Early Invasive Tx Best in Non–ST-Elevation ACS

BY BRUCE JANCIN
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STOCKHOLM — A routine early invasive strategy in patients with non–ST-segment elevation acute coronary syndrome has been shown for the first time to reduce the long-term risks of death or nonfatal MI.

Five-year follow-up in the Randomized Intervention Trial of Unstable Angina (RITA-3) showed a significant 22% reduction in the relative risk of the combined end point of death or nonfatal MI and a 24% reduction in all-cause mortality with a strategy of early coronary angiography followed by revascularization, as compared with a conservative strategy of symptom-driven angiography, reported Keith A.A. Fox, M.B., at the annual congress of the European Society of Cardiology.

Other trials have shown that routine early intervention in patients with non–ST-segment elevation acute coronary syndrome (ACS) results in reduced ischemia, but they have not shown a significant mortality benefit. However, those studies involved follow-up of only 6-24 months' duration—not long enough for the early hazards of percutaneous intervention or coronary artery bypass surgery to be outweighed by the longer-term benefits of the resultant improved coronary perfusion.

RITA-3 has shown that the mortality curves do not differ much in the first year, but they progressively separate over time in favor of the early invasive strategy, said Dr. Fox, the Duke of Edinburgh Professor of Cardiology at the University of Edinburgh.

The trial was a British Heart Foundation–sponsored multicenter U.K. trial in which 1,810 patients with non–ST-elevation ACS were randomized to intervention within 72 hours or to a conservative management strategy.

The incidence of death or nonfatal MI at a median of 5 years of follow-up was 16.6% in the early intervention arm and 20.0% with conservative management. All-cause mortality was 12.1% with routine early intervention vs. 15.1% with a conservative strategy. There were 62 cardiovascular deaths in the early intervention arm and 90 in the comparison group.

A key finding at 5 years was that the benefits of an early invasive strategy were concentrated in patients with a high baseline risk of death or MI. Indeed, the benefits of the interventional strategy were statistically significant only for those in the upper half of risk.

The 5-year results probably underestimate considerably the true benefits of an early invasive strategy.

DR. FOX

"What is perhaps remarkable is that patients in the top eighth in terms of risk had a profound 56% reduction in the odds of death or MI with the early intervention strategy; those in the lowest quartile of risk had no evidence of benefit," he said. "The clinical implications are that a strategy of routine angiography and intervention is appropriate for all moderate- and high-risk patients with non–ST-elevation ACS."

This is consistent with current European Society of Cardiology and American College of Cardiology/American Heart Association guidelines for management of non–ST-elevation ACS, Dr. Fox noted.

Because the data analysis in RITA-3 was by intention to treat and a substantial number of patients in the conservative arm eventually underwent a revascularization procedure, the 5-year results probably underestimate considerably the true benefits of an early invasive strategy, he added.

Discussant Freek Verheugt, M.D., said an early invasive strategy is preferable because it reduces the risks of acute MI and rehospitalization.

An early invasive strategy didn't show a significant mortality benefit in a meta-analysis of seven clinical trials (JAMA 2005;293:2908-17), including the 1-year RITA-3 results. Nor did it reduce 1-year mortality, compared with a more conservative strategy in the recently published Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial involving 1,200 high-risk troponin T-positive Dutch patients (N. Engl. J. Med. 2005;353:1095-104) in which Dr. Verheugt was a coinvestigator. And in RITA-3, the *P* value for all-cause mortality at 5 years was 0.054—close but not quite statistically significant, noted Dr. Verheugt, professor and chairman of cardiology at University Medical Center, Nijmegen, the Netherlands. ■

Tighter Control of Lipid Levels, Diabetes Reduces Events in ACS

BY MITCHEL L. ZOLER
Philadelphia Bureau

STOCKHOLM — Patients with acute coronary syndrome who are treated with a high-dose statin and other standard medications still have a high, 13% rate of cardiac events during follow-up, which suggests a need for more interventions to further lower event rates.

"Patients are not fully protected by a statin, aspirin, clopidogrel, an angiotensin-converting enzyme inhibitor, and a β-blocker. They need other treatments, too," Kausik K. Ray, M.D., said at the annual congress of the European Society of Cardiology.

In his analysis of more than 2,000 patients who received 80 mg of atorvastatin (Lipitor) daily in a recent major trial, Dr. Ray suggested that more diligent control of diabetes, raising the serum levels of HDL cholesterol, and anti-inflammatory treatment might push down event rates even more.

The data came from the intensive-treatment arm of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial (N. Engl. J. Med 2004;350:1495-504). That study randomized more than 4,000 patients with acute coronary syndrome to treatment with either an intensive (80 mg atorvastatin daily) or moderate (40 mg pravastatin daily) lipid-lowering regimen. The results showed that patients whose LDL cholesterol levels dropped below 70 mg/dL had better outcomes during 2 years of follow-up, compared with patients who had higher levels of LDL cholesterol.

The new analysis focused entirely on the patients who received 80 mg atorvastatin daily. During the first 4 months of treatment, 124 patients in this group died or had a myocardial infarction or unstable angina; the remaining 1,939 patients had no events. Beyond the first 4 months, another 140 patients had events and 1,777 were event free.

A multivariate analysis showed that the serum level of HDL cholesterol at baseline was a significant predictor of early events. For every 1-mg/dL rise in the HDL cholesterol level, the risk of an event during the first 4 months fell by 3%, reported Dr. Ray, a cardiologist at Brigham and Women's Hospital in Boston. Other significant determinants of early risk were age and smoking.

Patients whose LDL cholesterol levels dropped below 70 mg/dL had better outcomes.

DR. RAY

A second analysis showed that the 4-month serum levels of hemoglobin (Hb) A_{1c} and C-reactive protein (CRP) were significant predictors of late events. For every 1% rise in the level of HbA_{1c}, the risk of a late event rose by 28%. For every one-log rise in the serum level of CRP, the risk rate rose by 25%, said Dr. Ray. Other determinants of late risk were age, gender, and serum level of LDL cholesterol at 4 months.

Better diabetes control and a reduction in HbA_{1c} is a strategy that can be used in the clinic right now, commented Elliott Antman, M.D., director of the coronary care unit at Brigham and Women's Hospital. He noted that the average HbA_{1c} level in patients with events was 6.1%, compared with an average 5.7% level in those with no events. ■

Proteinuria Linked to MI Deaths

STOCKHOLM — Patients with proteinuria following a myocardial infarction had significantly worse outcomes than did patients without proteinuria, according to findings in 583 patients.

Treatment with an ACE inhibitor was especially effective at improving outcomes in patients with proteinuria after a myocardial infarction, Powell O. Jose said in a poster presentation at the annual meeting of the European Society of Cardiology.

"Assessing proteinuria in patients following an MI may improve their risk stratification," said Mr. Jose and his associates in their poster presentation. In addition, "proteinuria may define a patient subset that's most likely to benefit from ACE inhibitor therapy following an MI," said Mr. Jose, a researcher at Brigham and Women's Hospital in Boston. The analysis used data collected in the Survival and Ventricular Enlargement (SAVE) trial, one of the first studies to establish the efficacy of an ACE inhibitor in patients with left ventricular dysfunction after an MI (N. Engl. J. Med. 1992;327:669-77).

The post hoc analysis by Mr. Jose and associates focused on 583 of the 2,231 patients in the SAVE trial who were assessed for proteinuria with a dipstick test when they entered the study. The results showed 122 patients had proteinuria and 461 did not. During an average follow-up of 42 months, patients with proteinuria had a 31% total mortality and a 27% incidence of cardiovascular mortality, compared with a 20% total mortality and a 17% cardiovascular mortality in those without proteinuria.

In a multivariate analysis that controlled for several demographic and clinical measures, patients with proteinuria were 73% more likely to die from any cause and 81% more likely to die from cardiovascular disease, compared with MI patients without proteinuria. Both of these differences were statistically significant, reported the researchers.

The link between proteinuria and mortality was most dramatic in the 35 patients who had significant proteinuria. In this subgroup, the all-cause mortality during follow-up was 46%, whereas in the 87 patients with trace proteinuria, the all-cause death rate was 25%. In patients without proteinuria, mortality during follow-up was 20%.

The analysis also examined the impact of the ACE inhibitor treatment used in the study, a regimen of 50 mg captopril t.i.d., which was compared with placebo. In patients with proteinuria at baseline, treatment with captopril dropped total mortality by 54%, compared with placebo, whereas in patients without proteinuria at baseline, captopril treatment was linked to a 17% reduction in mortality.

A composite end point of death and nonfatal, major cardiovascular events was cut by 59% in patients with proteinuria who were treated with captopril, compared with control patients. But in patients without proteinuria, captopril dropped this end point by 13%, compared with the placebo group.

—Mitchel L. Zoler