Excess Deaths, MIs Seen With Drug-Eluting Stents

BY MITCHEL L. ZOLER
Philadelphia Bureau

BARCELONA — The cloud of uncertainty that has recently formed around the safety of drug-eluting coronary stents grew thicker when results from two meta-analyses suggested an excess of deaths and myocardial infarctions in patients who received these stents.

The new findings "raise concerns. I don't believe that they're convincing [of harm], but they're disconcerting," Dr. Salim Yusuf said in a talk that commented on the new studies at a joint meeting of the European Society of Cardiology and the World Heart Federation.

One of the metaanalyses used all of the published data from the four studies that led to approval of the sirolimus-eluting stent (Cypher), and from the five pivotal studies that tested the paclitaxel-eluting stent (Taxus).

The second study used data from 17 trials that were supplied by the two companies that make these stents. Sirolimus-eluting stents appeared to fare the worst in the new analyses.

In the published studies, sirolimus-eluting stents were tested in a total of 878 patients, including 828 who were followed for 3 years. The studies also involved 870 comparator patients who received bare-metal stents, with 820 followed for 3 years. The fully pooled analysis showed an incidence of death or nonfatal MI of 6.3% in the sirolimus-eluting stent arms and 3.9% in the bare-metal stent arms, Dr. Edoardo Camenzind reported at the meeting. The 2.4% absolute difference (a 38% relative difference) in event rates in favor of bare-metal stents was statistically significant.

The paclitaxel-eluting stents were tested in more than 1,700 patients in the published studies, with a similar number of patients getting bare-metal stents. About 900 patients in each arm were followed for 3 years. The fully pooled analysis showed a death or MI rate of 2.6% in the paclitaxel-eluting stent group and 2.3% in the bare-metal stent group, a 0.3% absolute difference (a 16% relative difference) that was not statistically significant, said Dr. Camenzind, a cardiologist at University Hospital in Geneva.

The apparent excess of adverse clinical events with drug-eluting stents warrants a systematic risk-benefit analysis, he said.

The second report at the meeting included mortality data that had not previously been released by the manufacturers, and included studies with follow-up periods that ranged from 1 to 4 years. An analysis of overall deaths showed some trends toward increased mortality with sirolimus-eluting stents, compared with bare-metal stents, reported Dr. Alain J. Nordmann, an epidemiologist at the Basel (Switzerland) Institute for Clinical Epidemiology. No trend toward excess total deaths was seen for paclitaxel-eluting stents, but the results also showed that these stents provided no mortality benefit.

The analysis did not show any notable excess of cardiac deaths among patients who received either type of drug-eluting stent, and for some follow-up periods there were trends toward reduced cardiac deaths with both types of drug-eluting stents.

The results also showed an unexpected trend toward an excess of noncardiac deaths in patients getting sirolimus-eluting stents, including 15 deaths from cancers and several other deaths caused by sepsis or pneumonia. In five studies with 2-year follow-up, the excess of noncardiac deaths in patients getting sirolimus-eluting stents was 2.7-fold higher than in the comparator patients getting bare-metal stents, a significant difference, Dr. Nordmann reported, but he cautioned that the noncardiac death finding must be interpreted very cautiously. He called for longer-term mortality follow-up for these drug-eluting stents.

"I'm completely puzzled by the excess of noncardiac deaths," commented Dr. Yusuf, director of cardiology at McMaster University in Hamilton, Ont., but it's a finding that deserves greater scrutiny, he said.

The new analyses follow several reports over the past few years of cases of late stent thrombosis in patients with drug-eluting coronary stents when they stopped dual antithrombotic therapy with aspirin and clopidogrel. Because of these studies and other reports of adverse events linked to drug-eluting stents, the Food and Drug Administration will convene a meeting of the Circulatory System Devices Advisory Panel by the end of the year, the agency said in a statement.

"It's important not to use drug-eluting stents indiscriminately in all patients," commented Dr. William Wijns, a cardiologist at OLV Hospital in Aalst, Belgium, and a collaborator on the analysis reported by Dr. Camenzind.

Also, he said, physicians should place drug-eluting stents in patients only when it's certain that they will be compliant with dual-antiplatelet therapy and will continue it for some period of time.

He also cautioned against thinking that all drug-eluting stents act the same. "It's not a class effect. You need to look at each type individually," Dr. Wijns said. ■

Overuse of Coronary Stenting Charged

"The entire field of angioplasty has been led astray by a preoccupation with restenosis, which study after study has shown has no prognostic value."

That was the theme of an impassioned and surprising talk by Dr. Yusuf at a joint meeting of the European Society of Cardiology and the World Heart Federation.

Called on at the meeting to comment on reports from two metaanalyses of safety data from clinical studies of the currently approved drug-eluting coronary stents, Dr. Yusuf admonished the cardiology community about its overuse of all forms of coronary stenting, including both bare-metal and drug-eluting models.

"We're chasing problems that are iatrogenic," he said. "The best way to prevent restenosis is to not do PCI [percutaneous coronary intervention] at all."

Dr. Yusuf acknowledged that stenting is the best way to deal with acute myocardial infarctions and unstable angina. But he focused on the problem of using PCI on patients with stable angina, a use that now constitutes about 50% of all coronary stenting.

"There is no evidence that it prevents clinical events," he said. And many studies show "it's cost ineffective. We should use PCI sparingly and judiciously." Patients instead should receive full medical management, he asserted.

"We have had a perverse financial incentive on the practice of cardiology. It's time to step back and reevaluate," he concluded. He called on the European Society of Cardiology to develop new recommendations on the role and use of PCI and drug-eluting stents.

Revascularization Recommended for Severe Refractory Angina

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — A consensus committee of 10 experts recommended transmyocardial revascularization to provide relief for some patients with severe refractory angina, Dr. Anno Diegeler reported at the annual meeting of the International Society for Minimally Invasive Cardiothoracic Surgery.

Transmyocardial revascularization provides relief to 'a small group of patients with diffuse coronary artery disease.'

DR. DIEGELER

"Transmyocardial revascularization is a palliative treatment," said Dr. Diegeler, of the University of Leipzig, Bad Neustadt, Germany. The treatment provides relief to "a small group of patients with diffuse coronary artery disease with severe, refractory angina," he said.

The committee reviewed the data on transmyocardial revascularization and formulated recommendations that will be published in the society's journal, Innovations.

They analyzed results from six randomized, controlled trials involving a total of 967 patients that compared transmyocardial revascularization with maximal medical therapy. In addition, they looked at studies that compared coronary artery bypass grafting (CABG) with CABG plus adjunctive transmyocardial revascularization, drawing on three randomized, controlled trials involving 327 patients and an additional three nonrandomized trials.

Dr. Diegeler, chair of the committee, outlined the recommendations at the meeting, dividing them according to two groups of patients.

The first group is stable patients with refractory, severe angina who are not amenable to conventional revascularization and who can be treated solely with transmyocardial revascularization or maximal medical therapy. For such patients, the committee recommended transmyocardial revascularization to provide sustained angina relief, reduce major adverse cardiac events, and improve exercise performance, on the basis of results of randomized, controlled trials (level A evidence); and to reduce readmissions and reinterventions, on the basis of one randomized, controlled trial and nonrandomized data (level B evidence).

The second group is patients with diffuse coronary artery disease and chronic angina who cannot be completely revascularized by CABG alone. For them the committee recommended adding transmyocardial revascularization to improve the likelihood of long-term angina relief (up to 5 years), reduce 30-day mortality and major adverse cardiac events, and improve 1-year exercise performance.

The recommendations for CABG plus transmyocardial revascularization rather than CABG alone were based on levels A and B evidence and were all class II recommendations encompassing conflicting evidence or diverging opinions. The recommendations regarding sole transmyocardial revascularization versus maximal medical therapy were all class I recommendations with solid evidence and general agreement, said Dr. Davy Cheng of the University of Western Ontario, London, who was also a member of the consensus committee.

Compared with maximal medical therapy, transmyocardial infarction reduced angina by at least two New York Heart Association classes and left more patients free of class III or IV angina at 1-5 years. The procedure also improved quality-of-life scores at 1 year.

The improvements in mortality and major adverse cardiac events seen at 30 days and in exercise performance at 1 year after CABG plus transmyocardial revascularization, compared with CABG alone, did not hold up at 5 years after treatment, Dr. Diegeler noted.

The difference between groups in exercise treatment test results at 1 year was a mean of 88 seconds favoring CABG plus transmyocardial revascularization (with a range of 52-123 seconds). The difference was statistically significant and was incorporated into the recommendations, Dr. Diegeler said. ■