

# A World Without CAS PMS Studies

What will the CAS landscape look like without postmarket surveillance studies, and what will it mean for our patients?

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When a medical device enters the United States market, its manufacturers and distributors are bound by certain US Food and Drug Administration (FDA) requirements. Multiple potential surveillance mechanisms may be mandated, including postapproval studies for those devices that followed a premarket approval pathway and post-market surveillance studies for those that pursued 510k clearance (for simplicity, both types of postmarket device registries will be referred to as PMS studies throughout the remainder of this article).

After market entry of the Acculink carotid artery stent (CAS) and Accunet embolic protection device (EPD) in the United States in 2004 (acquired by Abbott Vascular, Santa Clara, CA, in May 2006), a number of other CAS and EPD devices, alone or in combination, gained FDA approval and clearance. Multiple, large, single-arm CAS, CAS-EPD, and EPD PMS have emerged on the heels of these regulatory decisions. Most of these registry studies are now closed to enrollment, and the absence of further impending device approvals may signify the end of the CAS PMS era as we know it. Does this mean that the CAS “sky is falling” or does it simply represent the natural evolution of CAS from an experimental to an established therapy? What will the implications be if CAS PMS studies disappear altogether?

Although on the surface it might appear that we have gained all that we might from such registry endeavors, that assumption could not be further from the truth. CAS PMS registries have provided operators and patients alike with numerous, if not immeasurable, benefits during recent years, and their absence from the endovascular landscape would have deep and negative impact on the quality of care rendered to our patients with extracranial carotid artery disease.

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## CAS PMS

As a condition of their approval, the FDA mandated that CAS manufacturers conduct PMS studies to help ensure the continued safety and effectiveness of approved CAS systems outside of the clinical trial setting. These studies were, in part, established to detect rare or unanticipated adverse events. However, unique to CAS, these PMS registries were also designed to assess the adequacy of procedural training programs. There are a number of completed and ongoing CAS PMS of varying design, all of which have the typically required pre- and postprocedural neurological evaluation and adjudicated adverse clinical events, such as death, myocardial infarction, and stroke. Examples of the studies include CAPTURE 2 (Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events),<sup>1</sup> EXACT (EmboShield and Xact Post Approval Carotid Stent Trial),<sup>1</sup> CHOICE (Carotid Stenting for High Surgical-Risk Patients), CREATE (Carotid Revascularization With ev3 Arterial Technology Evolution Post Approval Study), CASES (Carotid Artery Stenting With Emboli Protection Surveillance-Post-Marketing Study),<sup>2</sup> and SAPHIRE WW (Stenting and Angioplasty With Protection of Patients With High Risk for Endarterectomy Worldwide).<sup>3,4</sup> In

aggregate, these PMS studies have enrolled tens of thousands of patients who have undergone protected CAS.

### PROCEDURAL REFINEMENT

As with other device and drug registries, CAS PMS studies have provided us with invaluable insight. Not only do PMS studies offer a window into outcomes among real-world patients who may substantially differ from those enrolled in the randomized and single-arm trials that preceded them,<sup>2</sup> they may also afford a closer look at subgroups that may have been underrepresented in previous clinical trials or those for which numbers may have been too small to allow one to draw meaningful conclusions. PMS studies also allow for a more accurate understanding of the epidemiology of infrequent periprocedural adverse clinical events<sup>5</sup> and may permit identification of clinical and technical factors that predict these adverse outcomes.<sup>6,7</sup> This ultimately enables the development of risk models/scores,<sup>3,8</sup> which may help to guide future patient selection, innovations in procedural technique, and next-generation device iterations.

### PATIENT ACCESS

CAS PMS may offer other unique patient benefits as well. A number of CAS and EPD devices have been approved or cleared for use among symptomatic and asymptomatic patients at high surgical risk for carotid endarterectomy (CEA) who have angiographic carotid artery stenoses  $\geq 50\%$  and  $\geq 80\%$ , respectively. Similarly, a number of such devices have been approved or cleared for use among symptomatic and asymptomatic standard-surgical-risk patients with angiographic stenosis  $\geq 50\%$  and  $\geq 60\%$ , respectively. Despite these regulatory approvals, the Centers for Medicare & Medicaid Services (CMS) provide coverage for carotid artery angioplasty concurrent with placement of an FDA-approved CAS only for patients who are at high surgical risk, symptomatic, and have  $\geq 70\%$  carotid artery stenosis. All other FDA-approved patient subsets, including high-surgical-risk, symptomatic patients with 50% to 70% stenosis; high-surgical-risk, asymptomatic patients with  $\geq 80\%$  stenosis; standard-surgical-risk, symptomatic patients with  $\geq 50\%$  stenosis; and standard-surgical-risk, asymptomatic patients with  $\geq 60\%$  stenosis, are only covered by CMS if they are participating in an investigational device exemption (IDE) or PMS study. Given that these latter cohorts represent the majority of patients with carotid artery stenosis, the patients prefer less-invasive endovascular treatment over more-invasive open surgical revascularization, and that CAS is noninferior/equivalent to CEA among similar patients

in United States randomized trials, it should come as no surprise that patients not infrequently opt for CAS over CEA. Were CAS PMS studies to disappear, and CMS coverage along with it, the patient's role in shared decision making when it comes to selecting the most appropriate mode of carotid artery revascularization for stroke prevention would surely be trivialized.

### OPERATOR LEARNING CURVE

Operator CAS volumes have been maintained in large part by the CMS decision to cover CAS under any circumstances in which FDA-approved CAS/EPD devices are permitted, as long as such patients participate in an IDE or PMS study. This has also helped maintain operator skill sets for this technically challenging and relatively high-risk endovascular procedure for which the early learning curve is steep.<sup>9</sup> Were all PMS studies to close, operators would be left performing CAS in only high-surgical-risk, symptomatic patients who have  $\geq 70\%$  stenosis. This change would most certainly culminate in falling national CAS procedure volumes, and procedural outcomes would likely suffer as a consequence given the well-established operator/institution CAS volume-outcome relationship. Ultimately, elimination of PMS studies might have the unintended consequence of making CAS appear to be a less attractive treatment option relative to CEA for patients in need of carotid artery revascularization.

### OTHER REGISTRY OPTIONS

To date, the American College of Cardiology's Carotid Artery Revascularization and Endarterectomy (CARE) registry, which began collecting data in 2005, has captured data from nearly 20,000 CAS procedures performed by more than 800 operators at approximately 200 sites in the United States. All consecutive adult patients at participating institutions are enrolled without exclusion. Independent neurological assessment is to take place (at the treating physicians' discretion) before, immediately after, and at 30 days after the CAS procedure. CARE includes CAS procedures that were performed as part of premarket approval or IDE studies, postmarket surveillance and other studies, or outside of clinical studies.

Although patients who participate in CAS PMS studies may be more "real world" than those enrolled in randomized trials, CARE data have demonstrated that PMS study participants are healthier and have better periprocedural outcomes than nonstudy participants.<sup>10</sup> This observation might lead some to conclude that national quality assurance registries, such as CARE, might supplant CAS PMS registries altogether; however,

the mandatory independent neurological evaluation and adverse event adjudication required by CAS PMS studies still provide an added degree of completeness and precision that is reassuring.

## CONCLUSION

Given the widespread diffusion of CAS PMS studies into our day-to-day clinical practice, it is hard to imagine a time or place where these registries would no longer exist. We owe the FDA a tremendous debt for mandating these postmarket studies; they have helped refine patient selection and procedural technique, and in conjunction with CMS coverage decisions, they have afforded patients access to a broader array of acceptable treatment options while simultaneously maintaining operator skill sets. Nevertheless, barring a change in the CMS National Coverage Determination for CAS, it is difficult to imagine how future patients will meaningfully participate in the shared decision making surrounding carotid artery stenosis treatment options or how current operators will remain adequately trained so as to meet the needs of these patients. ■

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