As the practice of carotid artery stenting (CAS) has grown over the past decade, along with a greater acquired experience with the procedure and equipment, and rapid improvement in outcomes, the natural progression of the field is to look for further opportunities to refine the technique and improve the technology so as to create an even safer and therefore more effective stroke-preventative procedure.

Among the possible improvements suggested as critical to reducing procedural stroke is in stent design. This discussion has come about for a variety of reasons, which have been well described by my opponent in this debate. I will submit here, however, that an analysis of the data—without the requirement to suspend disbelief—will lead away from the concept of the stent as being significantly responsible for procedure-related stroke in CAS. This determination is important because it means that we will not hang our hat on the advancement of technology in stents, but rather spend our efforts on more productive and effective pursuits.

For those of you unfamiliar with my opponent, she is not someone to be trifled with. She is well educated, having earned a PhD in embolic protection, highly experienced in complex carotid stenting, and exceptionally articulate in both spoken and written forms. Nevertheless, I will humbly offer my most reasoned arguments in hopes of dissuading you from this siren’s song.

The premise of this debate, in a nutshell, revolves around the concept that open-cell stents (which are made that way to increase flexibility and conformability) are too porous, and that, as compared to closed-cell stents, open cells are too large and permit emboli more readily. However, the physical basis of this argument is in question because the minimal circumferential unsupported area (MCUSA, the biggest circle that one can fit through a cell) does not materially differ based on cell structure, ranging between approximately 0.90 and 1.10 mm in diameter. Moreover, the filters that are used with these stents have pore sizes approximately one-tenth of this diameter, such that any liberated procedural debris this size should be adequately retrieved by a well-functioning filter.

Looking Beyond Intuitive Sense

Before presenting my perspectives on stent design in CAS, let’s deconstruct my worthy opponent’s arguments and see if they hold water. The first argument is that specialized stents for specific vascular territories make intuitive sense. In defense of this argument, stent grafts for endovascular aortic aneurysm repair are paired with superficial femoral artery stents, and the unique design requirements inherent in each are offered as de facto proof of specialized device requirements. The problem with this line of reasoning is that, in each case, an irrefutable failure mode and mechanism (device migration and stent fracture, respectively) was identified before the iterative improvements of these devices, such that the design goal was clear from the outset.

The topic of this debate and the arguments that follow will be evidence enough that no such unassailable proof of the failure mode of carotid stents exists on which to base design changes or subsequent testing. In other words, what shall we tell our engineers we want from their next design? What specifications shall we require based on what data, and what mechanism of failure can we test to?

Flawed Studies and Insufficient Data

The second argument offered is frankly not very robust, and although my adversary acknowledges this up front, she presents it anyway. The various publications
positing that stent design has any influence on CAS outcomes are so methodologically weak so as to be dismissed res ipsa loquitur, that is, as speaking for itself. Specifically, all of the data sets that are referenced by my opponent are not randomized, are retrospective, with only one being prespecified. Therefore, they are subject to profound operator stent selection bias. Selection bias can take several forms, such as using open-cell stents in more complex and tortuous anatomy, which could be compounded by the fact that such anatomy is found in older patients. Because these data were not controlled or corrected for such issues, it is easy to see how quickly confounded the outcomes and conclusions can be. Worse, in the Bosiers analysis, if one removes the non-standard component of transient ischemic attack from the composite endpoint, no significance between stent types remains.

Statistically, there are also flaws with the studies cited: an ad hoc retrospective analysis with multiple samplings no longer becomes significant at \( P < .05 \), but rather at a much smaller \( P \) value, something that these studies did not account for. Moreover, it would take significantly more than 5,000 patients to detect even a 1% difference in death and stroke based on stent design. If one wished to compare open-cell and closed-cell stents (which is what the cited studies purport to do), we do not have to look any further than the prospectively gathered and analyzed CAPTURE (open cell) and EXACT (closed cell) registries. These had the same inclusion/exclusion criteria, many of the same operators, they represent thousands of patients, and there were no differences in 30-day death/stroke/myocardial infarction outcomes (5.7% vs 5.1%, respectively).

In addition, many of the recent US trials performed to establish the safety of new embolic protection devices (EPDs) allowed the operators to use any stent type available, and no trend toward differentiated outcomes was seen by these various stent designs. In fact, outcomes in US trials appear to have improved independent of stent type being tested (Figure 1). Lastly, several clinical trials evaluating stent design, albeit underpowered, have not found even a suggestion of differences in patient outcomes. So, as this argument is concerned, there are no unconfounded, adequately powered clinical data to support a differentiation in outcomes based on stent design.

**THE TALE OF THE TAPE**

The nonclinical evidence of a difference in stent design is also very weak. The surrogate outcome measures of transcranial Doppler (TCD) and magnetic resonance imaging diffusion-weighted imaging (MRI DWI) abnormalities have no proven clinical correlative value.

**Figure 1. Outcomes of US trials over time according to the type of stent (open cell or closed cell) tested.**

**Figure 2. Outcomes in CAPTURE 3500 registry (solid lines with dashed confidence intervals) overlaid with the outcomes of clopidogrel testing for platelet reactivity (shaded bars).**

Accepting that, the data cited by Dr. Macdonald do not support her argument. The trial examining TCD and MRI DWI differences between covered and non-covered stents found no differences in MRI DWI and postprocedural 90-minute TCD monitoring; even the investigators concluded they could find no differences. More importantly, the trial had to be abandoned very early in its course because an excessive degree of restenosis was noted in the covered stent group. This raises the importance of this debate: modifying the carotid stent to address an as yet unclear excess risk and unclear putative mechanism of stent design “failure” does not represent all upside, and possible unintended consequences such as were seen here may be myriad. Accordingly, the justification to do so should be solid.

If we are to take seriously an analysis adequate enough to come to the conclusion that the stent is the significant cause of stroke in CAS, we will need to take many factors into account and do our best to rank the contribution of each. An exhaustive review of possible
factors is not possible within the scope of this debate, but some important elements will be highlighted.

**PATIENT AND OPERATOR FACTORS**

Our internal analysis of films from some of the previous angiographically controlled US trials suggests that operator error (balloon sizing, wire misadventure, EPD errors, etc.) is not a trivial factor in the creation of strokes in CAS. Second, there are patient-related factors, many of which will be unrelated to stent design, such as vulnerable plaque with resultant iatrogenically induced rupture and acute stent thrombosis, aortic plaque leading to stroke during access manipulations, and genetics related to incomplete clopidogrel metabolism leading to inadequate platelet inhibition. This thienopyridine issue, interestingly, seems to worsen with age much as the results from CAS do (Figure 2)—a possible explanation? Certainly as plausible as the stent design. And last, intraprocedural failure of EPDs due to lack of apposition, etc., can also contribute significantly to stroke in patients who have undergone CAS.

In fact, a relatively simple calculation of the known alternative causes of stroke in CAS patients is possible from the CAPTURE registry, which is a prospective, well-studied, and characterized experience in CAS. In CAPTURE, the overall 30-day rate of stroke was 4.8% in the high-surgical-risk population. Of these strokes, several categories unrelated to the stent can be eliminated. Specifically, if the nonipsilateral (clearly not stent-related), the hemorrhagic (generally not embolic in etiology), the procedural strokes (when EPD would have been protective, etc.), are discounted, then the strokes possibly related to the stent become approximately 1.0%, or about one-fifth of the total strokes. This clearly is not a significant cause of stroke in CAS as outlined in this debate’s proposition. Moreover, if the same analysis is done with presumably “at-risk” plaques (symptomatic and elderly patients), which would be expected to be particularly sensitive to defects in stent design, no difference is seen in the rate of plausible stent-related strokes.

**CLOSING ARGUMENT**

Although it is tempting to jump to the conclusion that stent design should be improved in order to reduce strokes occurring in patients who have undergone CAS, a critical analysis of the data does not support the stent as a significant contributor to stroke, does not reveal a specific failure mode of the stent such that specific design modifications would be a guess at best, and suggests that not only would a difference in outcomes after a change in design be difficult to ascertain, but that it is possible a negative outcome could result, as was seen in the covered stent experience. Other advances and modifications focusing on patient selection, procedural technique, access, EPD improvement, and possibly pharmacology modification are more likely to have a beneficial effect in CAS outcomes.

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. Dr. Gray has disclosed that he is a paid consultant to Boston Scientific Corporation, Cordis Corporation, Covidien Vascular Therapies, Terumo Interventional Systems, W. L. Gore & Associates, Medtronic, Inc., and Medrad. He has also disclosed that he is an owner of or shareholder in Amaranth Medical, Biocardia Inc., CoAptus, Coherex Medical, Contego Medical, Pathway Medical, QuantumCor, and Silk Road, and that he receives grant/research funding from Abbott Vascular, Pathway Medical, Bard Peripheral Vascular, and CREST/NIH. Dr. Gray may be reached at wg2131@mail.cumc.columbia.edu.