Will CREST Save CAS?

A look at the reimbursement history of carotid stenting in the United States, as well as the potential impact of CMS's next move.

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On August 1, 2011, Abbott Vascular (Santa Clara, CA) submitted a formal request for reconsideration of the Centers for Medicare & Medicaid Services (CMS) National Coverage Determination for coverage of carotid artery stenting (CAS). This will be the seventh time since 2000 that CMS (at one time Health Care Financing Administration, HCFA) will review their policy. Since 2005, when CMS put in place the current policy providing coverage for some high-surgical-risk patients, CMS has reviewed its policy three times, and none of those reconsiderations has led to a change in coverage.

This time is likely to be very different for a number of reasons. First, the major focus of the coverage review will not be high-surgical-risk patients, although formally that will be part of the reconsideration, but instead the reconsideration will focus on the vast majority of carotid patients who are also candidates for surgery. Second, rather than debating the scientific strength of registries and single-arm studies that have been the focus of discussion in previous coverage reconsiderations, the debate will revolve around CREST, the largest and most rigorous randomized study of CAS to date. Finally, one hopes that, given the strength of CREST, this review does result in an expansion of coverage, although the 25 years of carotid coverage controversy has shown that there are no certainties.

HISTORY OF CMS CAS COVERAGE

The CAS coverage debate has been going on for a quarter of century. In 1985, CMS (then HCFA) issued a national noncoverage policy for CAS, citing a lack of evidence and concerns over its safety and efficacy.[1] For the next 16 years, Medicare denied payment for all CAS procedures under any circumstances. That policy remained in force until 2001, when Medicare opened coverage for CAS when conducted in FDA clinical trials. That coverage decision facilitated a number of industry-sponsored studies, and Guidant Corporation (whose peripheral vascular division was subsequently bought by Abbott Vascular), Cordis Corporation (Bridgewater, NJ), and Boston Scientific Corporation (Natick, MA) completed trials designed to win FDA approval for their carotid stents and embolic protection devices.

All of the companies took aim at what they figured was the best target patient population to show the safety and efficacy of CAS: patients with carotid disease who, because of comorbidities or anatomical factors, were at high risk for carotid endarterectomy (CEA). Because of the high surgical risk these patients faced, the companies successfully argued that it was inappropriate to randomize against CEA, so—with the exception of Cordis's SAPPHIRE trial—all of the PMA studies were single arm. The single-arm studies may have facilitated FDA approval, but they have significantly complicated the task of gaining reimbursement.

In 2004, Guidant Corporation became the first company to receive FDA approval for its carotid stent system. The FDA granted a broad indication for Guidant's CAS system for patients at high risk for adverse events for CEA with 50% or greater stenosis if they had neurological symptoms and for 80% and greater stenosis if they were asymptomatic.

It wasn't until 2005, when Cordis Corporation obtained FDA approval based on the data from its randomized SAPPHIRE trial, that CMS opened cover-

age to patients treated outside of an FDA trial. While industry was hoping for a coverage policy that matched the FDA indication, CMS granted much more limited coverage. CMS only covered symptomatic patients with a stenosis of 70% or greater, and it denied coverage to any asymptomatic patients unless they were part of an FDA trial or postmarketing registry. In addition, CMS determined that CAS was reasonable and necessary only if performed in facilities that were determined to be competent in performing the evaluation, procedure, and follow-up necessary to ensure optimal patient outcomes. CMS created a list of minimum standards and required all facilities to meet them in order to receive coverage for CAS for high-risk patients. That has been the main outline of coverage since 2005, and despite reconsiderations, new studies, and increasing industry and physician frustration, that is where it remains.

WHY HASN'T COVERAGE BEEN EXPANDED?

CMS has refused to expand high-surgical-risk coverage for a number of reasons. First, it has been openly skeptical about the single-arm studies and registries that industry has performed. As CMS has consistently pointed out, these studies lack controls and are subject to selection bias. Second, although CAS results have improved over time, CMS has not been convinced that the perioperative complication rates are low enough to warrant coverage. Finally, the coverage debate for high-risk surgical patients has gotten bogged down in the discussion of what constitutes a high-risk patient. When industry or CAS operators have pointed at a study showing low perioperative complications, CMS has responded that it is not clear if the results can be applied to all the patient subtypes that make up the high-risk designation.

Given that CMS has reviewed its policy three times and made no changes in patient coverage, it is a fair question to ask why this time might be different, but CREST and this coverage review represent an entirely new chapter in the CAS coverage debate. First, CREST only provides data related to the two-thirds to three-quarters of carotid patients who are at standard risk for surgery. This means that all the concerns raised about the studies on high-risk patients are basically moot. However, while the high-surgical-risk coverage debate will not directly affect the standard-risk patient coverage decision, CMS's rationale in its previous coverage decisions provides some good insights into what CMS will need to expand coverage.

CMS has raised three concerns about CAS for the high-surgical-risk population: the lack of high-quality evidence showing that CAS perioperative stroke and death rates meet the AHA guidelines, questions about CAS results in real-world settings, and a desire to see CAS outcomes for asymptomatic patients compared to best medical therapy.

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The main reason CMS has given for not expanding coverage has been the lack of high-quality evidence showing that CAS has met the AHA guidelines of 3% perioperative stroke and death rate for asymptomatic patients and 6% for symptomatic patients. As CMS noted in its 2009 decision, "… As we have concluded in the last two decision memoranda, for CAS to be considered an alternative to CEA and improve health outcomes for asymptomatic patients with asymptomatic stenosis > 80%, the perioperative morbidity and mortality rates should be less than 3%. For symptomatic patients with stenosis > 50%, the benchmark is less than 6% death and stroke within 30 days of the procedure. The body of randomized trials and postapproval studies does not demonstrate that CAS can be performed at that level."[2]

The 3% and 6% guidelines derive from the landmark CEA versus medical management studies (NASCET, ACAS, and ACST), but CMS has set a tougher standard for CAS. First, the CEA studies excluded patients 80 years of age and older and should therefore only apply to younger patients, but CMS has not attempted to limit CEA's coverage or even review it. On the other hand, although two studies, CAPTURE 2 and SAPPHIRE WW, found a 30-day CAS stroke and death rate within AHA guidelines for patients younger than 80 years of age, CMS refused to expand coverage because the studies included patients 80 years and older and those patients had stroke and death rates higher than the accepted thresholds.[2] One can understand why CMS would be uncomfortable making coverage decisions based on age for its members, but more than anything, this illustrates the increased scrutiny and evidentiary requirements once CMS embarks on a coverage review.

CREST'S IMPACT ON CMS'S DECISION

CREST should address the concern regarding the adequacy of available and supportive data, particularly for

symptomatic patients. Not only were the perioperative stroke and death rates in CREST below the AHA thresholds (2.4% for asymptomatic patients; 5.9% for symptomatic patients), but as the largest and most rigorous trial comparing CAS and CEA, CREST found no statistical difference between the two procedures in the composite endpoint of perioperative death, stroke, and MI plus ipsilateral stroke out to 4 years.[3] Although some may point to the less favorable results of the three European trials that compared CAS and CEA, (EVA-3S, SPACE, and ICSS), CREST's US-based results and rigorous design should make it the single most important study CMS looks at when it begins its coverage reconsideration. As United States critics of the European studies have pointed out, those studies relied heavily on inexperienced operators, many of whom were tutored on the CAS procedure during randomized cases for the studies.

In addition, CREST is the only study that mandated the use of embolic protection devices, a requirement that mirrors CMS's coverage requirements. One of the chief differences between CREST and the European studies is CREST's inclusion of myocardial infarction (MI) in the primary endpoint and the use of biomarkers such as troponin to identify potential MIs. When the CREST results were first published, some questioned the appropriateness of including MI in the composite endpoint; however, there is a robust body of literature on the impact of MI on patient mortality, and the CREST investigators have since published an analysis of the data showing that the MIs in CREST were also a predictor of long-term mortality.

CMS may also be persuaded by the fact that CREST is in many ways the poster child for the kind of evidence development CMS wants to encourage. CREST was designed by independent academic investigators. The NIH/NINDS vetted the study design and provided funding. The FDA reviewed the protocol, monitored CREST's execution, and granted the devices involved an expanded indication for standard-surgical-risk patients.

As a randomized controlled trial, CREST can't speak to concerns about CAS results in the real world, but there are other ways to address that issue. In an attempt to monitor and improve CAS results, CMS has required hospitals to report data as a requirement of coverage. The agency has expressed a desire to relinquish that responsibility, and two organizations, the Accreditation for Cardiovascular Excellence (ACE) and the Intersociety Commission for the Accreditation of Carotid Stenting Facilities (ICACSF), have developed CAS accreditation programs in the hopes of getting CMS approval. The programs are fairly similar to each other. They involve significant data reporting requirements, set standards for facility capabilities, encourage sites to participate in registries, and allow for the revocation of accreditation if a facility fails to meet certain standards or benchmarks.

The coverage of asymptomatic patients has been the most controversial issue in past coverage reconsiderations of the high-surgical-risk patient population, and it is likely to be the biggest coverage question for the standard-surgical-risk population. In denying coverage to asymptomatic high-risk patients treated outside of an FDA study, CMS has cited general concerns that current medical therapy may be the better option than either CAS or CEA, and CMS has consistently expressed a desire for studies that directly compare CAS to medical therapy for treating asymptomatic patients. As CMS wrote in 2009, "the greatest concern is for asymptomatic patients who are at low risk (for stroke) and may benefit from medical therapy. Some experts have questioned the 3% value, as the benefits of medical therapy may have improved."[2]

CMS's past concerns may well have been appropriate for the high-risk surgical population. Almost by definition those patients have never been part of an RCT comparing surgical revascularization with medical therapy, and given that, there is no direct evidence showing that particular patient population benefits from revascularization.

However, the same reasoning should not apply to standard-surgical-risk asymptomatic patients. The best available evidence in the form of two RCTs, ACAS and ACST, shows a small but clinically meaningful benefit for patients treated with revascularization rather than medical therapy. While medical therapy, principally statin lipid and blood pressure control, has improved, there are no randomized data that trump the ACAS or ACST improvement in outcomes with revascularization.

An article by Anne Abbott published in *Stroke*[4] and mentioned in the December 2009 coverage memo, illustrates the problems with the evidence on medical therapy. The analysis tries to link together multiple studies, most of them single arm, conducted over a 30-year period in an attempt to show that stroke rates are declining. The studies incorporated often do not describe the medical therapy that was used; the analysis does not adjust for different carotid stenosis thresholds in the different studies and includes patients with stenosis < 60% who would be expected to have lower stroke rates and who would in the majority not be offered a carotid intervention. The studies analyzed were small, and the confidence intervals for the stroke

rates in each study overlapped with the 2% annual rates found in the medical management arms of ACAS and ACST. It is hard to believe if CMS reviewed a technology that had this type of evidence to support it that CMS would grant coverage. On the other hand, CMS has relied heavily on the AHA guidelines in its past decisions, and the most recent AHA guidelines reduced the level of recommendation for revascularization of asymptomatic patients.

In making its coverage determination, CMS will want to look closely at the 10-year ACST results that were published in late 2010[5] and were too late to be included in the AHA guideline review. The patients in ACST, who were followed into 2009, were on rigorous medical therapy, and revascularization continued to show a benefit over medical therapy alone.

WHAT IS THE PROCESS NOW?

Once a National Coverage Request (NCD) is made, CMS determines whether to open the NCD or not within approximately 60 days. If the NCD is opened, it takes approximately 9 months from the time the NCD is opened to the time a final decision could be made. During that time, an initial 30-day public comment period is opened, followed by an internal CMS review, which results in a draft decision memorandum that is posted publicly prior to the start of the final 30-day public comment period. Within 60 days following the end of the final public comment period, CMS will issue a final decision memo.

If CMS does expand coverage to standard-risk patients—particularly asymptomatic patients—the number of CAS cases will certainly increase. Published evidence and reimbursement drive adoption. Expanded coverage based on CREST will incent manufacturers and physicians to more liberally recommend CAS for appropriate patients. Increased marketing by manufacturers and physician awareness of the expansion of coverage will also help increase the use of CAS.

But while CAS procedures will increase, the legacy of the CMS coverage decisions will probably slow adoption. First, hospital accreditation requirements will continue to limit the number of facilities that offer CAS. Second, the years of controversy about medical management, surgical intervention, and stenting have created lingering skepticism, and many referring physicians will demand even more clinical evidence before significantly changing treatment recommendations for their patients.

However, if CMS does not expand coverage, it could signal the beginning of the end for industry support of CAS. For the past decade, industry has put money into CAS on the assumption that CMS would expand coverage. It has invested in technology development, physician training, registries and studies betting that those investments would lead to a larger CAS market, and for 10 years, that bet hasn't paid off. CREST was CAS's ace in the hole, and if CREST doesn't change CMS's policy, then industry may well walk away from the table.

Perhaps even more important than its effect on the CAS industry, a failure to expand coverage could have a chilling impact on the medical technology community as a whole. What industry wants is predictability. CMS has long had a reputation as not only a difficult payer but as an unpredictable and uncommunicative one as well. CMS coverage standard of "reasonable and necessary" is open to almost any interpretation one can think of, and CMS gives little guidance about what study with what kind of results will lead to coverage. This is particularly the case once a procedure or technology is targeted for a national coverage decision.

CMS has tried to make the process of obtaining coverage somewhat easier by creating the Coverage With Evidence Development program. The program's goal is to grant limited coverage to encourage high-quality evidence that can then be used to make a definitive coverage decision. CREST should represent the ideal coverage with evidence development study, the kind that CMS should strive for. If this doesn't lead to coverage, industry will be left to wonder what will. ■

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