The Effect of Limited CMS Coverage and Patient Access on CAS Outcomes and Device Development

National coverage decisions can play a critical role in creating the environment in which these improvements take place.

BY PATRICK VERTA, MS STAT, MD

On March 17, 2005, the Centers for Medicare & Medicaid Services (CMS) issued a national coverage determination (NCD) announcing that it was expanding coverage of carotid artery stenting (CAS) for patients at high risk for carotid endarterectomy (CEA) with symptomatic narrowing of the carotid artery of 70% or more. Under this NCD, Medicare also covered patients who met the Food and Drug Administration (FDA)-labeled criteria for carotid stents (ie, patients at high risk for CEA with a symptomatic carotid artery stenosis between 50% and 70% or with an asymptomatic carotid artery stenosis of 80% or more) enrolled in investigational device exemption (IDE) clinical trials, as a routine cost under the clinical trials policy, or enrolled in postapproval studies (PAS). The impact of the 2005 NCD on CAS outcomes across the spectrum of IDE trials, both in high-risk and standard-risk subjects, as well as in FDA-mandated PAS, has been significant.

CMS: THE AFFECT OF THE 2005 NCD

In order to become accredited and seek reimbursement, Medicare required facilities to meet certain minimum standards in performing CAS. These standards included physician training, facility support requirements, as well as data collection to evaluate outcomes in the future. Facilities can obtain accreditation after providing a written affidavit to CMS attesting that the facility had met the standards laid out by CMS.

The expansion of coverage by CMS to FDA-mandated PAS has been a driving force that facilitated and even enabled enrollment in these studies. For every stent system approved, the FDA required sponsors to conduct a PAS with data collection and to submit annual reports to the agency to assess the adequacy of training as well as to uncover any unanticipated or rare event not identified in the pivotal trials. By the end of 2005, CAPTURE, the first of these PAS, had enrolled and analyzed close to 3,000 subjects, while the other two active PAS, EXACT and CASES-PMS, contributed another 600 subjects to the pool in 2005 alone. In parallel (with some overlap) more than 7,000 CAS procedures were reimbursed by CMS by the end of 2005.

By the end of 2009, the year that the last high-risk IDE was initiated, the combined enrollment of all PAS totaled more than 26,000 subjects, while the total number of CAS procedures reimbursed by CMS reached approximately 43,000. The magnitude of CMS's impact can be measured from another perspective: by the end of 2005, within 9 months of the NCD, 768 sites had been accredited by CMS to perform CAS; this number increased by 50% to 1,087 sites by the end of 2009.[1]

IMPORTANCE AND IMPACT OF THE CMS DECISION

The importance and impact of the CMS decision is evident in the improvement in outcomes observed in the PAS that used the same stent system and embolic protection device (EPD). Between 2004 and 2010, outcomes from CAPTURE (N = 4,225) and CAPTURE-2 (N = 6,079) showed

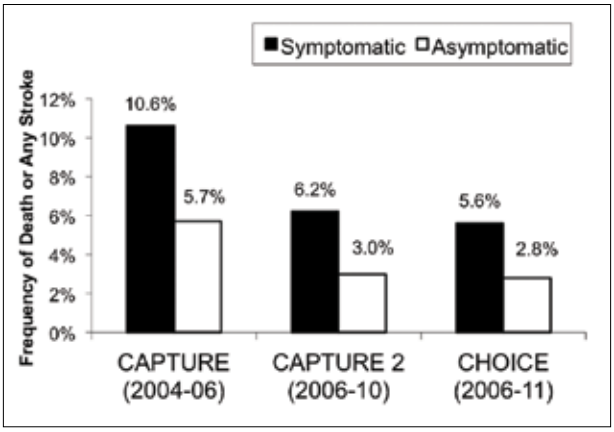

Figure 1. Thirty-day periprocedural outcome improvement over the past decade in postapproval studies using the Acculink stent system in high-surgical-risk patients. Adapted and reprinted with permission from Gray, Verta. The Impact of Regulatory Approval and Medicare Coverage on Outcomes of Carotid Stenting. Manuscript submitted for publication.

a decline in death and stroke rates, both in symptomatic and asymptomatic patients.[2,3] In the symptomatic subgroup, rates decreased from 10.6% to 6.2%, similar to the decrease observed in asymptomatic patients from 5.7% to 3.0%. Analyzing the same single-stent system from the CHOICE PAS (which enrolled an additional 6,000 patients in the Acculink carotid stent/Accunet EPD (Abbott Vascular, Santa Clara, CA) cohort between 2006 and 2011) shows that outcomes continue to trend down with death and stroke rates of 5.1% and 2.8% for symptomatic and asymptomatic groups, respectively (Figure 1).[4] Because the stent and EPD had remained unchanged, the patient demographics were similar, and sites overlapped for the most part across the three PAS, the most plausible explanation for these improvements resides in the presence of a learning curve.

LEARNING CURVE

An indirect and remarkable effect of the learning curve was brought to light during the January 26, 2011 Circulatory System Devices Advisory Panel. The panel was gathered by the FDA to review and discuss the results of the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), a physician-sponsored, NIH and industry-cofunded randomized clinical trial (RCT). CREST was designed to demonstrate the safety and efficacy of CAS in symptomatic and asymptomatic patients at standard risk for surgery. Although CAS successfully met all of the prespecified hypotheses of noninferiority to CEA, an amazing trend emerged from the analysis of the symptomatic cohort whose enrollment spanned over the entire course of the trial, from 2000 to 2008. After an initial increase in death and stroke rates from 4.4% in 2000 to 2004 to 7.0% in 2005, there was a steady and yearly decline thereafter to 1.8% in 2008.[5] In view of all the evidence presented, the panel overwhelmingly voted in favor of the risk-benefit profile of CAS, and on May 6, 2011, the FDA expanded the indication to use of the Acculink stent system in standard-surgical-risk patients.

It seems natural that a learning curve would be present in a very large clinical trial for a new therapy that ran for 8 years. However, the average enrollment in CREST was only six subjects per CAS operator, not enough to provide a learning platform in and of itself.

The follow-up questions for specialists in the field were: Where did the operators learn to perfect their skills, and how did they select more suitable patients for CAS within the RCT framework of the fixed inclusion/exclusion criteria?

The answer is twofold. The FDA-mandated CMS-covered PAS and the exponential growth of CAS literature published

TABLE 1. FIRST WAVE OF IDE CLINICAL TRIALS LEADING TO FDA APPROVALS (STENTS) AND 510(K) CLEARANCE (EPDS)

IDE Trial	N (CAS)	Enrollment Period	FDA Action	Stent System Approved	EPD Cleared
ARCHeR	581	2000–2003	2004	Acculink	Accunet
SECURITY	305	2002–2004	2005	Xact	Emboshield
SAPPHIRE	565	2000–2002	2006	Precise	Angioguard
CABERNET	488	2002–2004	2006	NexStent	FilterWire
CREATE	419	2004	2007	Protégé	SpiderFX
MAVErIC	449	2001–2004	2007	Exponent	GuardWire
BEACH	480	2002–2003	2008	Wallstent	FilterWire EZ

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since 2000 both played a complementary role. PAS provided formal training in addition to tens of thousands of cases, while operators could continue to learn via peer-reviewed articles, presentations, and live cases at major medical conferences.

FDA: THE TWO WAVES OF IDE CLINICAL TRIALS

At the time of the 2005 NCD, Abbott Vascular (then Guidant) was the only company with an FDA-approved carotid stent, the Acculink stent system, and an ongoing postapproval study (CAPTURE). After this first carotid stent approval in August 2004, six new stent systems were approved by the FDA between 2005 and 2007 (Table 1). This first wave of IDE trials enrolled between 2000 and 2004, and led to stent approval as well as to 510(k) clearance of their corresponding EPDs.

It is important to note that the first wave of IDE clinical trials carried key similarities in trial design, such as patient inclusions/exclusions, primary composite endpoint (30-day periprocedural death, stroke, and myocardial infarction), pre-, post-, and 30-day independent neurological assessment, and independent central adjudication of neurological events. Subsequently, baseline demographics were similar across studies. Not surprisingly, 30-day death and stroke rates were clustered, ranging from 4.0% to 6.9%, with a weighted average of 5.3% (95% CI, 4.6, 6.2%).

New EPDs seeking 510(k) clearance led to a second wave of IDE trials, with enrollment spanning between 2006 and 2010 (Table 2). Like the first wave of IDE trials, these studies included similar patient demographics and were assessed the same way as the first wave of IDE trials. Rates of 30-day death and stroke were also clustered, ranging from 1.8% to 3.6% with a weighted average of 2.6% (95% CI, 1.9, 3.7%).

Several observations can be made in comparing the first wave to the second wave of IDE trials. The enrollment periods do not overlap and are separated by a gap of 2 years (2000 to 2004 for the first wave, and 2006 to 2010 for the second wave). Importantly, outcome rates were halved, from an average of 5.3% to an average of 2.6%, a statistically significant difference of 2.7% (95% CI, 1.3, 3.9%; Fisher's exact test; $P < .0001$.)

Although improvement in EPD technology used in the second wave, such as proximal protection or better distal protection devices, may have played a role in the observed improvement in outcomes, when these IDE observations are considered along with the aforementioned outcome improvements on a single-stent system and EPD (Acculink and Accunet), the impact of CMS's national coverage decision for FDA-mandated PAS cannot be underestimated.

TABLE 2. SECOND WAVE OF IDE CLINICAL TRIALS LEADING TO FDA 510(K) CLEARANCE (EPDS)

IDE Trial	N (CAS)	Enrollment Period	FDA clearance	EPD
PROTECT	320	2006–2008	2008	Emboshield Nav6
EPIC	237	2007–2008	2008	Fibernet
EMBOLDEN	250	2009–2010	2009	Gore Embolic Filter
EMPIRE	245	2006–2008	2009	Gore Flow Reversal
ARMOUR	228	2007–2009	2009	Mo.Ma

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CONCLUSION

The medical device industry and venture capitalists invest large portions of their funds to create new therapies. The capital is used to demonstrate the safety and efficacy of devices to the FDA and to bring them to market. The products will then take years in the hands of trained practitioners who must overcome learning curves and translate new technologies into superior outcomes. From what we have seen, national coverage decisions by CMS, even if limited in scope, can play a critical role in creating the environment in which these improvements will take place. In addition, the expansion of FDA indications and CMS coverage decisions enable industry reinvestment in better technologies that ultimately benefit patient outcomes. ■

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