More Events Post CABG With Early ACE Inhibitor

BY BRUCE JANCIN
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STOCKHOLM — The initiation of ACE inhibitor therapy within 7 days of coronary artery bypass graft surgery does not improve clinical outcomes in low-risk patients without a conventional indication for it, Wiek H. van Gilst, M.D., said at the annual congress of the European Society of Cardiology.

In fact, just the opposite was observed in the 2,553-patient Ischemia Management With Accupril Post Bypass Graft via Inhibition of Angiotensin-Converting Enzyme (IMAGINE) trial, conducted in Europe and Canada.

The incidence of ischemic events was 52% greater in the quinapril (Accupril) group than with placebo during the first 3 months of follow-up, although at the end of the full 43 months, there was no significant difference between the two treatment groups, noted Dr. van Gilst, professor of cardiovascular and clinical pharmacology at University Medical Center, in Groningen, the Netherlands.

The rationale behind the IMAGINE trial was that the post–coronary artery bypass graft (CABG) period is known to be a time of increased local and systemic inflammation, thrombotic activity, and endothelial dysfunction, and ACE inhibitors have been shown to curb endothelial dysfunction and exert an anti-inflammatory effect. The hypothesis of the study was that quinapril, at a target dose of 40 mg once daily, would slow atherosclerotic progression and reduce ischemic events.

This specific issue had not been examined before. The earlier Heart Outcomes Prevention Evaluation (HOPE), European Trial on Reduction of Cardiac Events With Perindopril in Stable CAD (EUROPA), and Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trials included collectively more than 9,200 patients who had undergone CABG, and those patients experienced a significant reduction in ischemic events. In those trials, however, recent CABG was an exclusion criterion.

The primary end point in IMAGINE was a composite of cardiovascular death, resuscitated cardiac arrest, nonfatal MI, coronary revascularization, hospitalization for unstable angina, documented angina not requiring hospitalization, stroke, and congestive heart failure requiring hospitalization. The relative risk of this combined end point was 15% greater in the quinapril group, a rate not significantly higher than with placebo.

IMAGINE participants had higher rates of β-blocker, statin, and antiplatelet therapy usage than did patients in any previous clinical trial.

Moreover, none of the participants had a low ejection fraction or any other indication for an ACE inhibitor, which made this a very low-risk group. In fact, they were at lower risk of ischemic events than was the age-matched general population, according to Dr. van Gilst.


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Starting an ACE inhibitor within the first week after CABG was not beneficial, Dr. Wiek H. van Gilst said.

Discussant Michel E. Bertrand, M.D., called the IMAGINE results "somewhat surprising." He noted that every component of the composite end point save one—nonfatal MI—trended in favor of placebo.

He proposed several possible explanations for the findings. One is that the quinapril target dose may have been too high. The mean achieved daily dose was 28 mg. The 12% incidence of hypotension and 21% rate of cough in the quinapril group were also relatively high. It may be that the substantial quinapril dose led to an increase in the release of bradykinin, further promoting inflammation in a postsurgical population that had an ongoing highly active inflammatory process, with a resultant increase in ischemic events.

He also said that the negative results could have been due to a molecule-specific effect of quinapril. IMAGINE was not the first negative trial involving quinapril in patients undergoing coronary intervention, added Dr. Bertrand, professor of cardiology at the University of Lille (France).

Yet another possibility is that starting an ACE inhibitor within 1 week of CABG is just too soon. Dr. Bertrand noted that 2,399 HOPE trial participants had a history of CABG, and those on ramipril showed an 11% relative reduction in risk of ischemic events, compared with placebo. But CABG within the previous 4 years was a HOPE exclusion criterion.

Similarly, the 3,578 EUROPA participants who had undergone CABG a minimum of 6 months before enrollment enjoyed a 17% relative risk reduction with perindopril. In the PEACE trial, in which the interval between surgery and randomization was a minimum of just 3 months, the 3,232 participants with a history of CABG had a 4.7% relative risk reduction with trandolapril.

IMAGINE was sponsored by Pfizer Inc., which markets Accupril. ■

Routine Use of Drug-Eluting Stents Found Not Cost Effective

BY BRUCE JANCIN
Denver Bureau

STOCKHOLM — Routine use of drug-eluting stents in a real-world patient setting is not good value for money, according to the findings of the first-ever randomized trial that compared drug-eluting stents with bare-metal stents in unselected patients in a study free of industry sponsorship.

The results of the Basel Stent Cost Effectiveness Trial (BASKET) suggest that the use of drug-eluting stents (DESs) could reasonably be restricted to selected high-risk patient subgroups, Matthias Pfisterer, M.D., said at the annual congress of the European Society of Cardiology.

"Based upon these data, we can define some subgroups where these stents are more attractive. They are more cost effective in patients older than 65 years with three-vessel disease, more than one treated segment, longer lesions, and small treated vessels. This will hold true until the price of drug-eluting stents falls significantly," said Dr. Pfisterer of the University of Basel (Switzerland).

In a typical catheterization laboratory, perhaps two-thirds of patients fit that description, he added.

"Turning the data around," he continued, "we can say that younger patients with single- or double-vessel disease, short lesions, and large stent sizes fare very well with bare-metal stents."

BASKET involved 826 consecutive patients treated at University Hospital of Basel with angioplasty and stenting for 1,281 de novo coronary lesions. They were randomized to the sirolimus-coated Cypher stent, the paclitaxel-coated Taxus stent, or the cobalt-chromium–based Vision third-generation bare-metal stent (BMS). The study was funded by the university in response to questions from cardiologists and hospital administrators about the impact of the growing use of DESs on the hospital budget.

'It's a difficult task to tell a patient drug-eluting stents are better—as we have shown—but you aren't getting one.'

DR. PFISTERER

Unlike previous randomized stent trials that were funded by device manufacturers and featured highly selected patient populations, BASKET was designed to reflect everyday clinical practice in the catheterization laboratory. Three-fifths of the participants presented with acute MI or unstable coronary syndromes. Overall, 69% of enrollees had multivessel disease, and one-half of those had involvement of the left anterior descending coronary artery. Patients received a mean of 1.9 stents with a mean total stent length of 34 mm.

The 6-month combined efficacy end point of cardiac death, MI, or target vessel revascularization occurred in 12.1% of the BMS group and in 7.2% of the DES group. This difference was driven largely by the 43% reduction in target-vessel revascularization in DES-treated patients. There was a consistent trend for fewer major adverse cardiac events with the Cypher, compared with the Taxus DES; however, the sample size was too small to determine statistical significance. The cardiac event rate in the BMS group was lower than might be anticipated in such a relatively high-risk population, most likely because the Vision stent is more effective than the earlier-generation steel stents, the cardiologist observed.

The mean 6-month total costs were 10,544 euros per patient with the DESs and 9,639 euros per patient with the BMS. It cost a mean of 18,311 euros to avoid one major adverse cardiac event through the use of drug-eluting. rather than bare-metal, stents.

The estimated cost per quality-adjusted life year gained through the use of drug-eluting in lieu of bare-metal stents was 55,000-73,000 euros, depending on the quality of life measure that was used. Those estimates fall outside the range of what most health economists define as cost-effective therapy.

Kim M. Fox, M.D., professor of clinical cardiology at Royal Brompton Hospital, London, commented that the rapidly growing use of DESs is a huge issue in the United Kingdom, where there is concern that it is a potential hospital budget buster.

He added that although the BASKET trial provides important information about the limitations of the cost-effectiveness of DESs, interventional cardiologists will point to the devices' superior efficacy and find ways to expand their use.

"The interventionists will make all the lesions long and all the vessels small," Dr. Fox quipped.

"Patients will ask for drug-eluting stents more and more," Dr. Pfisterer agreed. "It's a difficult task to tell a patient drug-eluting stents are better—as we have shown—but you aren't getting one."

Discussant Petr Widimsky, M.D., D.Sc., of Charles University, Prague, noted that DESs emerged from BASKET looking a lot better than they would have if investigators had compared them with one of the earlier-generation steel BMSs, which cost roughly half as much as the Vision stent.

"Drug-eluting stents are not saving any costs by reducing the restenosis rate. The opposite is true: The routine use of drug-eluting stents increases health care costs," he said. "Until manufacturers drop the price and make them more affordable for all patients, it's got to be small arteries, large lesions." ■