretty impressive considering that we thought it would be more like 5% or 10% of the patients who wouldn't be able to tolerate Flow Reversal when we started the trial. I think it turned out to be 2% or 3% who had some intolerance. Part of that is because there was some selection going on there. Patients who clearly had an isolated territory problem were not entered into the trial.



I've also been impressed after the conclusion of the trial and the approval. I've used the system in a couple of patients in whom I cannot identify a collateral circulation for the life of me, but I try it anyway because there are not a lot of options for these patients. And when we do it, they get a little starry-eyed, but they don't lose consciousness, they don't have a seizure; they get quiet, but they don't really have a lot of trouble. You just move through your procedure quickly, and it goes fine. I've been very impressed, and I'm not sure how that happens. With literally no identifiable collaterals, they seem to do okay. That was in the right hemisphere, so that probably makes a difference.

Dr. Hopkins: I don't think I can explain it, but I can just tell you from an observational standpoint, we've been doing balloon test occlusions of carotid arteries for many, many years, and I can't ever predict them. It's sometimes the patient who has an isolated hemisphere who will have symptoms, then sometimes they won't, and I don't think there's any way to be sure. I suppose if you were doing Xenon flow studies, you might be able to get a better preoperative sense of whether or not they will tolerate it. But as Dan says, the important thing is that you know how to deal with it. Fortunately, we're keeping these patients awake, so if the patient has symptoms, you know it right away and you can deal with it.

The disadvantage to endarterectomy is that you may have an intolerance, and if you're doing it under general anesthesia, you won't know about it, which may be one of the causes of stroke in endarterectomy. Here, we know right away, and we can aspirate and re-establish flow. And, very often, I don't know why this works, but if you re-establish flow for a few minutes, give the patient some fluids, let the pressure come up a little bit, and try it again, then usually the second time around it works and the patient tolerates it. So it's something that is (1) infrequent and (2) fairly easy to deal with. All things considered, it doesn't seem to be an issue.

Dr. Gray: And there's a third part to that, which is it doesn't appear to have any clinical sequelae. If a patient has some intolerance, there doesn't appear to be an outcome related to that, be it stroke or other outcomes.

Dr. Clair: It's usually pretty easy to identify the patients who are intolerant. There may be some who are having relative ischemia because they're a little bit sleepy and that may be their manifestation, but for people who have significant ischemia, you know pretty much right away—they're having some kind of noticeable alteration in their mental status. We have the balloon in with the wire before we initiate Flow Reversal. We initiate Flow Reversal, cross the lesion with the wire, and take the balloon right behind it, predilate the lesion, and it's no more than 5 minutes before we have the stent in place after initiating Flow Reversal.

It's usually at about that point that they begin to manifest something. If so, we simply do active aspiration and open it up. It's pretty straightforward.

Dr. Hopkins: That's part of the learning curve—having everything prepared and ready to go minimizes the time that you're occluded, and you minimize the risk of having to have actually stop, aspirate, re-establish, and then start all over again. If you're well along in the procedure and the patient begins to exhibit some level of intolerance, usually you can just finish off the procedure and then re-establish flow.

PRACTICAL IMPACT

***Endovascular Today*:** How has the GORE Flow Reversal System changed your practice?

Dr. Hopkins: It has very definitely expanded our ability to treat patients, and it has improved our overall

CAS safety profile because we can now avoid using filters for patients whose anatomy is not conducive to using a filter. It's a wonderful addition to our armamentarium for treating carotid artery disease. There are patients we're treating now that we simply would not have attempted before.

Dr. Clair: The only problem right now is that we can only use it in symptomatic, high-risk patients. There's a large population of patients in whom this device isn't currently usable, and naturally we'd all like to see that change soon.

TIPS FOR SUCCESS

***Endovascular Today*:** What technical tips would you give to people who are going to embark on this? If they've never done a single Flow Reversal procedure before, what would you recommend?

Dr. Clair: I think the key issue is using the sheath just like using any other sheath. I would take a few minutes before the performance of the procedure to just confirm how it functions within a patient to ensure that you understand the concept of how to do active aspiration, the steps you need to take before you do that, such as tightening the Tuohy-Borst adapter at the back end of the sheath so that when you aspirate, you're not aspirating air from the back end of the sheath.

Those are things that are pretty routinely done by interventionists who are comfortable using Tuohy-Borst adapters, but if you're not routinely using them, you need to make sure you're taking that into account. Then it's just a matter of management—actively withdrawing through the sheath and then transmitting that fluid or that blood back into the patient through the venous system and through the filter. Doing that once or twice before you've actually even accessed the carotid, just so you're comfortable doing it, is not a bad thing to do. I can understand that before you do the procedure, you might feel uncomfortable. But after two cases with this system, you can manage it comfortably in any situation. It's a very short learning curve, and it really all focuses on dealing with the back end of establishing the Flow Reversal.

Dr. Gray: I agree, that's where the learning curve is.

Dr. Hopkins: The most important thing is to accept the initial concept that it's no different than anything else, getting the system up there. Once you accept that, I think you're over the hump.

Dr. Clair: Gore has been pretty good about providing on-site, preprocedural training with the back end, which I think is the biggest issue for people to get over. Doing that ahead of time was very helpful for me. It didn't necessarily even involve a simulator, but rather just looking at the device, understanding how you need to manipulate it in order to do active aspiration, return that blood to the patient through the filter, and then continue the procedure with imaging and pressure monitoring.

One of the neat things about this device that we really don't have with anything else is to assess the intracranial back pressure in the patient. It's actually kind of neat to be able to do that and to see how systemic hypertension actually can affect that. Driving patients' blood pressures can drive their collateral circulation up, and we've used that intraoperatively in some patients to manage what appeared to be the early mental status changes. The other thing is just understanding that this really is a significant issue for people, whether their collateral flow is adequate to that region or not.

Dr. Gray: In terms of tips for success, one thing we do for all of our stent procedures that I think is especially helpful with Flow Reversal is that we stack our equipment on the table towel, and we go top down. So if we're going to use a balloon and a wire, we get everything established, we turn on the Flow Reversal, the balloon and the wire are already in the patient, but there's a stent on the table all ready to go. We select it, and under that there's potentially a second balloon if we want to use it postdilation.

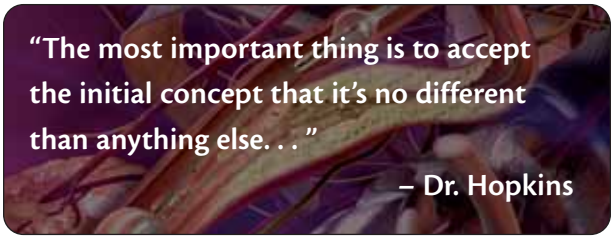
We're not waiting around, pulling stuff off shelves, and prepping it. It's all on the table ready to go. We can cut our Flow Reversal time down to less than 5 minutes—I mean very quick procedures once Flow Reversal is established because there is no filter to go get, there's nothing to clean up afterward, if you will. It's just basically in and out.

THE FUTURE OF EMBOLIC PROTECTION FOR CAS?

***Endovascular Today*:** What do you believe is the future of embolic protection in carotid stenting?

Dr. Hopkins: I don't know if there's a future without embolic protection. We'll never muster a trial enrolling the number of people to do a study that will tell us. It will be impossible to get the average person who has any common sense to be willing to undergo the procedure without it. We don't need a

trial to tell us that embolic protection is necessary, and most people who have any understanding, clinicians who have taken out a filter and seen debris that would have gone to the brain, are going to opt for embolic protection in every case.



Dr. Clair: I agree. There no longer exists equipoise in the community of people doing carotid stenting that there may be no difference between filter and no filter, or protection and no protection. If you polled 100 people, I doubt that even 50 percent of them would say there's no difference, or that they believe a randomized trial would be reasonable.

Dr. Gray: Much of the trial data we're seeing from EVA-3S, even ICSS, reflects a time in the early 2000s when carotid stenting was still very much in the early steps of its evolution, and the standardized technique had not been either developed or accepted in terms of filter protection, or available embolic protection. The data reflect an era that I think has largely passed, even in Europe, and certainly in the US. I don't think you'd find equipoise here. There are not enough people to do the trial who would believe that there's no difference between CAS with and without embolic protection. ■

Microembolization: The Achilles' Heel of CAS?

The incidence of procedural microembolization may depend on the type of EPD employed.

BY SUMAIRA MACDONALD, MBChB, FRCP, FRCR, PhD; BARRY T. KATZEN, MD, FACC, FACR, FSIR; AND CLAUDIO SCHÖNHOLZ, MD

Stroke is a major public health concern, with more than 750,000 incidents of stroke occurring each year in the United States.[1-4] It is the third leading cause of death after heart disease and cancer, and it is the leading neurologic cause of long-term disability.[5]

Approximately 30% of strokes are caused by carotid artery occlusive disease.[6] When patients with significant carotid artery occlusive disease develop symptoms, it is usually the result of embolization from the embolic site. The therapeutic goal of carotid endarterectomy (CEA) and carotid artery stenting (CAS) is to reduce the risk of ipsilateral stroke. However, both the surgical and endovascular treatment approaches carry a procedural risk of ischemic stroke, which results primarily from manipulation of the plaque that can lead to macro- and microembolization.

Since the introduction of CEA in 1954, the technique has improved to the point that two well-known randomized trials have proven CEA's superiority over medical treatment,[7,8] and it is currently considered to be the standard of care for patients with significant carotid artery disease. Thromboembolism is recognized as the most important factor in the pathogenesis of perioperative stroke associated with CEA.[9,10]

First performed 20 years ago, CAS has until lately had a limited effect on the management of carotid artery disease, mainly because it was performed only at a few institutions for a few selected indications, and its cost was not reimbursed by insurance carriers and government regulation. However, with the perfecting and standardization of endovascular techniques and improvements in stents and distal embolic protection devices (EPDs), CAS has become a viable alternative treatment for carotid artery occlusive disease.[11]

Periprocedural embolization is cited as a factor that prevents CAS from achieving optimal procedural safety. The greatest perceived risk associated with CAS is periprocedural stroke or asymptomatic brain infarction resulting from the release, migration, and embolization of debris during predilatation, stenting, and postdilatation of the carotid artery stenosis. Therefore, it is intuitive to attempt to prevent these presumptive emboli, whether they are composed of air or formed elements, from reaching the brain. This is the justification for the employment of cerebral protection, which may follow three philosophies: balloon occlusion (either proximal or distal), distal filtration, and flow reversal.[12]

Embolization has been shown to occur during every stage of CAS,[13] but embolic protection starts once the cerebral protection device is deployed and finishes when the device is retrieved. This means that embolization can still occur during the initial placement of the guide catheter in the artery and can also be seen after the procedure has been completed. Careful technique and limitation of instrumentation is crucial to reduce or suppress embolization during the initial phase of the procedure, and administration of dual-antiplatelet medication, statins, and appropriate use of stents of adequate size and cell configuration will sufficiently address most of the postprocedure emboli.[14]

Preprocedural identification of lesions with a high embolic potential has been studied as a means of optimizing the treatment algorithm of carotid revascularization. In a published study of carotid plaques after endarterectomy, Milei et al found that 24% of plaques have thrombus lining.[15] In another study performed at Stanford, the incidence was 49%.[16]

Reliable identification of vulnerable carotid plaque remains elusive.[17] Echogenicity, heterogenicity, and degree of stenosis (a surrogate marker of embolic load) have all been postulated to correlate with increasing procedural risk, although some of the findings are conflicting. An objective ultrasonic parameter, the grayscale median, has been used to specifically determine embolic risk during CAS.[18] A grayscale median < 25 is believed to be associated with increased risk of stroke during CAS. This technique is not widely available, perhaps because the evaluation of

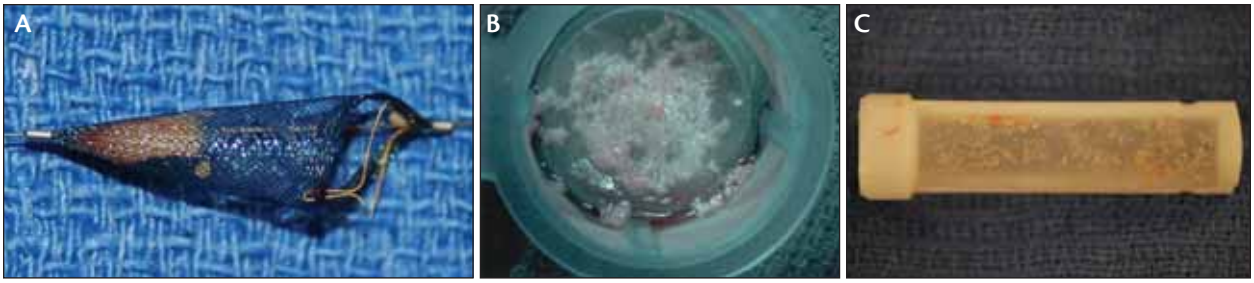


Figure 1. Macroparticles captured with a Spider filter (ev3 Inc., Plymouth, MN) (A). Macroparticles aspirated during CAS using distal balloon occlusion (B). Macroparticles captured by the external filter from the GORE Flow Reversal System (W. L. Gore & Associates, Flagstaff, AZ) (C).

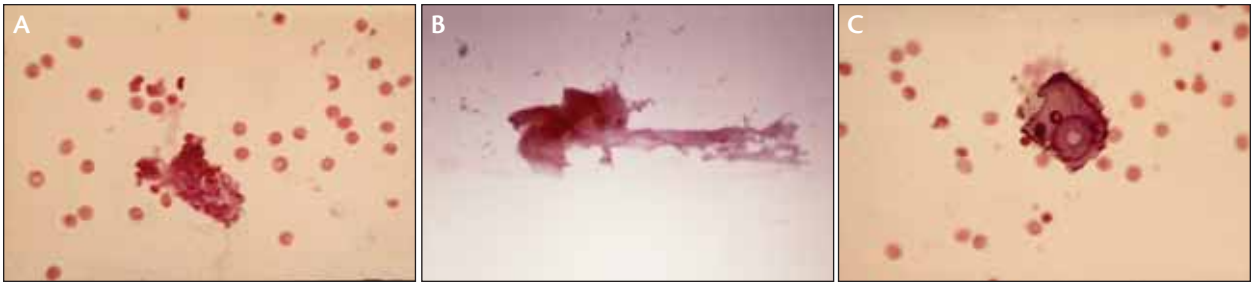


Figure 2. Histologic appearance of particles captured by a filter. Platelet clusters (A), fibrous tissue (B), and calcified plaque (C).

this parameter requires software modifications of the ultrasound machine and specific sonographer training. Lacking a definitive test that can identify embolic risk in specific patients, and with some evidence of benefit for the use of EPDs (albeit not level I evidence), their use has become mandatory in the United States as part of the reimbursement approval process. Payment is not allowed unless embolic protection is employed.

CEREBRAL PROTECTION DEVICES AND MACROEMBOLI

There is no doubt that macroemboli can be retrieved from each of the three types of cerebral protection (Figure 1). This includes devices affecting flow arrest, such as distal balloon occlusion (PercuSurge GuardWire, Medtronic, Inc., Minneapolis, MN) or proximal flow arrest (Mo.Ma, Invatec S.p.A., Roncadelle, Italy), flow reversal (GORE Flow Reversal System, W. L. Gore & Associates), or distal filtration. There is level IV and level V evidence to support this contention from reported series. In 2001, the first cerebral protection device to become available was the PercuSurge distal balloon occlusion system, and filters generally started becoming available thereafter. Early reports indicated that debris, including fibrin, cholesterol clefts, red and white cell aggregates, and organized thrombus, could be retrieved from filters (Figure 2).[19] It was thought that this material was likely to have been liberated by the endovascular manipulation of the carotid bifurcation plaque with subsequent entrapment rather than forming on the filter device in situ, although this remains unproven.

Although ex vivo work on the prototype of the Neuroshield (originally MedNova, now Emboshield, Abbott Vascular, Santa Clara, CA) suggested that 88% of the liberated embolic burden during carotid angioplasty was trapped, the in vivo capture rate is not known.[20] Distal filters are not designed to capture particles smaller than the pore size of the available devices (currently 60–140 µm) that may pass unhindered to the brain. Filters may also exhibit failure to capture debris when suboptimal wall apposition is achieved. In vitro testing showed that filters can allow particles much larger than the pore size to pass by the filter.[21] Supporting evidence for the passage of smaller particles (ie, particles < 60 µm) comes from ex vivo work analyzing carotid angioplasty.[1] Guidewire passage alone generated 40,000 microemboli, although emboli were generated at each procedural stage, and a substantial number of emboli < 60 µm were produced. These are likely to evade capture by currently available filters but may be controlled by alternative protection strategies. The reported mean size of trapped particles ranged from 4 to 5,043 µm, and the numbers released range from 12 to 34,000 µm for all earlier devices. Regarding contemporary CAS practice, visible debris was present in 169 of 279 filters (60%) evaluated.[22] This would imply that despite a number of technical advances since

the inception of percutaneous carotid intervention as a rudimentary angioplasty technique, there might still be a substantial macroembolic penalty.[12]

DISTAL PROTECTION DEVICES AND MICROEMBOLI

The majority of CAS procedures are performed under some form of mechanical protection. During procedures in which embolic protection is used, 90% of treatments involve distal protection/filtration devices. Even so, current protected CAS procedures yield microemboli that are detected on transcranial Doppler (TCD) and diffusion-weighted magnetic resonance imaging (DW-MRI) of the brain. TCD is the only examination that can monitor intracranial blood flow in real time, thus detecting both symptomatic and asymptomatic cerebrovascular embolic events as they occur.[23]

Microemboli Detected on TCD

Differentiating gaseous from solid emboli with a high level of sensitivity has been reported using insonation at two ultrasound transducer frequencies of 2.5 and 2 MHz (Embo-Dop system, Compumedics, Singen, Germany) and would help determine the embolic source. Differentiation between solid and gaseous microemboli is based on the principle that solid microemboli reflect more ultrasound at a higher rather than lower frequency, whereas the opposite is the case for gaseous microemboli. This technique is still under investigation.[24-26]

TCD was used to compare the frequency of microembolic signals (MES) during CAS without protection versus CAS using a distal occlusion balloon (PercuSurge GuardWire). In the group of patients protected by distal balloon, a significant reduction of MES (MES counts = 164 ± 108 in the control vs 68 ± 83 in the protected group; $P = .002$) was observed during predilation, stent deployment, and postdilation.[27]

A Dutch single-center prospective analysis of microembolic signals on procedural TCD for unprotected CAS and filter-protected CAS reported that the use of filters may be associated with an increase in the numbers of distal microemboli.[28] Patients were divided into three groups: 161 patients treated before filters had become available (group 1), 151 patients treated with filters (group 2), and 197 patients treated without filters after these devices had become available (group 3). The authors concluded that carotid angioplasty and stent placement yielded more microemboli in patients treated with filters than in unprotected procedures; however, the infrequent occurrence of cerebral sequelae did not allow comprehensive statistical comparison among groups. Within a clinical randomized trial performed at the Sheffield Vascular Institute (SVI), there were significantly more MES in patients in whom a filter-type cerebral protection device had been employed (Neuroshield). Furthermore, off-site analysis determined that a substantial proportion of these MES corresponded to particulate matter and could not be simply dismissed as air due to agitated contrast injection.[29] It is well established that TCD can detect small emboli, but predicting which of these emboli will result in focal brain ischemia is not yet possible with the current technology.

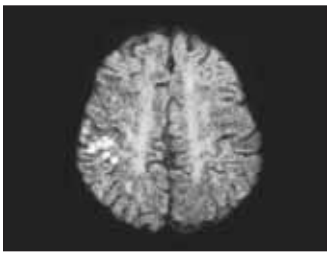


Figure 3. Right parieto-occipital new white lesions on DWI the day after right CAS.

DWI Findings

DWI is the most powerful tool for the detection of focal brain ischemia in the acute stage. It has been used for the detection of cerebral embolism (Figure 3) after acute ischemic neurologic events and for the detection of silent ischemic brain lesions after diagnostic cerebral angiography, coronary bypass surgery, CEA, and CAS. The hyperintense DWI lesions vanish over 2 weeks and may reappear as hypointense lesions thereafter. Therefore, optimal timing of the DWI is critical.[30] However, it should be noted that many DWI lesions reverse within months, and the extent of permanent injury may be overestimated.[31]

A comparison between 61 patients (including those who were symptomatic and asymptomatic) treated with CAS and 60 with carotid endarterectomy showed new DWI lesions in 11% in the surgical group versus 42.6% in the endovascular group, and clinical results were comparable. In the latter, 38.4% also had lesions in the contralateral hemisphere and 26.9% in the posterior circulation. These findings may be related to catheter manipulation in the aortic arch during the procedure.[30]

A prospective study that included 53 patients was conducted to determine the incidence of new areas of cerebral ischemia by DWI in high-surgical-risk patients undergoing filter-protected CAS. Postprocedural DWI detected new focal ischemic lesions in 21 patients (40%). The average number of lesions was 5.9 per patient, and the mean lesion volume was 1 mL or less in 19 patients (90%). Small differences were found in the lesion distribution: homolateral anterior circulation in eight cases (15.1%), other vascular territories in seven cases (13.2%), and homolateral anterior circulation plus other vascular territories in six cases (11.3%). The microembolization risk seemed nonpredictable on the basis of clinical parameters and internal

carotid artery lesion characteristics. An increased risk in the rate of ipsilateral hemispheric embolization has been observed in difficult carotid arch configurations ($P = .04$).[32]

In a prospective nonrandomized study including 48 patients, a DWI study was performed 1 hour before and 48 hours after filter-protected CAS. In the 23 patients imaged 1 hour postprocedure, new lesions were found in two (9%), and 18 (78%) had new lesions at 48 hours ($P < .001$). For the entire study group, the incidence of new lesions at 48 hours was 67% (36 of 54). The investigators believe that significant embolization continues for at least 48 hours postprocedure causing lesions on DWI when there is no mechanism for cerebral protection.[33]

A recent randomized trial compared unprotected CAS with filter protection using the Accunet filter (formerly Guidant Corporation, now Abbott Vascular).[34] This work postdates and references the SVI's randomized trial and had the same findings. There was a nonsignificant increase in lesions on DWI in the filter-protected group. The findings did not reach significance, probably because there were insufficient numbers (30 in the SVI trial and 35 in the Pittsburgh trial). Kastrup et al later stated that approximately 120 to 140 patients would be needed for a randomized trial based on DWI lesions to be adequately powered; however, Kastrup's article postdates the SVI trial.[35] Furthermore, it is important to note that Kastrup's estimated numbers are based on a "retrospective analysis of nonrandomized data with all its inherent limitations."[36] Although distal filters have been shown to capture emboli released during CAS, there is also evidence to indicate that emboli are missed either through the pores of the filters or around them due to suboptimal wall apposition. The evidence showing that filter-protected CAS produces more microemboli as detected with TCD or DWI when compared with CEA (and more microemboli than unprotected CAS) indicates that there is still room for improvement in filter design.

PROXIMAL PROTECTION OR FLOW REVERSAL AND MICROEMBOLI

The Mo.Ma system provides cerebral protection by endovascular occlusion of the common and external carotid arteries leading to a flow cessation in the target vessel. A TCD study comparing this device with the FilterWire (Boston Scientific Corporation, Natick, MA) showed that the Mo.Ma system significantly reduced MES counts during the procedural phases of wire passage of the stenosis, stent deployment, balloon dilation, and in total (MES counts for the filter device were 25 ± 22, 73 ± 49, 70 ± 31, and 196 ± 84 during the three phases and in total, respectively, and MES counts for the Mo.Ma system were 1.8 ± 3.2, 11 ± 19, 12 ± 21, and 57 ± 41, respectively; $P < .0001$).[37]

The GORE Flow Reversal System is a closed system that allows the arrest of common carotid artery flow, continuous passive internal carotid artery (ICA) flow reversal, or augmented active ICA flow reversal so that any particles released during CAS will pass retrograde through the catheter and be retrieved in the arteriovenous conduit filter outside the body. The three components of the device were designed specifically to allow retrograde flow in the ICA and minimize migration of particles or collection of material that could subsequently embolize. The establishment of a shunt (and subsequent flow reversal) allows for additional protection from uncovered collaterals that can contribute to continued antegrade ICA flow if the shunt is not in place. The functional principle behind this device is based on an observation made on TCD during CEA, that is, clamping the common carotid artery and the external carotid artery and inserting a shunt in the distal end of an arteriotomy-induced flow reversal in the middle cerebral artery (MCA) if the other end of the shunt was left open to the air.[38]

A preliminary evaluation of flow reversal in 28 of 30 patients in whom satisfactory reversal of flow could be established revealed a complete absence of MES on procedural TCD.[39] In a larger series including 200 patients, TCD monitoring was used in 132 patients, and no embolic signals were registered during reversal of flow. In some patients, TCD showed intracranial ICA or MCA flow reversal, in others, there was sufficient collateralization from the anterior cerebral artery.[40] The GORE Flow Reversal System is unique in this finding.

In an ongoing study at the Medical University of South Carolina, bilateral temporal monitoring TCD was performed in patients undergoing CAS. Seven patients were protected using various distal filters that had been approved by the US Food and Drug Administration and another seven using the reversal of flow technique with the GORE Flow Reversal System. Doppler spectral and M-mode signals from ultrasound probes mounted to a headframe were continuously recorded. The use of software detecting high-intensity transient signals allowed for real-time intraoperative feedback about the efficacy of the embolic protection method used, as well as the cerebral blood flow dynamics. The recorded data were digitally stored for postprocedural comparison between the findings obtained with the different protection techniques and phases of the procedures. Quantification of MES for statistical analysis was performed by manual review to allow for differentiation from injection and other artifacts. TCD signal recordings were evaluated for three stages of the procedure: (1) protection device deployment (PD); (2) stent delivery including pre- and postdilatation (SD); and (3) protection device removal (PR). MES were counted when

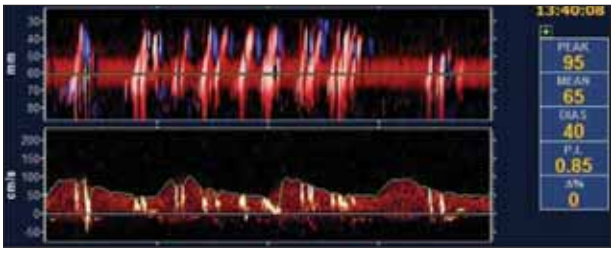


Figure 4. TCD during CAS using a filter: multiple MES are seen during the procedure.

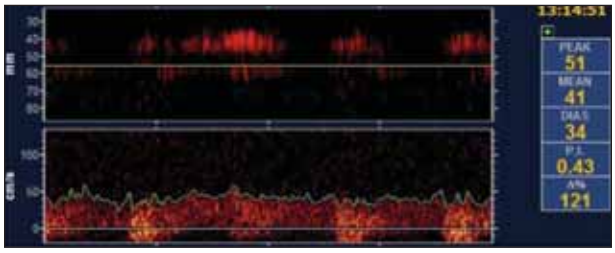


Figure 5. TCD during CAS using flow reversal: no MES were seen during the procedure.

detected in the MCA of the side of the treated carotid artery and are presented as filter versus flow reversal treatment group means. Patients undergoing CAS using the GORE Flow Reversal System demonstrated significantly less average total MES counts compared to procedures using filter devices (431.3 ± 65.4 vs 116.3 ± 20.8, N = 14; *P* < .001). Although the PD and PR phases were not significantly different (PD = 102.3 ± 28.4 vs 73.7.0 ± 19.6; *P* = not significant; and PR = 34.3 ± 24.4 vs 36.7 ± 8.9; *P* = not significant), in the SD phase, with the respective protection device in place, the average MES counts were significantly higher in patients treated with filter protection (294.7 ±5 6.2 vs 6 ± 1.03; *P* < .001). In conclusion, preliminary analysis of the study data suggests that patients undergoing CAS under reversal of flow with the GORE device have significantly fewer MES than patients protected with filter devices (Figures 4 and 5).[41]

A single-center, prospective, nonrandomized study compared DWI lesions in patients undergoing CAS with flow reversal and patients undergoing cerebral angiography alone. There was no statistical difference between the control group (12%) and the flow reversal group (18%). CAS with flow reversal can be performed with the same embolic risk as diagnostic angiography.[42]

Early TCD and DWI data from flow-reversal-protected CAS shows promise in reducing embolic activity during the most highly embologenic phases of CAS. Data from the EMPIRE trial show a low stroke and death rate of 2.6% for both symptomatic patients and octogenarians. Both are patient populations that are considered to be at high risk for ischemic events during CAS. These data hint at real clinical benefit for these high-risk subgroups in CAS. Whether these benefits remain through more extensive evaluation and are shown to be a result of reduced emboli injury during CAS needs further study.

The clinical effect of these "silent" ischemic lesions within brain areas without primary motor, sensory, or linguistic function ("noneloquent" brain areas) is debated. Subtle changes in cognitive function are currently being assessed after CAS. There is increasing evidence, however, that the cumulative burden of ischemic brain injury causes neuropsychological deficits or a steeper decline in cognitive function and increases the incidence of dementia in the clinical setting of coronary artery bypass surgery and in screened healthy populations with DWI lesions.[43-45]

CONCLUSION

Macro- and microembolization are associated with the treatment of carotid artery stenoses by carotid stenting. Various types of filter devices seem to be effective in preventing macroembolization but are not designed to provide complete protection from particles smaller than the pore sizes of the device and may in fact increase the number of MES. Microembolization remains the Achilles' heel of CAS, and the incidence of procedural microembolization may depend on the type of EPD employed.

A systematic review of MRI studies showed that cerebral protection devices appeared to significantly reduce the number of new ipsilateral DWI lesions after CAS. However, none of the evaluated studies were randomized trials, and many studies employed historical nonconcurrent controls in which important confounding variables such as type of stent, learning curve, and the demographics of the patient population were not corrected for. Furthermore, 33% of patients had new DWI lesions within the vascular territory of the treated carotid artery even after mostly filter-protected CAS, which documents that dislodgement of a large number of embolic particles to the brain is not prevented by the use of filter-type protection devices.[46] The flow reversal technique showed no MES during phases of the procedure when most particles are released.

There is not yet proof that MES are related to new lesions using DW-MRI studies. The correlation between these factors and cognitive function is still debatable and remains troublesome when observed. It is recognized, however, that MES are better tolerated in young patients with good cerebral functional reserve than in older individuals with low functional reserve.[47] It seems reasonable to say that MES cannot do any good to the brain, and their occurrence should be at least a reason for concern. Until we have conclusive evidence about MES and their

potential damage to the brain, it would seem preferable to try to suppress or minimize its occurrence. All embolic protection devices have advantages and disadvantages and likely vary in their efficacy. Although filtration devices clearly protect the brain from larger particles, which would otherwise likely cause major stroke, embolic events have been documented during their use. Proximal occlusion may offer some improvement in events in this regard; however, flow reversal appears to be closer to the ideal device in terms of providing complete protection from embolic debris through establishment of the reverse flow circuit. ■

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The Albany Vascular Group Experience

Embolic protection during carotid artery stenting using the GORE Flow Reversal System.

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The intent of carotid endarterectomy (CEA) or carotid artery stenting (CAS) is to improve the ipsilateral stroke-free survival rate. During the past decade, CAS with distal cerebral embolic protection devices (EPDs) has undergone intense scrutiny and, for the time being, survived with US Food and Drug Administration (FDA) and CMS approval of CAS for high-surgical-risk symptomatic patients with carotid stenosis > 70%. At the same time, the results of CAS have clearly improved, albeit difficult to assess whether the improvement is secondary to increasing operator experience, improving technology, or a combination of both.

Distal filters are the most extensively studied and most frequently used EPDs and have several advantages in that they limit distal cerebral embolization, have a relatively low crossing profile, and preserve cerebral flow during CAS. They also have several limitations in that they need to traverse the carotid lesion before establishing cerebral protection, require a considerable length of relatively straight internal carotid artery (ICA) beyond the carotid lesion (safe landing zone), can cause significant ICA vasospasm, allow microemboli < 200 to 250 µm (depending on the EPD) to escape, and have the potential to occlude during the procedure.[1-6] The other form of EPD includes a distal ICA occlusion balloon, which also requires the need to cross the carotid lesion before establishing cerebral protection, and although the balloons do not require significant length for the landing zone, they do lead to complete ICA occlusion, which can lead to cerebral ischemia and intolerance to the ICA occlusion balloon.[3] Based on these limitations, it is obvious that innovation of disruptive technology, which adds to our armamentarium the ability to provide embolic protection during CAS, will continue to carve out its niche in the treatment of carotid stenosis, stroke prevention, and possibly stroke treatment.

Earlier this year, based on the results of the multicenter EMPiRE (Embolic Protection With Reverse Flow) study, which evaluated the safety and efficacy of high-surgical-risk patients with carotid stenosis undergoing CAS, the FDA granted approval to the GORE Flow Reversal System (W. L. Gore & Associates, Flagstaff, AZ). The GORE Flow Reversal System for CAS is a disruptive technology, unique from all other FDA-approved EPDs in that it allows proximal common carotid artery (CCA) occlusion and establishes cerebral flow reversal via an ex vivo arteriovenous shunt before traversing the carotid lesion. By providing the ability to establish cerebral flow reversal before coming in contact with the carotid lesion, the GORE Flow Reversal System

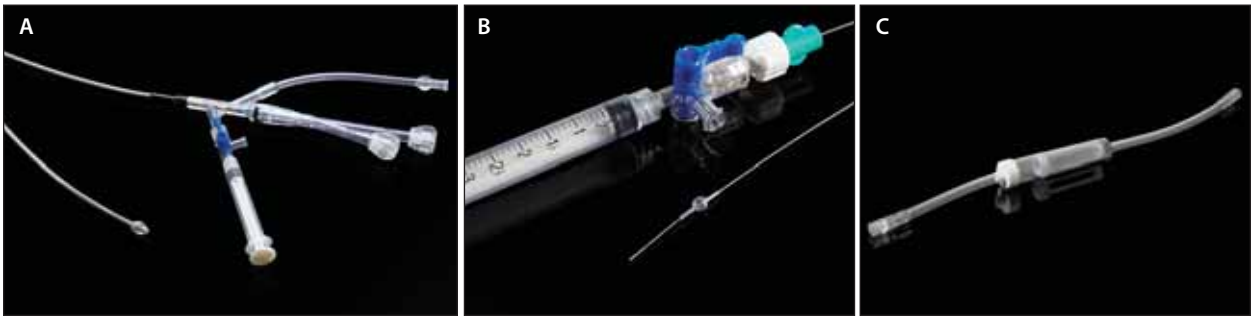

Figure 1. Balloon sheath (A), balloon wire (B), and external filter (C).

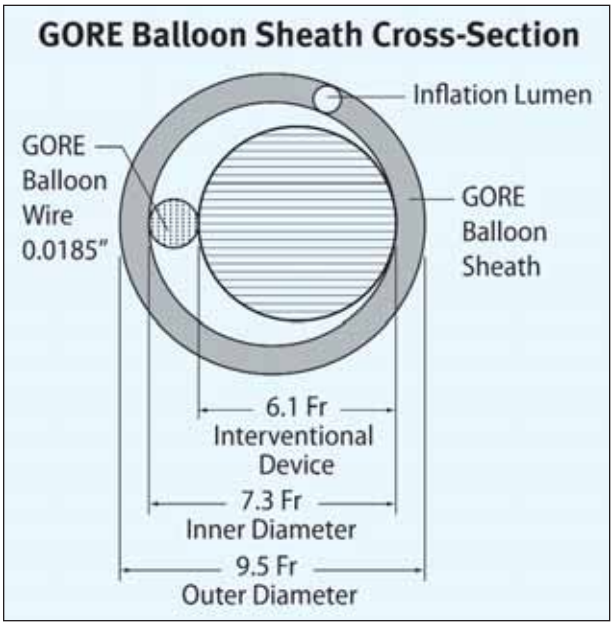

Figure 2. GORE balloon sheath cross-section.

overcomes some of the theoretic limitations of currently available EPDs in that cerebral protection is obtained before ever traversing the carotid artery lesion. Although the brain's ability to tolerate microembolization without any clinical manifestation of transient ischemic attack (TIA) or stroke remains a mystery, surrogate markers of transcranial Doppler (TCD) high-intensity transient signals (HITS) and diffusion-weighted imaging (DWI) lesions indicate the potential for ischemic damage beneath the level of TIA and stroke during CAS. Data from TCD monitoring during CAS with flow reversal indicate a reduction in embolic signals when compared to distal EPDs.[1,2] A small study evaluating the presence of new DWI lesions after CAS using flow reversal in comparison to angiography was comparable.[3]

THE ALBANY VASCULAR GROUP EXPERIENCE

From 2006 to 2008, The Albany Vascular Group was one of the 29 participating sites in the United States that enrolled a total of 245 subjects into the EMPiRE study using GORE Flow Reversal for cerebral protection during CAS (a prospective multicenter, single-arm trial). The EMPiRE trial evaluated symptomatic patients with ≥ 50% carotid artery stenosis or asymptomatic patients with ≥ 80% carotid artery stenosis. All 49 CAS procedures with GORE Flow Reversal performed at the Albany Vascular Group were performed under local anesthesia and conscious sedation. Antiplatelet therapy included aspirin (325 mg/daily) and clopidogrel (75 mg/twice daily), which was started at least > 48 hours before the procedure and was continued for at least 30 days after the procedure. During the CAS procedure, patients received intravenous anticoagulation (heparin or bivalirudin) to maintain an activated clotting time of > 250 seconds.

The GORE Flow Reversal System includes a balloon sheath (7 F), a balloon wire, and an external filter (Figure 1). The procedure steps are as follows:

1. Obtain femoral artery access (9-F Terumo Pinnacle Sheath [Terumo Interventional Systems, Somerset, NJ]) and femoral venous access (6-F sheath) (Figure 2).
2. Balloon sheath access into the CCA.
3. Balloon wire advanced into the external carotid artery (ECA).
4. The femoral arterial and venous sheaths are connected with the external filter to create an arteriovenous shunt.
5. The ECA balloon is inflated, and subsequently, the CCA balloon is inflated.
6. Flow reversal is established as the direction of blood flow is from the ipsilateral ICA into the balloon sheath, across the ex vivo femoral arteriovenous shunt and the

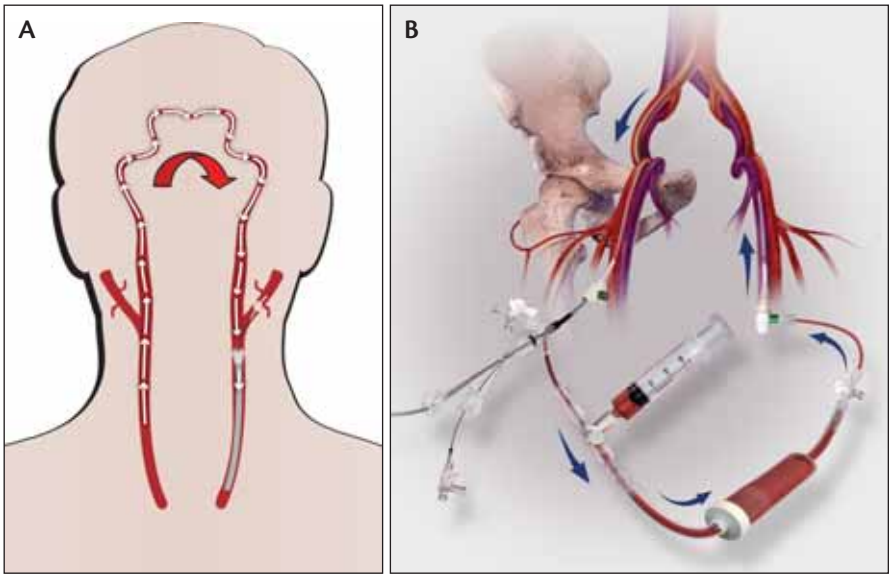

Figure 3. Flow reversal is established as the blood flows from the ipsilateral ICA into the balloon sheath (A) and across the ex vivo femoral arteriovenous shunt of the external filter and back into the femoral vein (B).

external filter, and back into the femoral vein (Figure 3).

7. Once flow reversal is achieved, a 0.014-inch wire is traversed across the ICA lesion, and a self-expanding stent is advanced across the carotid lesion and deployed. Pre- and postdilatation are carried out as needed.

8. Throughout the procedure, multiple active aspirations are performed at the level of the femoral arteriovenous shunt after stent placement and angioplasty.

9. Once an adequate result is obtained, the ECA balloon is deflated and removed, and subsequently, the CCA balloon is deflated, and the balloon sheath is removed.

During a 2-year period, we enrolled 49 patients into the study and will present our experience and lessons learned with CAS using the GORE Flow Reversal System in this article. The primary endpoint included TIA, stroke, death, and myocardial infarction within 30 days of CAS. The secondary endpoints included technical success of device placement and establishing flow reversal that was tolerated by patients (Table 1). The mean age was 69 years, 67% male, 25% symptomatic, 49% with previous CEA, and 14% of patients were octogenarians. High surgical risk was secondary to medical comorbidity risk factors in 35% of patients and due to anatomical risk factors in 80% (Table 2). Eleven (22.4%) of the 49 patients were considered to be high risk for a routine CAS procedure with the currently available distal EPDs due to significant carotid artery tortuosity, significant calcifications/ulcerations, or a combination of both.

Technical success was achieved in 47 (96%) patients, and in the remaining two (4%) patients, the procedure was discontinued due to hostile thoracic arch anatomy (type III arch with significant calcifications). Two (4%) patients experienced intolerance to flow reversal during the procedure; one patient required intravenous vasopressors to elevate systemic blood pressure, and the other required intermittent discontinuation of flow reversal by deflating the CCA balloon during parts of the procedure that were considered lower risk for embolization. Both patients were treated successfully and without any adverse sequela. None of the six (12%) patients with contralateral ICA occlusion developed intolerance to flow reversal. The median procedure time was 50 minutes (range, 23–126 minutes), and the median flow reversal time was 11 minutes (range, 4–51 minutes). The major adverse event rate, which included death, stroke, TIA, and myocardial infarction, was 4%; one patient suffered a minor stroke, one patient suffered a TIA, and there were no deaths or myocardial infarctions. The octogenarians accounted for 14% of the subjects, and none experienced any major adverse events.

In our experience with CAS, when compared to the distal cerebral EPDs, we have found the GORE Flow Reversal System to have several additional advantages:

1. Cerebral protection from embolization is established before crossing the carotid lesion.

2. Flow reversal continuously directs micro- and macroemboli away from the brain during the procedure and is associated with less microemboli reaching the brain.[1-3]

3. Flow reversal expands the treatment options for challenging carotid lesions, including tortuous carotid arteries that do not allow for safe crossing and placement of distal EPDs.

4. Anchoring a balloon in the CCA provides added stability during CAS.

5. Initial data are promising for treating all patients, including octogenarians.

Although we await the publication of the initial data from the EMPiRE trial, which led to FDA approval of the GORE Flow Reversal System, and certainly look forward to longer-term data with this device, our initial experience

TABLE 1. SECONDARY ENDPOINTS OF THE ALBANY VASCULAR GROUP

	GFRS: All Subjects
Number of subjects enrolled	49
SUMMARY OF EMBOLIC PROTECTION SYSTEM SUCCESS	
GFRS successfully deployed	47 (95.9%)
GFRS successfully deployed with technical difficulties	2 (4.1%)
- Tortuous anatomy	1 (2%)
- Unable to properly position balloons	1 (2%)
Technical failure (GFRS deployment not successful)	0 (0%)
SUMMARY OF STENTING PROCEDURE SUCCESS	
Stent deployment successful	48 (98%)
Stent deployment unsuccessful	1 (2%)

Abbreviation: GFRS, GORE Flow Reversal System.

TABLE 2. INDICATIONS FOR CAROTID ANGIOPLASTY AND STENTING

GFRS: All Subjects	Symptomatic	Asymptomatic	Overall
Number of subjects enrolled	14	35	49
Anatomic risk	71.4% (10/14)	82.9% (29/35)	79.6% (39/49)
Surgically inaccessible lesions	7.1% (1/14)	2.9% (1/35)	4.1% (2/49)
Postradical head/neck surgery or RT	35.7% (5/14)	22.9% (8/35)	26.5% (13/49)
Presence of tracheostomy stoma	7.1% (1/14)	5.7% (2/35)	6.1% (3/49)
Laryngeal palsy or laryngectomy	7.1% (1/14)	5.7% (2/35)	6.1% (3/49)
Restenosis after previous CEA	28.6% (4/14)	17.1% (6/35)	22.4% (11/49)
Comorbid risk	42.9% (6/14)	31.4% (11/35)	34.7% (17/49)
Age ≥ 80 years	14.3% (2/14)	14.3% (5/35)	14.3% (7/49)
NYHA Class III or IV	7.1% (1/14)	2.9% (1/35)	4.1% (2/49)
COPD with FEV1 < 50%	0% (0/14)	2.9% (1/35)	2% (1/49)
LVEF < 35%	0% (0/14)	5.7% (2/35)	4.1% (2/49)
Contralateral total occlusion of the ICA	21.4% (3/14)	8.6% (3/35)	12.2% (6/49)
Significant tortuosity/Ca+, high risk for CAS	28.6% (4/14)	17.1% (6/35)	22.4% (11/49)

Abbreviations: Ca+, calcium; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; GFRS, GORE Flow Reversal System; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RT, radiotherapy.

would suggest that the GORE Flow Reversal System has many advantages as described previously. In our experience, the learning curve varies depending on the expertise of the interventionist and probably ranges between three to five procedures. As an emerging disruptive technology, the GORE Flow Reversal System also has some nuances, such as flow reversal intolerance. Our initial experience would suggest that flow reversal intolerance is not easy to predict on the basis of patency of the contralateral carotid and vertebral arteries and the Circle of Willis. Fortunately, flow reversal intolerance is an infrequent event and most often can be managed by a few simple maneuvers. Intravenous vasopressors can be used transiently for elevating the systemic blood pressure during flow reversal, and flow reversal can be discontinued intermittently by deflating the CCA balloon during parts of the procedure that are considered lower risk for embolization. During catheter, balloon, or stent manipulation across the carotid lesion, the flow reversal can be re-established for a short duration.

Although our experience is only a subset analysis of the EMPiRE trial, it indicates the safety and efficacy of the GORE Flow Reversal System during CAS in high-surgical-risk patients, and this is validated by the FDA approval of the device. What is exciting about this disruptive technology is that it might have the potential for expanding the role of CAS to a broader patient population that might otherwise have been considered high risk for carotid stenting, including treatment of embolic stroke; of course, this must be validated by additional investigations. ■

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The Emory Experience

A review of carotid stenting, flow reversal, microembolization, and vascular dementia.

BY KARTHIKESHWAR KASIRAJAN, MD, AND LUKE BREWSTER, MD

Despite the US Food and Drug Administration approval of a variety of carotid artery stent (CAS) systems, the initial projections on the proportion of patients receiving percutaneous interventions have fallen short (Figure 1). This may be for a variety of reasons, including the limited reimbursement dictated by CMS, which in turn is related to the high death/stroke rate in nontrial hospitals. The higher death/stroke rate in nontrial hospitals may be related to inexperience, learning curve, improper patient selection, and incomplete protection provided by the distal filters.

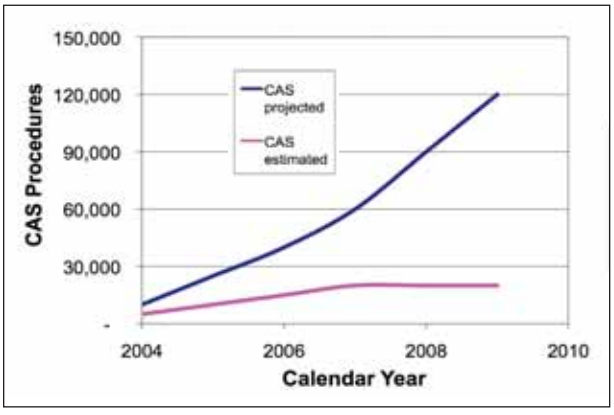

Figure 1. Estimated actual CAS versus projected CAS after initial FDA approval of distal filters.

DISADVANTAGES OF DISTAL FILTERS

Currently in the United States, seven different CAS systems are approved for use. They all use the same principle of a distal basket that traps debris released during the stent deployment and angioplasty. The pores in the filter allow antegrade blood flow, which provides uninterrupted antegrade cerebral perfusion and the ability to visualize the target lesion at all points. The majority of the filters have 100-µm pores that allow small embolic particles to reach the brain. Additionally, the filter basket has to cross the lesion in an unprotected fashion before distal deployment. Additional disadvantages include the need for a distal landing zone (Figure 2), filter-related internal carotid artery damage, and others that are given in Table 1.

TABLE 1. DISADVANTAGES OF DISTAL FILTERS

- Unprotected lesion crossing
- Inability to cross tight lesions
- Continued release of microembolic debris
- Vessel damage related to filter
- Need for a distal landing zone
- Improper filter-vessel apposition
- Release of debris during filter recovery
- Inability to recover filter

CONCEPT OF FLOW REVERSAL

Carotid endarterectomy (CEA) remains the gold standard and has been extensively evaluated in a variety of prospective randomized studies and other single-center reviews. Any percutaneous treatment option must meet the safety standards set by CEA. The most important concept of CEA involves achieving distal protection before the lesion is manipulated. The goal of distal control before lesion manipulation cannot be achieved by the use of distal filters. Flow reversal uses

TABLE 2. ADVANTAGES OF GORE FLOW REVERSAL SYSTEM

- Protection from cerebral remobilization at all points
- Guidewire of choice
- 0.014-inch or lower crossing profile
- No requirement for distal landing zone
- No filter-related internal carotid artery trauma
- Minimal cerebral microemboli (silent infarcts)

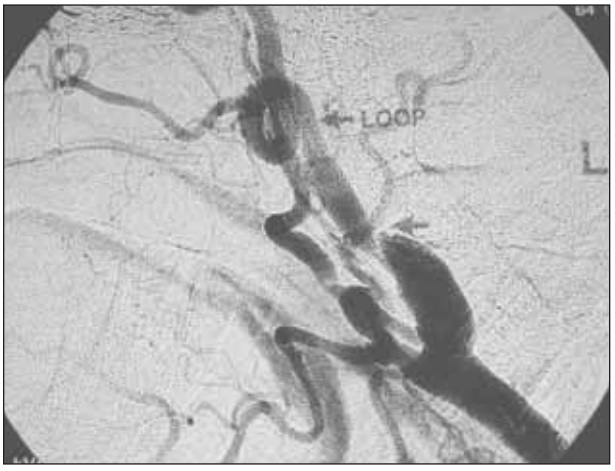

Figure 2. A loop in the internal carotid artery prevents the safe use of distal filters.

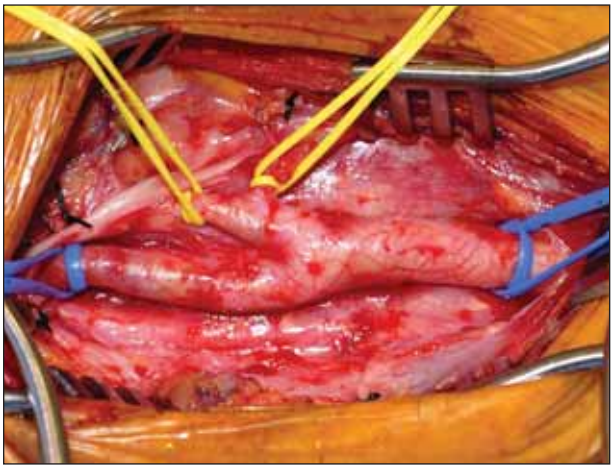

Figure 3. CEA showing distal control before manipulation of the lesion.

the concept of CEA (Figure 3) by avoiding guidewire manipulation of the target lesion before protection has been established. This technique involves balloon occlusion of the common and external carotid artery and siphoning the blood from the ipsilateral internal carotid artery via the femoral sheath. Lesion crossing is never attempted without establishing flow reversal in the internal carotid artery, thereby providing protection at all points. This provides a variety of advantages shown in Table 2. Disadvantages of the GORE Flow Reversal System (W. L. Gore & Associates, Flagstaff, AZ) include the need for a 9-F sheath and the learning curve associated with the concept of flow reversal. However, in the EMPiRE study evaluating the GORE Flow Reversal System, the complication rates did not change based on operator experience (Table 3). This suggests that this technique can be readily adapted with few complications, even among infrequent users.

EMORY EXPERIENCE WITH THE GORE FLOW REVERSAL SYSTEM

From March 30, 2007 to February 20, 2009, a total of 53 patients were treated with the GORE Flow Reversal System at Emory. Patient demographics are provided in Table 4. Overall, 20 out of 53 patients (38%) enrolled were symptomatic. Thirteen (24.5%) had a history of previous CEA. Indications for stenting are given in Table 5. All patients had a pre- and post-National Institutes of Health Stroke Scale evaluation by an uninvolved medical provider. Mean procedure time was 66 ± 28 minutes, mean flow reversal time was 11 ± 10 minutes, and mean fluoroscopy time was 14.1 ± 5.3 minutes. Intolerance to flow reversal was noted in four (7.6%) patients; however,

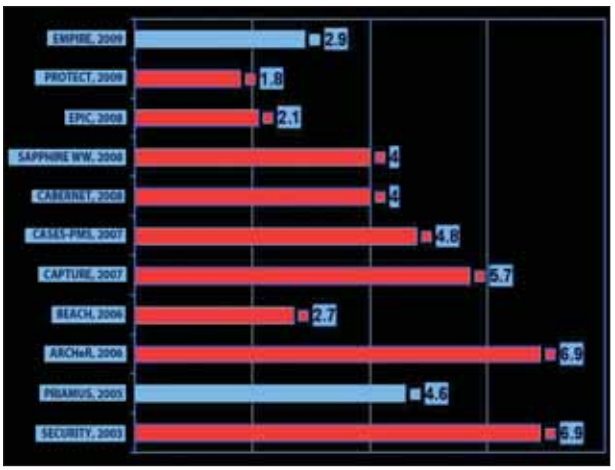

Figure 4. Composite death/stroke of various carotid trials.

the procedure was completed in all four subjects without any adverse clinical sequela. Flow intolerance manifested in the form of loss of consciousness in two patients and confusion in the other two patients.

The procedure was completed in two patients without the need for further manipulation or discontinuation of flow reversal. In the other two patients, the common carotid balloon was deflated, and systemic blood pressure was increased before reinstituting the flow reversal. This maneuver was successful in preventing the symptomatic cerebral steal. Six of the 53 patients enrolled had contralateral occlusion. Interestingly, none of the six patients had any flow intolerance, demonstrating that cerebral steal is a rare event and cannot be predicted based on the status of the contralateral internal carotid artery. Flow intolerance

TABLE 3. MAJOR ADVERSE EVENTS BASED ON OPERATOR EXPERIENCE

No. of GFRS procedures	MAEs
1–5	5.2%
6–10	3.85%
11–20	4.4%
21–30	3.85%

Abbreviations: MAEs, major adverse events (defined as death, stroke, transient ischemic attack, or myocardial infarction); GFRS, GORE Flow Reversal System.

may be more closely related to the adequacy of collaterals in the Circle of Willis. Given the low incidence of flow intolerance and the lack of adverse events related to this, the authors do not believe that additional imaging of the intracranial circulation is warranted in an effort to predict flow intolerance. In our experience with 53 patients, our death/stroke/myocardial infarction rate was 0%. The mean length of stay was 2 ± 1.9 days.

LEARNING CURVE WITH FLOW REVERSAL

In the authors' experience with 53 procedures, an improvement was noted in the total procedure time (P = .003) and the flow reversal duration (P = .107). Total fluoroscopy time and contrast volume had no statistical difference (Table 6). No difference was noted in the death, stroke, transient ischemic attack, or myocardial infarction rates (all remained at 0 for the 53 patients). The improvements in the time for the procedure may have been primarily related to device preparation and having ancillary equipment ready and prepared. The significant drop in the flow reversal time may be related to the practice of loading the 0.014-inch crossing wire and stent in the sheath before inflation of the external and common carotid balloon. Additional steps, such as the use of a 9-F, 45-cm sheath in the femoral artery at the start of the procedure, minimized the need for additional manipulations in the iliac artery to overcome tortuosity, iliac calcification, etc. The low complication rate in the early part of the study indicates that this may be a safe technology, even for the infrequent user.

MICROEMBOLIZATION DURING CAROTID ANGIOPLASTY AND STENTING

Experience with transcranial Doppler monitoring during filter-protected carotid artery angioplasty and

TABLE 4. PATIENT DEMOGRAPHICS

Number of subjects	53
Gender (male)	31 (58.5%)
Ethnicity (Caucasian)	50 (94.3%)
Age (y)	69.4 ± 11
General medical history	
Coronary	32.1% (17/53)
Neurologic (not vascular)	3.8% (2/53)
Respiratory	45.3% (24/53)
Musculoskeletal	54.7% (29/53)
Endocrine	24.5% (13/53)
Diabetes	37.7% (20/53)
Hyperlipidemia	67.9% (36/53)
Hypertension	84.9% (45/53)
Renal	18.9% (10/53)
History of tobacco use	39.6% (21/53)

CAS demonstrates hundreds of microembolic signals to the brain. This has not resulted in a higher incidence of clinically evident strokes in the various carotid stent trials (Figure 4). Therefore, the clinical implication of microemboli to the brain has often been disregarded and is considered by most physicians as being unimportant. This is further complicated by the finding of new microinfarcts seen on diffusion-weighted magnetic resonance imaging (DW-MRI) after carotid angioplasty and stenting. These microinfarcts are also clinically asymptomatic in the perioperative period, resulting in the term *silent infarcts*. However, recent clinical data appear to contradict earlier findings.

There is a cumulative burden of data that appear to suggest that the microemboli (resulting in the silent infarcts) may lead to long-term cognitive dysfunction termed as *vascular dementia*. In a Japanese study of patients with Alzheimer's disease, one-third of the patients had silent brain infarcts revealed by MRI. This finding is similar to autopsy findings in clinicopathological studies among patients with dementia. This is in stark contrast to population-based studies with a reported low incidence (2%–3%) of silent infarcts seen in MRI imaging among patients with no dementia. Furthermore, the results of the Rotterdam Scan Study showed that the presence of silent brain infarcts more than doubles the risk of dementia, including Alzheimer's disease. The Cardiovascular Health Study also confirmed that silent brain infarcts were a risk factor for mild cognitive impairment.

Based on current data, we can assume that microembolic signals during CAS result in silent

TABLE 5. INDICATIONS FOR CAROTID ANGIOPLASTY AND STENTING

	Symptomatic	Asymptomatic	Total
Number of patients enrolled	20	33	53
Anatomic risk	40% (8/20)	84.8% (28/33)	67.9% (36/53)
Surgically inaccessible lesions	15% (3/20)	39.4% (13/33)	30.2% (16/53)
Postradical head/neck surgery	30% (6/20)	36.4% (12/33)	34% (18/53)
Spinal immobility of the neck	0% (0/20)	3% (1/33)	1.9% (1/53)
Presence of tracheostomy stoma	0% (0/20)	6.1% (2/33)	3.8% (2/53)
Laryngectomy	0% (0/20)	9.1% (3/33)	5.7% (3/53)
Laryngeal nerve palsy	0% (0/20)	0% (0/33)	0% (0/53)
Restenosis after previous CEA	5% (1/20)	24.2% (8/33)	17% (9/53)
Comorbid risk	75% (15/20)	42.4% (14/33)	54.7% (29/53)
Age ≥ 80 years	35% (7/20)	9.1% (3/33)	18.9% (10/53)
NYHA class III or IV	35% (7/20)	9.1% (3/33)	18.9% (10/53)
COPD with FEV1 < 50%	25% (5/20)	6.1% (2/33)	13.2% (7/53)
LVEF < 35%	0% (0/20)	0% (0/33)	0% (0/53)
Uncontrolled diabetes	0% (0/20)	3% (1/33)	1.9% (1/53)
Unstable angina with ECG changes	5% (1/20)	9.1% (3/33)	7.5% (4/53)
MI within 30 days of procedure	0% (0/20)	3% (1/33)	1.9% (1/53)
Two or more diseased arteries	5% (1/20)	0% (0/33)	1.9% (1/53)
CABG or valve replacement surgery	0% (0/20)	3% (1/33)	1.9% (1/53)
Contralateral ICA occlusion	10% (2/20)	12.1% (4/33)	11.3% (6/53)

Abbreviations: CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; FEV1, forced expiratory volume in 1 second; ICA, internal carotid artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

TABLE 6. LEARNING CURVE BASED ON THE AUTHORS' EXPERIENCE

	Procedure Numbers				*P* Value
Operator volume	1–2	3–10	11–20	> 20	
Procedure time[a]	133.5 ± 33.2	87 ± 35	73.2 ± 33	53 ± 13	.003
Flow-reversal time[a]	36 ± 28	13.8 ± 5.4	13.9 ± 15.3	8 ±3.5	.017
Fluoroscopy time[a]	18	16 ± 9	13.7 ± 3.8	13.8 ± 4.8	.537
Contrast volume[b]	105	87.3 ± 45.2	95.1 ± 29.7	138.5 ± 24	.258

[a]Minutes.
[b]Milliliters.

TABLE 7. TOTAL NUMBER OF MICROEMBOLIC SIGNALS REACHING THE BRAIN DURING THE PROCEDURE

	CAS[a]	GFRS[b]
Total HITS	322 ± 95	184 ± 110
Preprotection	129 ± 66	115 ± 86
Protection	187 ± 67	33 ± 19
Postprotection	21 ± 15	36 ± 48

Abbreviations: GFRS, GORE Flow Reversal System; HITS, high-intensity transient signals.
[a]Carotid angioplasty and stenting with distal filters.
[b]Carotid angioplasty and stenting with the GORE Flow Reversal System.

infarcts, as seen in DW-MRI images, and this in turn may result in long-term cognitive dysfunction. Based on this hypothesis, we evaluated the incidence of microembolic signals to the brain during filter-protected CAS and compared this to flow-reversal-protected CAS. There was a significantly lower incidence of embolic debris reaching the brain using the GORE Flow Reversal System (Table 7). The major decrease in microembolic signals to the brain happened during the protection phase.

The authors believe that cerebral infarcts, silent or not, cannot be disregarded. It would be safe to assume that most patients would prefer not to have any infarcts seen in their cerebral hemispheres. If in fact these silent infarcts are proven to result in long-term cognitive dysfunction after carotid angioplasty and stenting, the current distal filter technology may become unacceptable and unethical. This urgently calls for prospective studies evaluating cerebral microemboli and their long-term implications, as well as studies comparing the different techniques of percutaneous carotid revascularization to open surgery and best medical therapy. ■

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Stroke Prevention in Carotid Artery Stenting

Gary Ansel, MD, discusses the goals and challenges of embolic protection, the potential of flow reversal, and how stroke rates have improved over the past decade.

What are the primary goals of neuroprotection during carotid artery stenting (CAS)?

The primary goals of neuroprotection during CAS are to prevent debris from embolizing to the distal vascular bed and causing a stroke while acting as a stable platform from which to deliver the balloon and stent.

What do you feel are the current limitations based on clinical evidence for CAS to date?

The current distal embolic protection devices each have one or more of the following limitations. First, they must pass through the carotid blockage before establishing protection. They have difficulty passing through severely stenotic stenoses and/or significant vessel tortuosity. They also let blood flow through pores that allow some amount of distal embolization, require a landing zone for the device, and have difficulty maintaining wall contact if used in noncircumferential vessels. Lastly, they must be recaptured and removed through the stent.

What has been improved in outcomes since CAS was first introduced?

The biggest change in outcomes since CAS was introduced over a decade ago is primarily centered on the decreased incidence of stroke. Since the early trials with overall stroke rates of approximately 5%, the last few trials have had stroke rates of less than 3%. This decrease may be attributed to several factors including improved device profile, filter efficiency, etc., but the improvement may also be attributed to better patient selection. Just as there are markers for increased surgical risk, there also appears to be markers of increased risk from carotid stenting.

What will help clinicians to achieve better results?

I think clinicians will continue to achieve better results as experience increases, and we will learn more about what actually leads to strokes both intraprocedurally and after the procedure. As we become more insightful, we may improve our decision-making process as to which protection type, stent type, etc., to use.

Considering the recent Embolic Protection with Reverse Flow (EMPiRE) study results, what role do you think flow reversal has in helping CAS reach its potential?

The recent proximal protection device results are very encouraging regarding the potential of continuing to lower the patient risk during carotid stent procedures. I feel the addition of this unique approach will increase the number of patients that can be offered a safe procedure. As physicians become more insightful as to which patient populations are best suited for proximal versus distal embolic protection, we will help the field mature. ■

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