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Perspectives on the Current State of Major Carotid Revascularization Trials

A multidisciplinary roundtable of carotid experts discusses recent trial data, difficulties in comparative analyses, the search for definitive conclusions, and the new questions arising with every published dataset.

PANEL

William A. Gray, MD, is Associate Professor of Clinical Medicine and Director of Endovascular Services, Center for Interventional Vascular Therapy, New York-Presbyterian Hospital/Columbia University Medical Center in New York.

L. Nelson Hopkins, MD, is Professor and Chairman of Neurosurgery, Professor of Radiology, and Director of the Toshiba Stroke Research Center at the State University of New York at Buffalo in New York.

Barry T. Katzen, MD, FACC, FACR, FSIR, is Founder and Medical Director of Baptist Cardiac and Vascular Institute and Clinical Professor of Radiology at the University of South Florida College of Medicine in Florida.

Sumaira Macdonald, MBChB (Comm.), FRCP, FRCR, PhD, is a Consultant Vascular Radiologist and Honorary Clinical Senior Lecturer at Freeman Hospital in Newcastle upon Tyne, England.

Frank J. Veith, MD, is Professor of Surgery at New York University Medical Center in New York and Professor of Surgery and William J. von Liebig Chair in Vascular Surgery at the Cleveland Clinic in Cleveland, Ohio.

Dr. Gray: We have entered a very critical period for carotid revascularization, and this is an excellent time to conduct a roundtable taking a closer look at today's data regarding carotid revascularization, including carotid artery stenting (CAS), endarterectomy (CEA), and best medical therapy. New and robust data are available from both ICSS and CREST, and the topic of CAS, particularly in the United States, is going to become increasingly relevant from both the regulatory and reimbursement standpoints. As such, we thought it would be a good idea to try to make sense of the currently available data in hopes of finding common ground and a greater understanding of carotid arterial disease and its treatments as we go forward in the field. In order to best apply the data derived from the many, at times conflicting, sets of trial results, we must first understand how those data were generated, and how exactly they compare to other past and contemporary data.

Dr. Macdonald, would you like to begin by describing some of the most relevant differences in the datasets in terms of definitions and the potential effects they may have on our interpretation?

OF APPLES AND ORANGES

Dr. Macdonald: I think it begins with the definitions of major stroke; the major stroke outcomes are not standardized across current trials. In ICSS, differences in the treatment effect were largely driven by

the high number of nondisabling strokes, many of which lasted for more than 7 days. However, the term "major stroke" in CREST would appear to equate to "disabling stroke" in the European trials. I think many would argue that an excess of nondisabling stroke is perhaps an acceptable tradeoff for fewer cranial nerve injuries (CNIs) and myocardial infarctions (MIs), but clearly patients would not want to accept a major disabling stroke as a tradeoff for anything.

Dr. Veith: I'm not sure I would agree with that. I think if you look at CREST, the cranial nerve injuries were mostly minor and resolved within a short period of time. A stroke is a bad outcome even if it's nondisabling, and the CREST data show that the quality of life after any stroke was moderately to severely diminished, whereas the quality of life after a relatively moderate or small MI was pretty much unchanged. CNIs come in all different sizes and shapes. If a CNI is a minor thing, it is very minor. If, on the other hand, the patient has trouble swallowing and it persists, that is terrible. That is worse than a stroke. And it may ultimately end up in aspiration pneumonia and death. So I cannot equate minor CNIs with much else, and I think a minor stroke is still a bad thing to have.

For more on cranial nerve injury in relation to stroke and composite endpoints, please see accompanying articles on pages 84-85.

Dr. Gray: The issue of the quality of life has been somewhat confusing for many people. In the CREST Appendix, there was a nice outline of what the respective quality of life measures looked like between minor stroke, major stroke, and MI. And as you referenced, major stroke was an obvious loser, minor stroke trended toward the negative, and MI was not as much to the negative. But what we haven't seen from CREST is a breakdown of quality of life by treatment given or treatment received. We have seen some of that from the SAPPHIRE quality of life dataset, which actually doesn't show any difference, despite the fact that there were more MIs and a few more events in the surgical group in that trial. From what I understand, when you average out all the quality of life scales in a 2,500 patient trial, the events with potential differences in quality of life get swamped because they are relatively few in number, and it's difficult to see a definitive signal regarding the quality of life for the population being treated.

Dr. Katzen: As I understand it, we are looking at 30-day stroke rates, and the minor strokes in CREST were defined as events that, in addition to the NIH score, were basically resolved by 3 months. It seems to me that regardless of the quality of life measurements, the cranial nerve injury rate approximates the minor stroke rate, and functionally, many of them had the same level of NIH score changes. In CREST, those two things may counterbalance each other. The minor stroke rate, at least at 90 days, left the patient without any significant disabling findings; the cranial nerve injuries achieved the same endpoint at 90 days, which would wind up being a wash, leaving the major stroke rate as a standalone difference. I think those are important points to measure. If you were to use that scale, or maybe even a ranking scale, significant CNI would be a very clinically significant event from an NIH point of view.

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Dr. Gray: So to that point, maybe the group here could come to some consensus. Instead of having a 30-day stroke, death, and MI endpoint, maybe we should be looking at something called a 30-day neurologic outcome, death, and MI. Would that be a reasonable way to capture all of the relevant neurologic outcomes, including CNI?

Dr. Veith: I think that is reasonable, and I agree somewhat with Dr. Katzen. I certainly do not want to be viewed as a non-enthusiast for carotid stenting because I am an enthusiast. However, strokes have to do with the brain, and cranial nerve injuries have to do with a nerve that has a specific distribution. If a patient has a stroke and recovers to what appears to be a normal neurological evaluation, he or she can still have defects in mentation, mood, and memory that are very difficult to measure. So I think strokes are in a different ballpark, and yet you can make a case that the two are equivalent. Certainly, the difference in cranial nerve injuries in CREST was real and highly statistically significant.

Dr. Gray: It's interesting that we can't really determine the functional or prognostic implications of having a minor stroke, that we don't have any really solid data on that point. So we could argue forever that all events are equally bad, and that there will be an irreducible minimum of MI with surgery and of minor strokes with CAS. But I think we should focus on the evolution of the CAS technology, which has been nothing short of stupendous. It's amazing what's happened in 15 years. Our mission should be to try to figure

out the lessons from past and recent trials and apply them to practices going forward into the next trials.

Dr. Veith: I agree. I have heard many discussions about CREST and ICSS, and there is a belief by some that we don't need any more trials. I think that is totally wrong. CREST is a study of CAS at a distinct point in time. It has defects in part because of that, and I do not think it is or should be the end of the road for gathering CAS data. I'm an enthusiast for carotid stenting—ultimately, and for randomized trials. We still need more trials to look at the latest improvements in CAS, with newer, more advanced technologies, which I think are going to make a huge difference. In fact, there is already evidence that flow reversal and flow cessation will diminish the number of adverse events from CAS. In addition, we still need membrane-covered or some other kind of improved stents that will prevent cerebral events after the cerebral protection device has been removed.

We also already have a better understanding of who should and should not be treated with CAS. We have learned that the procedure should not be applied across the board, but rather be restricted to perhaps non-elderly patients and those with suitable anatomy. If you add all those things together, we will get much better results with CAS than we presently have. Having said that, I also think the critical trial that needs to be done is to look at asymptomatic patients to see which ones need to be treated, comparing best medical treatment as it currently exists with both CEA and CAS.

Dr. Hopkins: The most important thing is to focus on what we learn from each trial about each procedure, not to argue which procedure is better. At this point, we are clearly at equipoise. It is now time to really start rigorously dissecting all the subsets in these trials to further draw out points that can help us in our daily practices.

I'm not sure how much better we're going to get with endarterectomy; it's an amazingly good procedure and the results are pretty tough to beat, but we also still have a ways to go before determining the ideal carotid procedure. For example, there's a lot of angst about stenting elderly patients and stenting symptomatic patients. Frankly, when it comes to the elderly, if we apply what we've learned about the anatomy to the elderly patient subset, we'll be back in the driver's seat in terms of CAS being a better procedure than surgery. We've known for years that the risk of surgery goes up as the patient gets over age 75. It's just that in the recent trials, the stenting risk goes up more, and that's because we haven't paid enough attention to the anatomy.

Dr. Katzen: There is a significant amount of data suggesting that stenting is at higher risk in octogenarians. However, I agree 100% with Dr. Hopkins in that carotid stenting is much more sensitive to anatomic variations and other challenges than carotid endarterectomy is. Along the way, we've learned what "high risk" means for carotid stenting as well. I believe we can actually treat patients over the age of 80 with a high degree of safety, with clinically acceptable safety levels, but that remains to be proven in a clinical trial.

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IMPACT OF OPERATOR TRAINING ON TRIAL RESULTS

Dr. Gray: One of the major discussion points in comparing the US and European datasets is the impact of operator training, which obviously has implications not only for the broader primary outcomes of these trials, but also for their substudies. In the US, we have been fairly careful in trying to get good operators with standard sets of qualifications into the trials, whether they be CREST, ACT-1, or even some of the more mundane PMA trials, if you will. What are we doing—right or wrong—on both sides of the Atlantic, and how can we make it better?

Dr. Hopkins: We've learned an enormous amount from the European trials. We learned about the importance of experience. We all thought that beforehand, but when SPACE was published, it was crystal clear to everyone that experience has been one of the major factors. Although we had a much more rigorous credentialing process in CREST, I would say that we faced the same recruitment issues that they did in Europe, and our credentialing became increasingly relaxed as recruitment became slower and slower. It's a matter of learning all of these things from the trials, focusing not on which procedure is better, but on the subsets, and learning how to perform these procedures more safely.

Dr. Macdonald: One of the particular problems for European trials is the discrepancy in requirements for the operators within the trial. Operators performing endarterectomy had much more stringent criteria to get into the trial than those performing carotid stenting. And there was the drift Dr. Hopkins mentioned toward less-experienced operators coming in for recruitment purposes, because the trials weren't reaching recruitment targets, and that was a prob-

lem. The other main concern that I had is that within the European trials, such as ICSS, the authors quoted that at randomization, patients had to be deemed suitable for both surgery and stenting by the investigator. But, of course, how would they know? Randomization in this trial and some others was allowed on the basis of duplex alone. It is arguable, therefore, that the collaborators would not know whether patients who were randomized were suitable for carotid stenting. This is particularly important for relatively inexperienced operators performing carotid stenting within ICSS; they simply would not recognize a "difficult" anatomy in a patient randomized to stenting (on the basis of duplex alone) who arrived in their cath lab or angio suite expecting a definitive procedure. The incentive to proceed must have been substantial, and this is borne out by the number of crossovers to CEA in the recent trials.

Dr. Hopkins: That was a real issue in CREST. As a matter of fact, the *New England Journal of Medicine* reviewers raised the issue of why there were so many more crossovers from carotid stenting than there were from surgery, and the answer is exactly what Dr. Macdonald just said—that you could randomize on the basis of Doppler without knowing the anatomy.

Dr. Macdonald: They didn't know whether the patients were suitable for both procedures at randomization.

Dr. Hopkins: That's right, and the perilesional anatomy, of course, is far more critical for carotid stenting than it is for carotid surgery. I think that clearly explains why there are more crossovers from the stenting arm.

Dr. Gray: And it goes without saying that it depends on the operator's experience in patient selection to make that critical decision in terms of crossing the patient over. I think that may be as relevant or more relevant in Europe than in the US based on some of the qualification issues.

Dr. Katzen, do you think there is a difference by specialty engagement in some of the European trials like we see in the US, where, like it or not, cardiology is a significant contributor to a lot of these trials, but in the UK and other European settings, radiology and vascular surgery are, but not so much cardiology? Do you think that there are any meaningful related outcomes that are worth exploring?

Dr. Katzen: In any given trial there will be variations, but I think it's something of a confounding problem. It's not just variance by specialty, but by degree of experience. I'm not sure at this point that we can say anything regarding discipline. We can say that operator experience, insofar as carotid stenting is concerned, is important, and I would venture to say it's extremely important in carotid endarterectomy as well, as proven in previous studies. At least with regard to carotid stenting, operator experience is very important, but I'm not sure that there are sufficient data to draw any conclusions regarding specialty-specific outcomes.

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WHAT'S NEXT?

Dr. Gray: Dr. Macdonald, some British and European physicians have called for a moratorium on carotid stenting trials but, obviously, you and many others seem to disagree, and continue to work on clinical studies. Can you tell us about the progress in the ACST-2 and SPACE-2 trials? How do they address the asymptomatic question, and how does their construction differ from previous studies?

Dr. Macdonald: I don't think CREST was powered to be a standalone trial with regard to asymptomatic patients, so my feeling is that it shouldn't fatally undermine the ongoing trials in asymptomatic populations by shifting equipoise. ACT-1 is ongoing in the United States, and we have ACST-2, which is UK-based, from the Oxford Clinical Trials Unit, but still an international trial, and it's a 1:1 randomization. SPACE-2 is a three-arm construct, one of which is best medical therapy, and then there's TACIT and/or CREST-2, which have yet to open or be funded in my understanding. But in terms of ACST-2 and SPACE-2, they're actively recruiting, but there is quite a major difference in the ethos of these asymptomatic trials.

ACST-2 is a trial of two revascularization techniques in a patient population in whom a decision to intervene has already been made. In SPACE-2, there are two levels of uncertainty. Firstly, you are telling the patient that you don't know whether there is any rationale to intervene. Secondly, if they do randomize to the intervention group, then there is a further uncertainty in terms of whether stenting or surgery would be preferable. That is quite a difficult sell to the patient population. I know from speaking to some of the Germans involved in SPACE-2 that they are struggling to recruit for that reason.

Dr. Gray: While the construct of SPACE-2 may actually be an important one to answer the larger question of med-

ical therapy versus revascularization, and then revascularization therapies against each other, I think some of the concern on this side of the pond is that we'll get another ASTRAL trial—one in which the equipoise is not set at a trial level, such that patients with variable appropriateness are being recruited at individual centers via varying means. Do you see that potential emerging from the SPACE-2 construct?

Dr. Macdonald: Yes, absolutely. I honestly think they're going to struggle to complete this. I hope they can, but I'm really not sure that it will be possible.

Dr. Veith: Obviously we should not hang our hats waiting on SPACE-2 because of some of the points that have been made, and also, it will take at least 5 years to get any meaningful results—if they ever do. Dr. Katzen, where do we stand with TACIT? Is that going to be funded and proceed as planned? I think it is a trial that is desperately needed.

Dr. Katzen: Yes, many of us feel the same way. Regarding funding, it will likely be dependent on the steps that CMS takes, because I don't believe the trial funding will come from government sources. We've been there twice, and they were seemingly not very interested, although they thought the trial had huge amounts of merit. However, there is significant funding interest waiting in the wings, depending on what happens in the US regarding reimbursement.

Dr. Veith: I would have hoped the NIH would support this trial because of the phenomenal amount of money that is being spent to treat asymptomatic patients. In most studies, more than 70%, and in others, more than 90% of carotid endarterectomy or carotid stenting procedures are being done in asymptomatic patients.

Dr. Katzen: It has huge public health implications in the US, and we have been talking with Dr. Tom Brott, the principal investigator of CREST, to perhaps organize something that might be a CREST-2 trial that would essentially encompass a TACIT plan as well.

Dr. Veith: I would like very much to see that supported.

ASYMPTOMATIC PATIENTS

Dr. Gray: Dr. Hopkins, my neurologic colleagues do not routinely send patients for asymptomatic revascularization. They're not against stenting overall—they just don't believe in either surgery or stenting for asymptomatic patients. They tell me that there are better options than sending an entire population of asymptomatic patients for revascularization. Is there a better way of sub-selecting these patients by virtue of cerebral vascular reserve, asymptomatic but spontaneous embolic hits, or other criteria?

Dr. Hopkins: Just to comment on cerebrovascular reserve, I think it's useless because if you have compromise in cerebrovascular reserve, you have a hemodynamic situation, and that's not what causes most strokes in patients with carotid disease.

Dr. Gray: But the neurologists will tell you there are data to suggest that if you look at the asymptomatic patients with or without preserved cerebrovascular reserve, that those with abnormal cerebrovascular reserve do worse, and that they actually may benefit.

Dr. Hopkins: I agree. They are a much more stroke-prone group, but only in terms of considering whether or not to treat someone. Clearly you would treat if the patient had compromised reserve, but we're talking about an embolic disease, and the great majority of patients don't have compromised reserve. Those are the ones we need to parse out and decide whether we want to treat them. As for asymptomatic hits, we're doing that with Doppler studies. If we see evidence of asymptomatic hits on transcranial Doppler, then we lean toward treating an asymptomatic lesion. There are a lot of questions to be answered for asymptomatic patients. I would hope we'd answer some of those questions in the ACT-1 trial, and we need to do another registry or trial where we start looking at some of these other ways of evaluating a plaque's risk.

Dr. Veith: There are definitely going to be ways to evaluate the plaque. I think at the present time the best thing we have relates to Spence's work, in which he has shown that if you put patients on a statin, their transcranial Doppler hits decrease dramatically. I think the asymptomatic patients that should be subjected to some form of intervention are those in whom statin treatment doesn't reduce the number of hits. In other words, with persistent embolization, they are the ones who are likely to have a stroke and as such should be treated. These are not hard, randomized data, but to me, this is a promising finding because they are assessing the efficacy of the medical therapy in making the plaque less vulnerable. If plaques continue to be invulnerable, they should be operated on or stented.

Dr. Macdonald: I think it's a sound idea to try to assess which asymptomatic patient is likely to go on to have a stroke, but we need a validated methodology to do so, and we don't have one yet. However, there are patient subsets among the asymptomatic population that we know are likely to benefit (from ACAS and ACST). For example, you

were talking about patients with compromised cerebrovascular reserve, and we know that patients with an asymptomatic stenosis and contralateral occlusion are at significantly higher risk of stroke. We also know that younger patients, particularly males (on the basis of CEA versus best medical therapy trials) are likely to benefit from a carotid intervention. They will live long enough to benefit. Regardless of whether you think the patient has TCD hits or vulnerable plaques, we already know there are some patients who might benefit from an intervention on clinical grounds, although our understanding of this may change because, for example, females may expect lower procedural hazard with CAS than with CEA.

Dr. Katzen: In our practice, we're still relying on ultrasound plaque configuration similar to what the CREST study demonstrated, which does have its limitations. I understand the issue of hits, but I'm sure all of us have seen in our practices that since the event rates are so low, and the progression of disease can be altered with statin therapy in most patients, most of the patients we're following will never need therapy. But, in terms of trying to predict which patients may be high risk, we use primarily ultrasound appearance.

IMPROVING OUTCOMES

Dr. Gray: What are the major things we can do to improve outcomes in carotid stenting? We have already touched on operator experience and patient selection, but there are those who believe that the embolic protection devices make a considerable difference (ie, which one you use, proximal vs distal, etc.). There is also a belief that current stent technology has not yet reached its potential. It's possible that stents may be improved such that they can prevent not only procedural strokes, but more importantly, those strokes that occur or are finally observed—and we have to be careful about how we term those things—within a day or two after the procedure. This latter group may comprise up to one-third of the overall strokes in carotid stenting. Many people think this is related to plaque protrusion and embolization through an already safely implanted stent.

Dr. Katzen: Technology is definitely a key factor in improving carotid stenting outcomes. It has been since we started, and favorable outcome rates have generally improved over the past decade. Much of this has been due to increased operator experience, but improved technology has had a large role as well.

We are likely to see continued improvement, but part of the issue is there are very few industry vendors working in this space; the practicalities of how trials are funded and conducted have led to the fact that we have no head-to-head device comparisons in this space.

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We have a margin for improving significantly. The question is, what should be the target level of results, and how can we measure it? Is the target clinical in nature, or should it be something more sensitive than clinical outcomes, like either diffusion-weighted MRI or TCD hits, etc.?

Dr. Macdonald: I personally believe that stenting and endarterectomy are complementary, rather than competitive. But, if you want to have a majority of the population that may be suitable for stenting, the current differences in 30-day risk will have to be addressed. It's all about the 30-day risk, and the battle for supremacy between the two procedures will hinge on that outcome measure, as intermediate and longer-term outcomes for CAS and CEA are comparable.

Anecdotally, if we look at the events that happen in experienced units, they're not on the table—they're minor, off-table events, going back to the question of plaque prolapse. It may or it may not relate to plaque prolapse, but certainly we need to understand what is causing those minor, off-table events before we can fix the problem. That answer will probably point us toward advances in technology.

There are some things we already know regarding protection devices. In terms of microembolization, we can evaluate surrogate markers such as TCD hits or new white lesions on DWI. We know that proximal systems will significantly reduce the procedural microembolic burden, and we've known for a while that distal filters will not. That's what we are seeing in the ICSS DWI substudy—a lot of filter protection effects with new white lesions on the brain, and we've seen that on a number of occasions in the past. Proximal protection will make a difference in those surrogate markers if people wish to believe in them. Whether or not they have an impact on clinical event rates is another matter, and it would be very hard to conduct a trial sizable enough and sufficiently powered to prove this. I routinely use proximal protection, not only because of the microembolization, but because more than two-thirds of my patients are symptomatic.

Dr. Hopkins: With most of it, we have to also use common sense because we don't have enough data to really be

sure. I love the way Dr. Macdonald positions things, highlighting "off-table" events. It's an interesting subdivision, isn't it? As she points out, off-table events may all be solvable with advances in technology, and delayed stroke is the biggest. Stroke in the opposite hemisphere is another one, and it obviously relates to arch anatomy and how we can more safely treat the arch or avoid the arch.

One of my most awful experiences, but a great teaching case, was one in which we had a beautiful carotid stent placement, and everyone was patting themselves on the back. All of a sudden, the patient had a hemiparesis ipsilateral to his lesion. CTA showed that he had a shaggy arch, and we never should have touched that patient. We are constantly so focused on the carotid plaque itself that we often don't think about the arch until we get there. As far as off-table events, the microembolic load is obviously a surrogate for something, we're just not sure what.

Dr. Gray: What about embolic protection choices? Starting with proximal protection, based on your experiences and data from the GORE® EMPIRE Clinical Study and ARMOUR, when do you use this option?

Dr. Hopkins: Proximal protection fits very nicely in patients with recent symptoms, large plaque burdens, and the obviously ugly plaques—the ones that when we operate surgically, we see a clot on the plaque itself and a hemorrhage inside. Logically speaking, proximal protection is the way to go with those kinds of patients. It may be the way to go with everybody, given the fact that we seem to see reduced embolic surrogate on MRI with proximal protection, although we don't have a lot of solid data on that yet. We need more data.

The other striking thing for me in the proximal protection studies was that I fully expected to see a fairly high failure rate. The success rates were 96% and 98%, meaning that the concern over an inability to get the device there safely was really not borne out. These devices will also continue to improve and I encourage Gore and Medtronic to keep working to make them as small and as safe as they can be.

US REGULATORY AND REIMBURSEMENT ISSUES

Dr. Gray: What will CREST lead to from a regulatory standpoint?

Dr. Veith: I think the results will have an effect on both approval and reimbursement. Personally, I don't believe it is definitive enough that it should have an impact, but I still think it will. The defect in CREST is that it combines symptomatic and asymptomatic patients, which I think are different disease processes. As a result, I think it ended up being underpowered. Also, the specialists in CREST were better trained, vetted, and more skilled than the average CAS operator around the world. Recent population-based studies with higher stroke and death rates are evidence of that.

Dr. Gray: If you could create or enforce any distribution of carotid stenting in the US, would you put into place a model based on centers of excellence, with defined parameters for volume, keeping operators well experienced and vetted?

Dr. Veith: Yes, but we live in an imperfect world, so that won't happen. There is no question that if I needed a stent, I would only go to a specialist who has performed the procedure hundreds of times. I am not going to an interventional cardiologist who does 13 per year, nor a surgeon who does 13 per year. In Britain, they are trying to do this with vascular centers specifically for aneurysms. I believe there are too many people who are trying to do everything. And, ideally, fee-for-service should be separated from the mix because it prompts people to do cases that do not need to be done.

Dr. Macdonald: In the UK, there are currently only two centers doing carotid stenting in any sort of reasonable numbers (those being Sheffield and Newcastle). I've been asked how we are supposed to serve a country of several million patients who require a carotid stent with only two centers offering the procedure in any sort of volume, and clearly it will require service reorganization. We are trying to accomplish that, along the lines of the aneurysm centers of excellence, as Dr. Veith was just mentioning.

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>
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Dr. Hopkins: In spite of the fact that the devices used in CREST were first-generation technologies that are no longer used, the results were so good that I don't think there is going to be any issue from a regulatory standpoint.

From a reimbursement standpoint, I find it hard to conceive of how the federal government can have a clinical trial in which more than $80 million of their money is spent, the primary endpoint shows equivalence, yet they can't authorize reimbursement.

To the previous point about centers of excellence, they probably will put in some specific requirements, establishing

some required level of expertise and experience before a physician can perform CAS. Then the question becomes how they can effectively place and enforce those requirements with so many doctors placing a stent in any patient who has a noise in his neck.

Dr. Veith: Why not limit surgery the same way? It's been on the table for years but it's not done.

Dr. Gray: This is clearly the poster child for all of those issues. It has all come to roost at carotid stenting's door.

Dr. Hopkins: The standard of care in this country—the way medicine is practiced—is that the patient goes to the primary care doctor, who discovers a noise in the neck, sends the patient to the vascular lab. The patient comes up with a carotid stenosis, and he usually goes to surgery. I think 70% of carotid endarterectomies, or more, are done for asymptomatic disease. If that can't be policed, I don't know how carotid stenting will be limited. CEA is the standard of care, and it has level-one evidence behind it. We can disagree about what the neurologists think and what the best medical therapy is, but CEA is the standard of care in this country.

Dr. Veith: But why is it the standard of care? I believe it is the standard of care because surgeons make money doing carotid endarterectomy.

Dr. Gray: Well, ACAS and ACST support it from a dataset standpoint.

Dr. Veith: Yes, but those data are no longer relevant.

Dr. Hopkins: Until you have new data, how can you argue with it?

Dr. Veith: That's why TACIT needs to be done.

Dr. Gray: Agreed, but until that time, revascularization is a reasonable practice supported by two separate trials.

Dr. Hopkins: The practical reality in this country is that's the standard of care, and with level-one evidence to support carotid stenting, it's hard for me to see how CMS is going to walk away from covering it.

Dr. Veith: Most surgical patients are now getting endarterectomy on the basis of duplex and nothing more. Then, on the operating table, it is found that they do not have much of a lesion. That's just wrong for carotid surgery, and I think all of us would agree we would not do it that way. Yet, we are saying that the standard of care is to fix it? Surgeons can make a good living by doing these cases; they have a low complication rate, which looks good for the operator, but it is not providing the best care, because some of these cases should not be done.

Recent annual numbers showed that 96% of the carotid stents placed in New Jersey were for asymptomatic disease. You cannot tell me that these were all 80% stenoses or more. I am sure they were not. How do we prevent that? That's why I do not believe complete reimbursement for carotid stenting for asymptomatic disease should be granted. However, I do think it ultimately will be granted.

Dr. Gray: I would argue that there are data for surgery—ACST and ACAS, and there are now data for stenting. CREST, although not powered for it, clearly has some good results for asymptomatic treatments. Now the issue of patients being treated appropriately or inappropriately is wide open, and I agree with you. One of the advantages that carotid stenting has is that we get an angiogram on everybody.

Dr. Hopkins: Everybody talks about how CREST was not powered for asymptomatics, and I am no statistician, but if you talked with Tom Brott and George Howard, they would defend the asymptomatic data to the hilt. With 1,150 patients, there is enough data and power to show the safety and efficacy of CAS in asymptomatic patients.

Dr. Veith: If the procedure is really necessary. Regarding CREST, I am under the impression that when the trial was designed, it was to be restricted to symptomatic patients because they were the ones, even back then in the late 1990s, who posed the greatest uncertainty. The reason that they began including the asymptomatics was that they could not recruit enough symptomatic patients.

Dr. Hopkins: That is actually a misconception about the change in enrollment. The real reason we switched and started enrolling asymptomatics in 2005 was because of ACST. Yes, enrollment was a concern, but when ACST came out, the executive committee met and agreed that we had to have an asymptomatic arm.

This brings me to an important question. Do you think that we could recruit a trial with an asymptomatic arm in this country or in Europe if we started today?

Dr. Gray: I think it's a great question. My major concern with that trial is that we would get a stripe of patients between 60% and 80% lesions, and that doesn't answer the larger question of the lesions being broadly stented in this

country, which are the 60% to 95% asymptomatic lesions. What we really want to know is, can that 80% lesion be left alone, or is it better off being treated?

I worry about those trials given what Dr. Veith has described well here as the practice patterns in the US, and I think it will be difficult to enroll them anyway. The people who see the patients routinely, the surgeons and the interventionists, would have a difficult time with equipoise. I personally would have a difficult time with the equipoise of it. I think that was probably one of the issues in the UK with ACST-2; I understand why they have gone in that direction, as opposed to what SPACE-2 did, which is not necessarily accept ACAS and ACST results when trial planning.

Dr. Hopkins: Considering the fact that a whole trail of neurologists would line up to testify, you might have a real medical-legal issue with that kind of a trial. That's a terrible reason not to study something, but it is a reality we live with in the US. I worry about it when I see a patient with an 80% stenosis. I tell the patient, "I would leave it alone in myself, but the standard of care is to fix it. You sign in the chart that I've told you that."

VOLUMES OF CAS GOING FORWARD

Dr. Gray: Dr. Macdonald, there are two things I want to ask you about the current situation in the UK and Europe. First, do you think that the practice of carotid stenting will increase, decrease, or stay the same over the next 5 years, over the course of SPACE-2 and ACST-2?

Dr. Macdonald: I think the number of CAS treatments will increase because the number of asymptomatic patients treated in mainland Europe is increasing. People are seeing that carotid stenting can be performed safely in asymptomatic patients, and they are increasingly treating these patients. The numbers of procedures will rise, due in large part to asymptomatic patients.

Dr. Gray: What do you look for in terms of outcomes of those trials, as well as ACT-1? Do you think they will support carotid stenting as an alternative to surgery within the construct of the trials? For SPACE-2, to the extent that it's completed, will surgery and stenting be preferable or at least noninferior to medical therapy?

Dr. Macdonald: We'll probably see very similar results to those seen in CREST as long as we can maintain the experience level of the operators. For ACT-1, I think the operator entry criteria are likely to be strict in part because it is an industry-sponsored trial.

We're trying our best with ACST-2 to not make the mistakes that ICSS and EVA-3S made in terms of experience level. Hopefully we'll find results showing that stenting can be performed safely in centers of excellence/experienced units. I think we are likely to see that the procedures are as durable as one another in the intermediate term, and hopefully longer.

Dr. Hopkins: I say a little prayer every night that the results in ACT-1 will be similar to the CREST lead-in. If they are, then ACT-1 blows any conservative management out of the water.

Dr. Veith: I think there are two different aspects of this—what's going to happen and what should happen. To speak to Dr. Macdonald's earlier point, I agree that asymptomatics will be increasingly stented in Europe. Why? Because with the exception of Britain, doctors have a financial incentive to do more cases.

The same motivations are at work in the US, and as long as physicians continue to be paid per procedure and the reimbursement continues to go down, there will be incentive to do more procedures, even those that many of us feel are unnecessary. In fact, for some, there is more incentive to do the cases that are unnecessary because they yield better results and are easier to do. I worry not only about the public health aspects of this, but also about the cost. To pay for more carotid stenting procedures, CMS will decrease reimbursement in other areas.

Dr. Gray: I think you are right on most of those counts. The only thing I would bring up to counterbalance the conversation focused on treating asymptomatics is that the cost of a stroke is not insignificant, and at least half the strokes that present in asymptomatic patients are major strokes. It's not an insignificant issue.

Dr. Veith: I agree.

CONCLUSION

Dr. Gray: Largely on the basis of improving outcomes over the past decade due to the advent of dedicated and evolving technology, improved patient selection, and growing operator experience, carotid artery stenting has earned a place as a complementary procedure to endarterectomy. Ultimately, this is good for patients, as it may provide them lesion- and patient-specific therapies tailored to their unique needs or conditions. Future technique and technology developments will almost certainly continue to provide even safer outcomes. The role of medical therapy is critical as a baseline treatment, but it remains to be proven in randomized trial data versus any form of carotid revascularization. ■