



Bill Boden, MD

STUDY CHALLENGES EFFICACY OF ANGIOPLASTY, STENTING
FOR STABLE HEART DISEASE

Paradigm adrift

BY  LOIS BAKER

The news Dr. Bill Boden would deliver to the American College of Cardiology (ACC) at its 2007 annual meeting would cause an uproar, he knew. The clinical trial on which he was coprincipal investigator had proved that the vastly popular and highly lucrative angioplasty and stenting procedure was no more effective than aggressive medical therapy in preventing heart attack or death from myocardial infarction in patients with stable coronary disease.

Introduced in the early 1980s, angioplasty was quickly embraced by physicians as the preferred first-line treatment for reducing angina in patients with stable heart disease. Development in the early 1990s of stents to prop open arteries after they were cleared of blockages made the procedure even more popular, despite the fact that treatment guidelines continued to recommend aggressive medical therapy with these patients before turning to angioplasty. Today, about 85 percent of all angioplasties in the U.S. are done electively in patients with stable disease, at a cost of between \$15,000 and \$35,000 per procedure, making it a multibillion dollar industry.

A Landmark Study

The clinical trial—called the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial—was conducted from 1999–2004 in 50 sites in the U.S. and Canada. It was the first large-scale randomized trial to compare optimal medical therapy alone versus percutaneous coronary intervention (PCI, the medical term for angioplasty) plus optimal medical therapy since the procedure's introduction 17 years earlier.

Boden, who is professor of medicine and public health at UB and chief of cardiology at Kaleida Health System, moved to Buffalo from the University of Connecticut in 2006. As lead author on the report of the trial, he was prepared for a donnybrook.

"This is going to be one of the most scrutinized, dissected, analyzed, criticized, interpreted, and probably misinterpreted studies of the early 21st century," he predicted prior to the ACC meeting.

He could not have been more prescient.

The ACC, in conjunction with the *New England Journal of Medicine* (NEJM), which planned to publish the

study online immediately after Boden's scheduled presentation on Tuesday, March 25, were determined to keep the controversial results under wrap until then.

However, at a Sunday evening symposium sponsored by Boston Scientific, a major stent manufacturer, Martin B. Leon, MD, a well-known interventional cardiologist and Boston Scientific advisor who had reviewed the paper for the *NEJM*, prematurely revealed and disparaged the trial results, preempting a strict embargo the media had agreed to honor.

Leon asserted that the study was rigged to fail, critically flawed and shouldn't affect treatment patterns, and that medical therapy does not work very well. Reporters from the *Wall Street Journal* attending the symposium published his remarks on the *Journal's* website Monday morning.

The ACC and the *NEJM* were furious, Boden recalls. "They were extremely upset. The physician had breached an ethical standard. He divulged that he was a reviewer of the paper, and worse, by prematurely disclosing the results of the study, he essentially denied us, as the investigators, the right to be the first individuals to present our findings to our peers and colleagues."

The breach had serious consequences. The *NEJM* barred Leon from reviewing research or authoring reviews and editorials, and the ACC's executive committee is considering disciplinary action. At this writing, the matter is in the hands of the ACC's ethics committee.

As it happened, however, the breach worked to the investigators' advantage. The ACC hastily organized a press conference for early Monday afternoon that was devoted exclusively to the COURAGE trial. Attended by a crush of media, it lasted 90 minutes. The study headlined the national television evening news programs on Monday and appeared on page one of major daily newspapers across the U.S. Tuesday morning.

Boden presented the trial results at the appointed Tuesday morning session. The format didn't permit questions from the floor, but after he spoke, a number of conference attendees openly congratulated Boden for conducting a very difficult and demanding study.

Results of the trial were published in the April 12 edition of the *NEJM*. An editorial accompanying the article, written by Judith S. Hochman, MD, from the Cardiovascular Clinical Research Center at New York University School of Medicine, and P. Gabriel Steg, MD, from Centre Hospitalier Bichat-Claud Bernard, University of Paris, supported the study findings.

"The COURAGE trial should lead to changes in the treatment of patients with stable coronary artery disease, with expected substantial health-care savings," wrote the authors. "PCI has an established place in treating angina but is not superior to intensive medical therapy to prevent myocardial infarction and death in symptomatic or asymptomatic patients such as those in this study."

Weeks after the results became public, plaudits still reverberated. Steven Nissen, MD, chair of the Department of Cardiovascular Medicine, Section Head of Clinical Cardiology at the Cleveland Clinic and outgoing president of the American College of Cardiology, said the trial deserved all the attention it received.

"This obviously is a landmark study," said Nissen, "and Dr. Boden should be applauded for undertaking it under adverse conditions. This is a study that will be cited for years to come. I think Boden and his colleagues pursued it with a passion of helping patients that was really very admirable."

A "Trialist" at Heart

A native of Rochester, New York, Boden graduated from LeMoyne College and received his medical degree from State University at New York Upstate Medical University (formerly SUNY Upstate Medical Center), both in Syracuse. He completed his residency in internal medicine at Boston University Medical Center, where he served as chief resident and teaching associate at University Hospital. He then completed a clinical fellowship in cardiology at Tufts–New England Medical Center.

Boden held subsequent positions as assistant professor of medicine at Brown University School of Medicine and associate professor of medicine at Wayne State University

before spending two years as professor of medicine at Boston University's School of Medicine. He returned to his medical roots in 1996, when he accepted positions as professor and associate chair in the Department of Medicine at Upstate Medical University and chief of medical service at the Syracuse Veterans Affairs Medical Center.

He left Syracuse in 2000 to become professor of medicine at the University of Connecticut School of Medicine and chief of cardiology at the Henry Low Heart Center at Hartford Hospital, where he worked for six years before joining the UB faculty and Kaleida Health.

Boden describes himself as a cognitive cardiologist—a noninvasive clinical cardiologist and "trialist." He jumped into research in 1978, four years out of medical school, and has been "full speed ahead" since. His clinical studies fall into four general categories: post-myocardial infarction secondary prevention; secondary prevention in post-myocardial infarction/coronary artery disease hyperlipidemia; acute coronary syndromes and unstable angina; and congestive heart failure.

Several of these investigations are ongoing, including the AIM-HIGH Trial, a six-year, \$43 million investigation funded by the National Heart, Lung and Blood Institute and Abbott Laboratories, on which Boden is project director and study co-chair. The trial—which is being carried out in 72 centers in U.S. and Canadian through 2011—compares two drug treatment strategies in 3,300 patients who have abnormally low levels of HDL cholesterol.

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Absence of Evidence

The idea for the ground-breaking COURAGE trial was kindled in 1994 while Boden was at the VA and Upstate Medical University. That year was significant, he says, because coronary stents just had been approved for clinical use.

From 1977 to 1994, simple balloon angioplasty was the only approved method to open blocked arteries. One of its limitations was the 40- to 50-percent restenosis rate, which meant the procedure had to be repeated in many patients. With the advent of stents—which hold open arteries after the blockage is removed—angioplasty’s position as the first-line treatment for occluded vessels in stable heart disease patients was sealed, despite clinical guidelines to the contrary. Boden and his non-interventional colleagues, who had successfully treated many such patients using the recommended aggressive medical therapy, wondered why a properly designed and conducted randomized trial evaluating the efficacy of angioplasty and stenting versus medical therapy never had been conducted.

“I think one reason was that there really hadn’t been a groundswell of interest or enthusiasm from within the academic community to undertake such a trial,” says Boden of that time. “We also knew it would be bloody difficult to do such a trial in the States.

Everybody had so bought into the concept that angioplasty was the preferred or

optimal therapy that we were concerned this study would never get done.”

Individual investigators who had tried to identify funding for such a trial had come up empty-handed. Boden and other interested clinicians then decided to form a coalition of North American investigators who would develop a joint proposal and see if they would have better luck.

Their first proposal, with a budget of \$24 million, went to the Department of Veterans Affairs in 1996. The VA approved the proposal, but with strings attached: It would give the investigators \$8 million, but that \$8 million would come off the table in 18 months if they didn’t come up with the remaining \$16 million from other sources.

The investigators approached the NIH to see if it would partner with the VA to fund that part of the trial. They soon were engulfed in a bureaucratic quagmire. The VA and the NIH couldn’t decide who would run the trial and who would subcontract from whom, Boden recalls. After a year spent in negotiations, the VA-NIH collaboration came apart.

With the NIH out of the picture, the VA turned to Canada. Ultimately, the Canadian government’s Institutes for Health Research donated \$3 million to a budget that had grown to \$36 million, and the VA increased its portion to \$12 million. The remaining \$21 million, plus study drugs, was funded by pharmaceutical companies, primarily Merck and Pfizer, which had been watching developments from the sidelines. The major device companies also were approached repeatedly for funding but they declined, Boden says.

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By the end of 1998, funding was in place. Investigators launched the trial in January 1999 and enrolled their first patient in June.

Outcomes and Implications

The COURAGE trial compared survival and heart attack rates in 2,287 persons with stable heart disease who were randomized to receive either optimal medical therapy or angioplasty and stenting, followed by medical therapy.

Participants were followed for a median of 4.6 years. Death from any cause and nonfatal heart attack were the primary outcomes. The results showed that there were 211 such events in the angioplasty group and 202 in the medical treatment group. The cumulative primary events rates over the 4.6 years were 19 percent in the angioplasty group and 18.5 percent in the medical therapy group.

There also was no significant difference between groups when frequencies of death, heart attack and stroke were analyzed, nor was there a significant reduction in subsequent hospitalizations for unstable angina in angioplasty patients.

Angioplasty did significantly reduce the amount of stable angina, the trial showed, although medical-treatment patients also experienced substantial relief from angina, especially during the first year, with further improvement at five years.

“To me, that was one of the biggest surprises,” says Boden, “and it resonated throughout the discussion with both the press and symposium attendees. One of the major benefits expected of angioplasty was substantial relief from chest pain. Two-thirds to three-quarters of medical treatment patients became completely angina-free during the follow-up period. These were unexpectedly positive outcomes.”

Despite these results, and despite comments from E. Murat Tuzco, MD, professor of medicine at the Cleveland Clinic Foundation, who told reporters the study “may very well change practice,” Boden speculates that, in the

short term, it will have little effect on the number of angioplasties for stable coronary disease, at least in the U.S., although several European cardiologists have told him the results will change practice there.

“I don’t think interventional cardiologists will have a sudden epiphany that intensive medical therapy should replace angioplasty as the initial approach to management of stable heart disease,” says Boden. However, he ventures that, in time, clinical practice may evolve to embrace the study’s findings.

“For interventional cardiologists, the procedure provides such a powerful and positive feedback loop,” Boden observes. “You do an angiogram on a patient and see significant narrowing. You do balloon dilation and put in a stent, repeat the angiogram, and the artery looks completely normal. You have immediate, visual, positive feedback that you’ve just done something good for the patient, and the patient feels better. Plus there’s the prevailing concern that if you don’t do the procedure, something bad may happen to the patient.”

“I think most interventional cardiologists are doing this for the right reasons,” he continues. “They believe deeply in what they are doing. But it’s been predicated on the unproven assumption that if you fix the artery, you are going to improve prognosis, and I think most patients who undergo angioplasty do so because they think they’re going to have a lower likelihood of developing a heart attack, or that they’re going to live longer.”

“What COURAGE tells us,” Boden says, “is that if you opt for an initial strategy of medical therapy, you are not putting your patients in harm’s way. Their prognosis is equally as good without putting them through an invasive procedure as an initial approach.”

Results of the trial had shown that while one-third of the medically-treated patients ultimately required a first revascularization during the seven-year follow-up, two-thirds fared very well without it.

“That is the good news,” Boden notes. “I think that should be very reassuring to both physicians and patients.” **BP**

