Medical Therapy as Good as PCI in Stable Disease

The estimated rate of death or nonfatal MI was 19.0% with PCI and 18.5% with medical therapy.

BY BETSY BATES
Los Angeles Bureau

NEW ORLEANS — Percutaneous coronary intervention adds no benefit to optimal medical therapy for extensive but stable coronary artery disease, according to results of the COURAGE trial, and that finding has set off a debate about the medical necessity of PCI in many patients.

As an initial management strategy, PCI added to optimal medical therapy in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial did not reduce the rates of death, nonfatal MI, or hospitalization for acute coronary syndromes during a mean follow-up of 4.6 years, Dr. William E. Boden reported at the annual meeting of the American College of Cardiology.

"I think we can say with some degree of conviction that if you opt for an initial strategy of medical therapy, you are not putting patients in harm's way," Dr. Boden said at a press briefing preceding his formal presentation. "What was remarkable was how well optimal medical therapy did in this trial."

At the press briefing, Dr. Boden said, "Historically, there has been an unproven assumption that if you have significant angiographic coronary disease or if you have inducible ischemia that you must proceed to revascularization. … Lost in the shuffle in all this has been medical therapy. It has gotten a bad rap over the years. It sort of seems old-fashioned."

But he said the COURAGE trial clearly shows that physicians who help patients meet targets for cholesterol, blood pressure, diabetes control, and lifestyle modification can have a strong and favorable impact on prognosis.

The findings fly in the face of what has become standard practice in the United States. As many as 85% of more than a million PCI procedures performed each year are done electively in patients with stable CAD, according to Dr. Boden and colleagues in an article published online at the time of the press briefing (N. Engl. J. Med. 2007 [Epub doi:10.1056/NEJMoa070829]).

COURAGE assessed 2,287 patients enrolled during 1999-2004 at 50 U.S. and Canadian medical centers and followed for a mean of 4.6 years. The subjects showed stenosis of at least 70% in at least one proximal coronary artery, plus either objective evidence of myocardial ischemia or classic angina.

A total of 1,138 patients were randomly assigned to receive optimal medical therapy alone and 1,149 were randomized to optimal medical therapy plus PCI. The entire study population showed high rates of adherence to medications and a regimen of diet, regular exercise, and smoking cessation. Seventy percent achieved target cholesterol levels, 65% reached target systolic blood pressure, 94% reached target diastolic blood pressure, and 45% of those with diabetes achieved target glycolated hemoglobin levels.

The estimated cumulative event rate, a composite outcome of death from any cause and nonfatal MI, was 19.0% in the PCI group and 18.5% in the medical therapy group, a nonsignificant difference. Similarly, there were no significant differences in rates of stroke, hospitalization for acute coronary syndromes, MI alone, death alone, or coronary artery bypass surgery, reported Dr. Boden of the Veterans Affairs Western New York Healthcare System, Buffalo.

Both study groups showed a substantial reduction in the prevalence of angina, and there was a significant difference in favor of PCI for the first few years of follow-up. But by 5 years, that difference had dwindled to the point that 74% of subjects in the PCI group and 72% of those in the medical therapy group were free of angina.

"Our findings reinforce existing clinical practice guidelines, which state that PCI can be safely deferred in patients with stable CAD, even in those with extensive, multivessel involvement and inducible ischemia, provided that intensive, multifaceted medical therapy is instituted and maintained," the researchers noted.

But those guidelines have not been followed, according to Dr. Salim Yusuf, a panelist at the late-breaking trials session where the study was presented. For too long, the belief has persisted that stenosis is directly related to MI risk, or that PCI would prevent MIs and save lives if only its imperfections could be remedied by better stents, he said.

"We would all have liked to see PCI prevent MIs, prevent death, because surely spreading somebody's chest open is not a nice thing to do," he said. "Unfortunately, the truth doesn't go that way."

"The time has come to confront ourselves about why these myths have persisted," he said. Sometimes, PCI is performed because "the referring doctor wants it," maintained Dr. Yusuf, professor of medicine and director of the Population Health Research Institute at McMaster University in Hamilton, Ont.

Dr. Gregory J. Dehmer, president of the Society for Cardiovascular Angiography and Interventions (SCAI), said that the proportion of PCI procedures in patients with stable CAD is far lower than the COURAGE researchers' estimate. Most PCI procedures are performed in patients having severe acute MIs, those with unstable angina, and those with high-risk disease characteristics that would have made them ineligible for inclusion for the COURAGE trial, he said in an interview.

Also at the press briefing, Dr. William S. Weintraub of Christiana Hospital in Wilmington, Del., released lifestyle and economic findings of the study. Both optimal medical therapy and PCI quickly and markedly improved patients' angina frequency and quality of life.

Over most of the course of the study, PCI held a slight edge over medication in terms of reducing angina symptoms, leading to a significant but "very slight trend" to improved quality-of-life-years, he said.

The incremental cost-effectiveness ratio at 3 years favored PCI by $217,000, meaning that the cost of the procedure was beneficial in terms of quality of life gained.

The COURAGE study was funded by the U.S. Department of Veterans Affairs Office of Research and Development, the Canadian Institute of Health, and unrestricted grants from Merck & Co., Pfizer, Bristol-Myers Squibb, Fujisawa Healthcare Inc., Kos Pharmaceuticals Inc., Datascope Corp., Astra-Zeneca Pharmaceuticals, Key Pharmaceuticals, Sanofi-Aventis, First Horizon Pharmaceutical Corp, and GE Healthcare. ■

Mary Ann Moon contributed to this report.

Continued Clopidogrel Use Beneficial With Drug-Eluting Stents

BY SHERRY BOSCHERT
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SAN FRANCISCO — Continued use of clopidogrel significantly decreased the risk of death or MI at 2 years in patients with intracoronary drug-eluting stents, compared with bare-metal stents or in patients with either kind of stent who stopped clopidogrel after 6 months of use, Dr. John S. MacGregor reported.

Patients with drug-eluting stents who stopped taking clopidogrel after 6 months of use fared the worst, compared with the other three groups, according to a study published online by investigators at Duke University, Durham, N.C., Dr. MacGregor said at a meeting sponsored by the California chapter of the American College of Cardiology.

All patients had been free of major cardiac events after stent implantation and 6 months of clopidogrel use. Patients with drug-eluting stents who stopped clopidogrel were more than twice as likely to die or have an MI by 24 months, compared with patients with drug-eluting stents who continued clopidogrel, said Dr. MacGregor of the University of California, San Francisco.

Rates of death or MI in patients with bare-metal stents who were on or off clopidogrel fell between rates for the drug-eluting–stent groups, and were significantly higher than in patients with drug-eluting stents who continued clopidogrel (JAMA 2007;297 [Epub doi:10.1001/jama.297.2.joc60179]).

Similar findings emerged for patients who were free of major cardiac events at 12 months after stent insertion. By 24 months, the rates of death or MI were 0% in patients with drug-eluting stents who continued clopidogrel, 5% in patients on drug-eluting stents who stopped clopidogrel or in patients with bare-metal stents who continued clopidogrel, and 4% in patients with bare-metal stents who stopped clopidogrel, he said at the meeting, also sponsored by the university.

Multiple investigators in the Duke study disclosed receiving research funding or having other financial ties with the companies that market clopidogrel, Sanofi-Aventis and Bristol-Myers Squibb.

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DR. MACGREGOR

Previous studies have shown that drug-eluting stents decrease the risk for major adverse cardiac events in the first 3-6 months after insertion, compared with bare-metal stents. Use of clopidogrel is recommended for 3 months after insertion of a sirolimus-coated stent or for 6 months after insertion of a paclitaxel-coated stent.

In a study presented at the 2006 American College of Cardiology meeting, however, the risk for death or MI, or for nonfatal MI, more than tripled in patients with drug-eluting stents who stopped taking clopidogrel, compared with patients with bare-metal stents who continued clopidogrel, he said. The 743 patients in the randomized Basal Stent Kosten Effektivitäts-Late Thrombotic Events (BASKET-LATE) trial had been event free after 6 months of clopidogrel use, and were followed for another 6-12 months off the drug.

These and other studies raise concerns that the recommended regimen of clopidogrel after insertion of drug-eluting stents is insufficient.

"My bias is to have people with drug-eluting stents take Plavix [clopidogrel] indefinitely unless they have bleeding problems," Dr. MacGregor said.

Further studies are needed to determine the optimal duration of clopidogrel therapy after stent implantation and to include rates of side effects from extended-duration clopidogrel. Two out of three recent placebo-controlled trials of long-term clopidogrel use found that taking clopidogrel plus aspirin for 1-2.5 years significantly increased the rate of major or moderate bleeding events, compared with taking clopidogrel plus placebo, he said.

About 600,000 U.S. patients receive intracoronary stents each year. One year of clopidogrel therapy costs about $1,400, so therapy for 1 million patients would cost $1.4 billion per year, he noted. In addition, long-term clopidogrel use might interfere with valuable procedures such as colonoscopy or noncardiac surgery. ■