

Debate: Current Stent Design Is Inadequate and  
Contributes Significantly to Procedure-Related Stroke

# Why Should Stent Design Not Have an Impact on Procedural Outcomes?

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**W**hen faced with a debate such as this, against a more-than-worthy opponent, one feels the need to point out that the debate really ought to pivot solely on an exposé of the influence of stent design on outcomes for carotid artery stenting (CAS) and not on nonstent-related causes of adverse outcomes, which are, of course, myriad.

It is accepted that patient factors such as age, sex, and precategorized presenting complaint significantly affect CAS outcomes, as does patient sensitivity to the prerequisite dual-antiplatelet regimen (sensitivity being largely variable even when exact dose, dosing schedules, and named drug are explicitly described in the inclusion criteria of either a randomized trial or independently audited registry). The well-recognized influence of operator experience on outcomes also cannot be easily overlooked. Lastly, it should be accepted that while the European Union has been in somewhat of a “comfort zone” regarding the use of a bewildering array of CE Marked carotid stent and embolic protection devices, the United States has been subject to a relatively controlled environment enforced by federal regulatory restrictions. This means that United States datasets are not geared to compare stent systems and their possible differential influence on outcomes, but rather, by necessity, sizeable United States cohorts evaluate a single stent (and often the same manufacturer’s embolic protection device).

I would like to frame my argument based on a number of considerations that I hope the *Endovascular Today* readership might see as at least thought provoking.

## WHY ARGUE AGAINST DEDICATED CAROTID STENT DESIGNS?

I would like to turn the question on its head for Dr. Gray: Why should stent design *not* have an impact on outcomes?

Individual arterial territories demand individualized solutions. The inexorable drive to improve aortic stent graft parameters (profile, conformability, and the use of novel materials that better mold a rigid structure to a compliant major vessel that has undergone expansion as a result of weakness in the arterial wall) is intended to improve outcomes with respect to length of stay and late interventions to better secure aneurysm exclusion from the circulation (the 30-day mortality benefit over open repair being already well documented).

The superficial femoral artery, a traditionally hostile territory for stent placement on account of unique hemodynamics (a relatively low-flow, high-resistance circuit) and exacting standards regarding the ability of any endovascular stent to rise to the challenge of unparalleled mechanical forces, has benefited from advances in stent design. Dedicated third-generation systems show significantly improved intermediate-term patency compared with generic balloon-mounted historical stents and second-generation models adapted from iliac platforms.

The carotid bifurcation lesion presents a unique endovascular challenge, requiring that a stent couples conformability with scaffolding properties sufficient to “brace back” friable plaque.

### DEDICATED DATASETS

Studies specifically formulated to evaluate differences in outcomes relating to stent design are few and far between. These are largely of European origin and, when specifically formulated to examine differences, exclusively use surrogate markers of stroke and death—namely diffusion-weighted (DWI) magnetic resonance imaging new hyperintensities or procedural transcranial Doppler (TCD) microembolic signals. Secondary datasets also exist—sizeable real-world registry data outcomes that enable us to retrospectively explore differences in outcomes based on stent type, although none of these sources were powered to answer this seminal question. Under these circumstances, the inevitable confounding variables can only be partially accounted for, if at all. Having acknowledged this, the European data (that allow liberal use of CE Marked systems, resulting in registries in which many different stents are included) indicate that stent design significantly affects outcomes in the symptomatic population.

The Bosiers Belgian-Italian registry, which included more than 3,000 patients, clearly indicates the benefit of closed-cell over open-cell designs for symptomatic patients (there being no such relationship in asymptomatic patients).<sup>1</sup> As a stand-alone piece of evidence, this is perhaps of esoteric interest only. However, the Schillinger registry, subsequently published, with the specific aim of refuting any relationship between stent design and outcomes (and into which data from my own unit were entered) showed, if not statistical significance, a clear trend toward improved outcomes in symptomatic patients when closed-cell stents were used.<sup>2</sup>

Stent design issues were further evaluated as a prespecified analysis within the SPACE trial (German/Austrian/Swiss 1:1 randomized trial of carotid endarterectomy versus stenting in an exclusively symptomatic population). The ipsilateral ischemic stroke/stroke death rates were significantly lower when closed-cell systems (Wallstent, Boston Scientific Corporation, Natick, MA) were used compared to the Precise (Cordis Corporation, Bridgewater, NJ) or the then-Guidant Acculink (now Abbott Vascular, Santa Clara, CA) systems.<sup>3</sup>

There is a clear common thread running through the available datasets, suggesting that in symptomatic patients, closed cell-stents are associated with better procedural outcomes.

The key is the definition of those populations in whom stent design is a crucial consideration and those in whom it is of secondary relevance.

### MEANINGFUL POPULATIONS

There exists a sizeable discrepancy in the differential magnitude of benefit when one compares a symptomatic patient with an asymptomatic patient. Based on NASCET and ESCT pooled data, the numbers needed to treat for symptomatic patients in order to prevent one subsequent stroke are an order of magnitude different.<sup>4</sup> We perhaps need to treat approximately seven unselected symptomatic patients to prevent one stroke compared to approximately 20 unselected asymptomatic patients.

In health care environments that are increasingly constrained around the globe, we will be forced to justify our procedural expenditure. Furthermore, it is known from enumerable datasets that symptomatic patients incur a higher procedural hazard than their asymptomatic counterparts.<sup>5,6</sup> In a population that has so much to gain from carotid intervention and in whom the procedural risks could be modified, why should we not focus diligently on these risks and try to evaluate the procedural variables that may affect patient outcomes?

### MEANINGFUL SURROGATES

The use of surrogate markers of clinical endpoint (stroke and death) allows a more convenient comparison of outcomes stratified by stent design (compared with stroke and death) owing to the simple fact that new hyperintensities on DWI magnetic resonance imaging of the brain and microembolic signals on TCD during/after CAS are florid by comparison with stroke and death. Although there are differences in these parameters based on stent design, an important limitation is that these surrogates may be dismissed as clinically dubious or irrelevant, and it is true that both the clinical relevance and fate of new DWI lesions require further elucidation.

However, if one were to suspend disbelief for even a short while, it is clear that closed-cell systems are associated with significantly fewer new brain lesions than open-cell systems for both symptomatic and asymptomatic lesions (regardless of embolic protection),<sup>7</sup> and a prototype of a covered stent system (Symbiot, Boston Scientific Corporation) was associated with significantly fewer TCD-measured embolic signals than an uncovered closed-cell stent (Wallstent) in a mixed patient population.<sup>8</sup>

Although pilloried in some circles, surrogates, such as those described, may serve as valid endpoints for the scientific community who wish to advance medical science without practicing on thousands of patients. Furthermore, I would like to ask the readership what

they would prefer: Would they like a reduced microembolic burden to their brains (or to the brains of their loved ones) regardless of the fact that we still cannot determine the longer-term consequences of these subclinical events?

### ADEQUATE POWER

When the overall event rates for CAS fall to 2.7% or 2.9%, all stroke/death in independently reviewed registries with independent adjudication of adverse events (ARMOUR and EMPIRE registries evaluating proximal embolic protection systems such as Mo.Ma [Medtronic Invatec, Frauenfeld, Switzerland] and the GORE® Flow Reversal System [W. L. Gore & Associates, Flagstaff, AZ], respectively),<sup>9,10</sup> it becomes a statistical challenge to derive any meaningful difference in outcomes between open-cell and closed-cell carotid stents unless there are several thousand patient outcomes to compare. It goes without saying that any such comparison should also be separately powered for asymptomatic and symptomatic patients because the procedural hazards and the net gain for carotid intervention in these two populations is markedly discrepant. Anyone attempting to embark on such an endeavor will find that the United States registry data comprise a majority asymptomatic population—a conservative estimate reflecting that asymptomatic patients represent perhaps 60% to 80% of all carotid interventions.

### CLOSING ARGUMENT

Dr. Gray might argue that in the EXACT (closed cell)/CAPTURE 2 (open cell) combined registry<sup>5</sup> and, for example, the EMBOLDEN registry, in which a variety of stent designs were used with a single-filter-type embolic protection device, stent design did not have an impact on outcomes. True. However, the majority of these patients were asymptomatic (87.9% and 85%, respectively). The lesion demands for symptomatic and asymptomatic patients are wholly different. Furthermore, these registries were simply not powered to answer the question inherent in the title of this debate.

And so I rest my case. When we deal with the most deserving population (patients with symptoms attributable to a significant carotid lesion) in whom procedural hazard is substantial, if there is a recurring theme

in the world literature in favor of closed-cell stents, why would we not want to tentatively endorse current findings, to further explore, and to refine our procedural paradigms to improve outcomes by focusing on specific technical parameters?

The jury may still be out, but I hope that I have provided enough fodder for the intellectually curious to at least sit on the fence, if not quietly accept that more work needs to be done. ■

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