COMMIT Has Mixed Results for β-Blocker in MI

Investigator finds 'excess risk largely in people whose heart function is already compromised.'

BY BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — Initiation of β-blocker therapy in the setting of acute MI should generally be delayed for several days, until a patient's condition has stabilized, Rory Collins, M.D., said at the annual meeting of the American College of Cardiology.

Dr. Collins reported the main finding of the β-blocker arm of the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2). In this trial, patients were immediately randomized double-blind to placebo or three doses of 5 mg IV metoprolol within 15 minutes followed by 200 mg/day of oral metoprolol.

The results indicate that optimal use of β-blockers in MI is more complicated than previously appreciated.

Current American College of Cardiology/American Heart Association guidelines, as well as those of the European Society of Cardiology, generally recommend prompt administration of a β-blocker soon after MI onset, unless contraindicated. But COMMIT has shown that the benefits of doing so are essentially cancelled out by increased harm, said Dr. Collins, professor of medicine and epidemiology and codirector of the clinical trial service unit at the University of Oxford (England).

More specifically, in-hospital mortality was 7.7% in patients in the metoprolol arm and 7.8% with placebo. Early therapy resulted in an 18% reduction in the relative risk of in-hospital reinfarction and a 17% reduction in ventricular fibrillation (VF), which translated into a modest absolute reduction in each of these serious adverse events of 5 fewer cases per 1,000 treated patients. But these benefits were entirely offset by a 29% increase in the relative risk of developing cardiogenic shock, which occurred in 3.9% of the placebo patients and 5.0% of those on metoprolol, he continued.

The increased risk of cardiogenic shock in the metoprolol group was seen mostly in the first 24 hours following admission. Moreover, it was largely confined to patients who were Killip class 3 upon presentation.

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DR. COLLINS

"We're seeing the excess risk largely in people whose heart function is already compromised. Lowering their heart rate and blood pressure further is just pushing them into shock. It's a negative inotropic effect of β-blockade in someone who's got a failing heart," Dr. Collins explained.

The merits of long-term oral β-blocker therapy following an MI—reduced reinfarction and mortality—are beyond question. The rationale for studying early β-blockade in COMMIT lies in its uncertain value on top of current standard treatment. When the use of intravenous β-blockers in emergency treatment of MI was studied in more than two dozen trials in the 1970s and 1980s, it did show a moderate benefit; however, those trials mainly enrolled lower-risk patients. As a result of the uncertain efficacy, the use of intravenous β-blockers during acute MI varies widely, from more than 50% of cases in Sweden, to 20% in the United States, and less than 1% in the United Kingdom.

"We know β-blocker therapy is beneficial long-term in people who have heart attack or heart failure. This trial is really telling us when to start, and perhaps how to start—more gradually, more carefully, targeting people when they're stable," he said.

Discussant Christopher P. Cannon, M.D., said, "we really should think of avoiding IV β-blockade for patients with evidence of compromised left ventricular function, and in those patients ... start a β-blocker after a day or two when the patient is stable," said Dr. Cannon of Brigham and Women's Hospital, Boston. ■

Urgent Angioplasty Is Beneficial Even Later Than 12 Hours Into MI

BY BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — Prompt percutaneous intervention in acute MI patients who present more than 12 hours after onset of chest pain and are no longer symptomatic results in significantly reduced final infarct size, compared with standard medical management, according to the findings of the first randomized trial of an acute invasive strategy in such patients.

These late presenters make up roughly 20% of all acute MI patients. Current American College of Cardiology/American Heart Association guidelines don't recommend mechanical or fibrinolytic reperfusion in late presenters unless they show up with a stuttering course and persistent pain. But the guidelines ought to be changed in light of this new evidence supporting the benefit of mechanical reperfusion in asymptomatic patients—even when applied late, Adnan Kastrati, M.D., said at the annual meeting of the American College of Cardiology.

He presented the results of the Beyond 12 Hours Reperfusion Alternative Evaluation (BRAVE-2) trial. The study involved 365 acute MI patients who had become asymptomatic by the time they presented 12-48 hours after onset of chest pain. Participants were randomized to prompt percutaneous intervention or standard medical therapy at 16 medical centers in Germany, Italy, and Austria.

The primary end point in BRAVE-2 was infarct size as determined by technetium-99m sestamibi scintigraphy 5-10 days postrandomization. The scans showed the infarct involved a mean 8% of the left ventricle in patients who underwent mechanical reperfusion, significantly less than the 13% in those managed medically, said Dr. Kastrati of the German Heart Center, Munich.

The secondary study end point, the 30-day combined rate of all-cause mortality or recurrent MI, was 4% in the invasive group and 6% in those managed conservatively, a nonsignificant difference. The disparity in the 30-day incidence of unplanned percutaneous intervention was far more dramatic: 1% in the invasive group vs. 33% in those managed conservatively.

Cindy L. Grines, M.D., a member of the task force responsible for the ACC/AHA guidelines for management of acute MI, said the reason for the recommendation that reperfusion therapy generally be given only within 12 hours of symptom onset is the persuasive evidence from fibrinolytic clinical trials that the benefit drops off sharply when this therapy is applied more than a few hours after MI onset. The same phenomenon has been shown in animal studies.

However, BRAVE-2 shows a "pretty striking" reduction in infarct size, and it's plausible that late restoration of high-grade coronary blood flow—readily achievable with mechanical reperfusion but not with thrombolytic therapy—might revive hibernating myocardium as one potential explanation for this benefit, said Dr. Grines of William Beaumont Hospital in Royal Oak, Mich.

Before the guidelines are changed, however, it will be important to see a confirmatory study, preferably one that addresses the question of whether all asymptomatic late presenters ought to go to the catheterization laboratory, or just those who have larger infarcts.

Noting that the mean time from randomization to coronary angiography in BRAVE-2 was a mere 1.5 hours, Dr. Grines commented, "I don't know about you, but I don't routinely get out of bed at 2 in the morning to do angioplasty in patients who are 36 hours into their infarct and totally asymptomatic. It would be nice to have some additional information from trials."

BRAVE-2 was funded by the German Heart Center, Lilly Deutschland, and Guidant. ■

Early Angiography Improves Survival in Women With ACS

ORLANDO, FLA. — Early angiography is associated with improved survival in women presenting with acute coronary syndrome, Rasha N. Bazari, M.D., reported at an international conference on women, heart disease, and stroke.

Women who underwent coronary angiography within 2 days of presenting with ACS had significantly lower 3-year mortality rates than did those who had later procedures (7% vs. 20%), said Dr. Bazari of the Henry Ford Heart and Vascular Institute, Detroit.

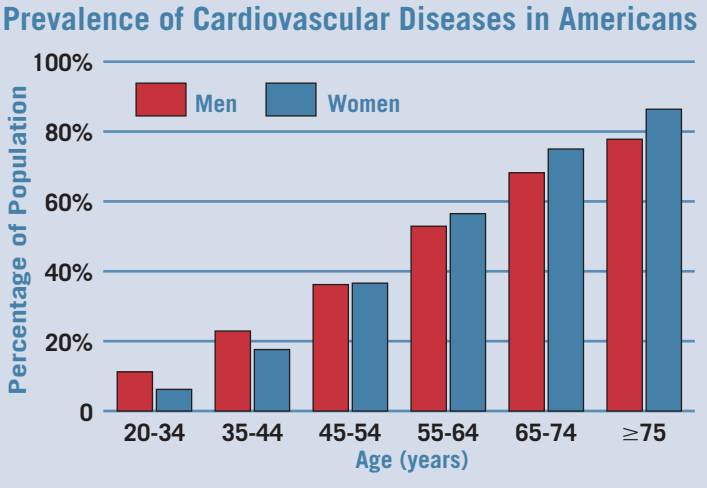
Angiography beyond 48 hours after presentation was the most significant predictor of mortality, after adjustment for confounding variables (odds ratio 3.7). Marginal predictors of mortality included older age and lower diastolic blood pressure, she said.

Dr. Bazari and associates reviewed the records of 836 patients (350 women and 486 men) admitted to the hospital during 1997-2000 who had angiography during their stay. The study also showed that fewer women than men admitted during the study period underwent early coronary angiography (63% vs. 74%), she noted.

"Gender should not be a reason to delay early angiography" she said.

—Sharon Worcester

DATA WATCH



Note: Data include rates of coronary heart disease, heart failure, stroke, and hypertension from 1999 to 2002.
Source: Centers for Disease Control and Prevention

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