CABG, Stents Tied to Same Cognitive Changes

BY KERRI WACHTER
Senior Writer

WASHINGTON — There doesn't appear to be any difference in long-term cognitive function following coronary artery bypass graft or stenting.

This finding comes from an assessment of cognitive function at 6 years in 152 patients whose coronary artery disease (CAD) was treated with coronary artery bypass graft (CABG) and 92 patients whose CAD was treated with stents. Dr. Guy McKhann, professor of neurology and neuroscience at Johns Hopkins University, Baltimore, and his colleagues found that cognitive declines noticed after surgery are related to the presence of vascular disease. "The real attention should be on modifying risk factors," he said, adding: "We think that how these people do is very much dependent on how their brains are going in [to surgery]."

In terms of cognitive change over 6 years, there was minimal decline, but essentially these two groups were the same, Dr. McKhann reported at the annual meeting of the American Neurological Association. The average Mini-Mental State Examination (MMSE) score was 27.4 for the CABG group and 27.9 for the stent group. The average Center for Epidemiologic Studies–Depression (CES-D) scale score was 9.5 for the CABG group and 9.0 for the stent group. (See table.)

The issue of long-term cognitive decline following coronary artery surgery is an important one, given that there continues to be uncertainty over the best approach to treat coronary artery disease—surgery or stenting. "This issue of late decline has gotten into this debate" and is used as an argument for stenting rather than surgery, he said.

"We don't think there is any selective long-term decline after CABG that cannot be seen in other groups with significant coronary artery disease. We don't think late decline should be an issue in the choice of what procedure you're going to have done," said Dr. McKhann.

The researchers have been studying the issue of neurologic outcomes following coronary surgery since 1992. "What we set up then was a prospective evaluation of all heart surgery patients within the intensive care unit," said Dr. McKhann.

Starting in 1997, the work that Dr. McKhann and his colleagues were doing with acute-care patients became a four-arm study involving those undergoing conventional CABG, those with off-pump CABG, cardiac controls who received stents, and heart-healthy controls lacking traditional risk factors for heart disease. The researchers looked at cognition at baseline, 3 months, 1 year, 3 years, and 6 years.

In this CAD intervention population, 3%-5% have strokes, 10%-15% have encephalopathies, and about 25% have short-term cognitive problems. In-hospital mortality is 22% following a stroke, 7.5% following encephalopathy, and 12% following both.

"If you have coronary artery disease … you're going to be lower at baseline than the heart-healthy controls but not in all cognitive domains," he said. ■

No Significant Difference in Cognitive Function After CABG or Stents

	CABG (n = 152)	Stents (n = 92)
Age (at enrollment)	64 years	66 years
Death	17%	21%
Statin use	84%	76%
Average MMSE score	27.4	27.9
MMSE score < 24	7%	8%
Average CES-D score	9.5	9.0
CES-D score > 15	13%	15%

Notes: Based on a 6-year follow-up. MMSE stands for Mini-Mental State Examination. CES-D stands for Center for Epidemiologic Studies–Depression.
Source: Dr. McKhann

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Assist Device *from page 1*

sisted Circulatory Support (INTERMACS), which is a joint effort of the National Heart, Lung, and Blood Institute, the FDA, the Centers for Medicare and Medicaid Services, and individual clinicians, scientists, and industry representatives in conjunction with the University of Alabama, Birmingham, and the United Network for Organ Sharing.

"I think the sentiment here is that [HeartMate] has met reasonable assurance of effectiveness despite the fact that the data did not meet the prespecified performance goal," said panel chairman Dr. Warren K. Laskey, chief of cardiology at the University of New Mexico, Albuquerque.

The device 'has met reasonable assurance of effectiveness despite the fact that the data did not meet the prespecified performance goal.'

Thoratec studied the HeartMate II in 126 patients in the pivotal study, conducted at 26 sites. As with previous trials of bridge-to-transplant devices, the Thoratec HeartMate II study was prospective and not randomized. Six such devices have been approved, including right, left, and biventricular assist devices and a temporary artificial heart. Unlike those devices, the HeartMate II was subject to a new FDA performance goal that was set in 2002.

That goal was defined as survival of the patient to transplant or 180 days of left ventricular support while remaining listed for a transplant as status 1A or 1B. According to the FDA criteria, the HeartMate II did not meet the definition of success: getting the one-sided 95% lower confidence limit of the true success rate to exceed 65%.

In all, 89 (70%) of the 126 patients were considered a total success: 72 received transplants, 4 recovered, and 13 were supported for 180 days while listed. This resulted in a lower confidence limit of 64%.

Although Thoratec missed the statistical cut-off, the advisory committee members said they believed that the device had shown clinical effectiveness.

Safety was comparable to other devices, including Thoratec's two approved bridge-to-transplant devices, the HeartMate VE and the IVAD, said the FDA. There were 29 deaths; 6 patients died of sepsis, 5 died of ischemic cerebrovascular events, and 4 died of multisystem organ failure. One death was considered to be related to device failure. In terms of serious adverse events, 59% of patients (74) had a bleeding episode, and 29% (37) required surgery to stop the bleeding. Stroke occurred in 9% (11) of patients, and sepsis in 20% (25) of the group.

Eighty patients had reoperations; 73% were in the first 30 days, according to the FDA. The most common reason for another surgery was bleeding.

Bleeding was of concern to Dr. L. Henry Edmunds Jr., thoracic surgeon at the University of Pennsylvania, Philadelphia, and Dr. John C. Somberg, chief of clinical pharmacology at Rush University Medical Center, Chicago. Dr. Edmunds pushed for a prescriptive protocol in the label for anticoagulation, but his motions were not approved by the committee. Dr. Somberg also was cautious with his vote to approve the HeartMate II, noting, "There's a lot of science to be investigated here, especially problems related to bleeding."

In the ongoing continued access protocol study, 2 of the 138 patients enrolled have required a HeartMate II replacement or exchange to another device because of pump thrombosis. Both patients died while on support, according to the FDA.

And, with primary end point data available on 58 of the patients, so far, only 55% met the FDA's statistical cut-off for success, according to the agency.

Despite unanswered questions, panelists felt that the device should be available. "This is an important new technology," said Dr. Richard L. Page of the University of Washington, Seattle.

"This is an exciting device because of its small size and ability to be implanted in many more patients," said Dr. Norman S. Kato, in private practice at the Cardiac Care Medical Group in Encino, Calif. ■

Human Thrombin OK'd to Stem Bleeding in Surgery

BY ELIZABETH MECHCATIE
Senior Writer

The Food and Drug Administration has approved a thrombin product derived from human plasma to help control bleeding during surgery.

Evithrom, is the first human thrombin approved since 1954 and is the only such product currently licensed by the agency, according to an FDA statement announcing the approval. The approved indication is "as an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible and control of bleeding by standard surgical techniques is ineffective or impractical."

The approval "offers an important additional option for surgeons and their patients to help control surgical bleeding," and provides surgeons the choice between human thrombin and bovine-derived thrombin, Dr. Jesse L. Goodman, director of the FDA's Center for Biologics Evaluation and Research, said in the statement.

Evithrom is applied to the surface of bleeding tissue and can be used with an absorbable gelatin sponge. The safety and efficacy of Evithrom were "comparable" with those of cattle-derived thrombin in a study of 305 patients, according to the FDA. In the study, 63 patients who received Evithrom were over age 65. No differences in product safety or efficacy were documented between elderly and younger patients, according to the product's label.

The label cites immunogenicity data from the study, which compared the presence of antibodies to bovine thrombin, bovine Factor V/Va, human thrombin, and human factor V/Va at baseline and 5 weeks after surgery in most of the patients. About 3% of those who received Evithrom developed antibodies to any of these four antigens, compared with nearly 13% of those who received bovine-derived thrombin. Nearly 8% of those in the latter group developed antibodies to bovine thrombin, and nearly 10% developed antibodies to bovine factor V/Va, while none of those treated with Evithrom had detectable antibodies to human thrombin or to human factor V/Va.

Manufactured by Omrix Biopharmaceuticals Ltd., based in Ramat Gan, Israel, Evithrom is made from pooled human plasma derived from U.S.-licensed plasma collection centers, using carefully screened donors. Johnson & Johnson Wound Management (a division of Ethicon Inc.) will be distributing it in the United States.

Evithrom contraindications include treatment of severe or brisk arterial bleeding. ■

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