Combo First to Improve MI Mortality in 12 Years

Dual antiplatelet therapy—aspirin plus a short course of clopidogrel—shines in two large studies.

BY BRUCE JANCIN
Denver Bureau

Orlando, Fla. — Adding a brief course of clopidogrel to standard aspirin therapy in patients with ST-elevation MI improves arterial patency and saves lives, according to two major studies presented at the annual meeting of the American College of Cardiology.

Indeed, this dual antiplatelet therapy strategy constitutes the first advance in drug treatment shown to improve mortality in acute MI in a dozen years, since the landmark Global Utilization of Streptokinase and t-PA for Occluded coronary arteries (GUSTO I) trial showed a survival advantage for tissue plasminogen activator over streptokinase.

Giving this to 1 million acute MI patients would save 5,000 lives and prevent an 5,000 strokes or repeat MIs.

DR. CHEN

Marc S. Sabatine, M.D., presented the results of the Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction trial (CLARITY–TIMI 28), a double-blind study in which 3,491 patients presenting with ST-elevation MI (STEMI) within 12 hours of symptom onset received a fibrinolytic agent, aspirin, and heparin and were then randomized to oral clopidogrel or placebo. The clopidogrel regimen consisted of a 300-mg loading dose followed by 75 mg once daily. By study design, all patients underwent coronary angiography 2-8 days later. Clopidogrel was then stopped unless a stent was implanted, as occurred in nearly 60% of patients, in which case open-label clopidogrel was recommended, as is standard therapy.

The primary end point in CLARITY was a composite comprising an occluded infarct-related artery upon angiography a mean of 3.5 days after starting clopidogrel, repeat MI prior to angiography, or death. The rates were 15.0% in the clopidogrel arm and 21.7% with placebo, for a highly significant 36% reduction in the risk of the end point with clopidogrel.

The secondary end point was the 30-day combined rate of cardiovascular death, recurrent MI, or recurrent ischemia leading to urgent revascularization. The rates were 11.6% of patients in the clopidogrel arm and 14.1% on placebo, for a significant 20% risk reduction favoring clopidogrel.

There was no excess in major or minor bleeding or intracranial hemorrhage in the clopidogrel group. Surprisingly, there was no significant increase in the rate of major bleeding even among patients who underwent coronary artery bypass graft surgery less than 5 days after discontinuing clopidogrel, added Dr. Sabatine of Brigham and Women's Hospital, Boston.

A few days of clopidogrel prevented one primary event for every 16 patients treated. The number of patients needed to be treated to avoid one secondary study end point was 36.

The rationale for CLARITY was that the efficacy of fibrinolytic therapy is limited by inadequate reperfusion and/or early reocclusion in one-quarter of treated patients. An occluded infarct-related artery is associated with a twofold increase in long-term mortality.

CLARITY was designed to mimic how STEMI is managed at the 80% of U.S. hospitals lacking the capability to perform primary percutaneous intervention within a 90-minute window. Patients presenting to these hospitals receive thrombolytic therapy. Roughly three-quarters of them are referred for angiography a few days later, as a result of which two-thirds undergo a coronary revascularization procedure.

The other major clopidogrel study was the mammoth Clopidogrel and Metoprolol in Myocardial Infarction Trial/second Chinese Cardiac Study (COMMIT/CCS-2). Unlike CLARITY, COMMIT was powered to detect a short-term mortality benefit for the antiplatelet agent. It involved 45,852 acute MI patients, 93% with STEMI, who presented to 1,250 Chinese hospitals within 24 hours of symptom onset. They were randomized to 75 mg/day of clopidogrel or placebo for an average of 16 days in addition to aspirin and other standard medications.

COMMIT featured a two-by-two factorial design in which patients were also randomized to intravenous metoprolol or placebo, with mixed results (see accompanying story).

In-hospital mortality occurred in 7.7% of the clopidogrel group and in 8.1% of those on placebo. This represents a highly significant 7% relative risk reduction favoring clopidogrel, reported principal investigator Zhengming Chen, M.D., of the University of Oxford (England).

The other primary outcome was the combined rate of death, repeat MI, or stroke within 28 days. The rate was 9.3% in the clopidogrel arm and 10.1% with placebo, for a significant 9% relative risk reduction. Rates of major cerebral and noncerebral in-hospital bleeding, at just over 0.5%, were not significantly increased with clopidogrel.

Clopidogrel showed a consistent benefit regardless of patient gender, age, or use of thrombolytic therapy.

The main difference between the clopidogrel regimens in CLARITY and COMMIT was the use of a loading dose in CLARITY in order to achieve a more rapid antiplatelet effect. Nevertheless, a significant outcome benefit was seen with the 75 mg/day used in COMMIT even on the day of randomization.

COMMIT showed that, on average, roughly 2 weeks of clopidogrel produced an absolute benefit of 10 fewer deaths, repeat MIs, or strokes per 1,000 treated patients, with no increased risk of bleeding. Among the 12,000 participants aged 75-100 years, the absolute benefit was even greater, at 13 fewer events per 1,000 participants.

Extrapolating from COMMIT, Dr. Chen said that giving this simple, inexpensive, safe, and modestly effective treatment to 1 million acute MI patients would save 5,000 lives and prevent an additional 5,000 strokes or repeat MIs. There are an estimated 10 million acute MIs per year worldwide, a third of which are STEMI, he added.

Discussant Christopher P. Cannon, M.D., said CLARITY and COMMIT are complementary trials that collectively provide important information about how clopidogrel fits into the whole spectrum of STEMI therapy, since the management strategy was 100% noninvasive in COMMIT and entirely invasive in CLARITY.

There was a suggestion of slightly better outcomes with the 300-mg loading dose used in CLARITY. However, CLARITY included patients only up to age 75 years. So a rational, evidence-based ap-

Continued on following page

Don't COMMIT to Quick -Blocker in MI

Initiation of -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 when reporting the main finding of the -blocker arm of COMMIT/CCS-2, in which 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 optimal use of -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 -blocker soon after MI onset unless contraindicated. But COMMIT has shown 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).

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

DR. COLLINS

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 five 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.

"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 -blockade in someone who's got a failing heart," Dr. Collins explained.

The merits of long-term oral -blocker therapy following an MI—reduced reinfarction and mortality—are beyond question. The rationale for studying early -blockade in COMMIT lies in its uncertain value on top of current standard treatment. When the use of intravenous -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 -blockers during acute MI varies widely throughout the world, from more than 50% of cases in Sweden, to 20% in the United States, and in fewer than 1% in the United Kingdom.

"We know -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 Dr. Cannon said his take from COMMIT regarding early -blocker therapy was that "one size—or dose in this case—does not fit all."

"We really should think of avoiding IV -blockade for patients with evidence of compromised left ventricular function, and in those patients. … Start a -blocker after a day or two when the patient is stable," he said. "On the other hand, low- to medium-risk patients did have a benefit in reduction of recurrent MI and VF, and this therapy was safe and beneficial in thrombolytic-treated patients, so these patients would be appropriate candidates for the IV followed by oral -blocker."

Pages 14a—14b

Continued from previous page

proach drawn from the two trials would be to employ a loading dose of clopidogrel in STEMI patients up to age 75 who present within 24 hours of symptom onset, and to skip the loading dose in patients beyond that age, since there is good evidence of efficacy for the 75-mg dose in the very elderly from COMMIT but no safety data for a loading dose in that age group, said Dr. Cannon of Brigham and Women's Hospital, who together with Dr. Sabatine was co–principal investigator in CLARITY.

Dr. Cannon added that the worldwide public health implications of this new addition to the management of STEMI are profound.

Two weeks of clopidogrel costs $50-$100—compared with several thousand dollars for a single dose of a modern fibrinolytic agent—placing dual antiplatelet therapy within reach of many patients, even in developing countries.

"The evidence provided by these two studies with 50,000 randomized patients is very, very strong," Dr. Cannon told this newspaper. "Obviously I can't speak for the [American College of Cardiology/American Heart Association] guideline committee, but I have heard members of the committee say these studies provide about as strong evidence as you would want to add a new treatment to the guidelines for management of STEMI."

The combination of clopidogrel and aspirin has previously been shown to reduce coronary risk in patients with unstable angina and in those undergoing percutaneous intervention. An ongoing study that has completed enrollment is examining whether adding long-term clopidogrel is of benefit in a broad group of patients with high-risk vascular disease.

CLARITY was funded by Sanofi-Aventis and Bristol-Myers Squibb Co. Dr. Sabatine and Dr. Cannon have served on paid advisory boards for both companies. COMMIT was funded by those companies along with AstraZeneca, the British Heart Foundation, and the U.K. Medical Research Council. ■

Fish Oil Supplements Touted as Alternative to Treat High Triglycerides

BY BRUCE JANCIN
Denver Bureau

COLORADO SPRINGS — Omega-3 fatty acid capsules are an excellent alternative to the traditional fibrates or niacin for triglyceride lowering, John A. Merenich, M.D., said at a meeting of the Colorado chapter of the American College of Physicians.

"I am a huge advocate of the omega-3 fatty acids. If you haven't been using them, you've really got to try it," asserted Dr. Merenich, an endocrinologist who directs population-management programs for Colorado Kaiser Permanente in Denver.

Fish oil supplements are distilled to achieve purity. Concerns about contamination have not been borne out in independent lab studies.

The American Heart Association recommends consumption of at least 1 g/day of the omega-3 fatty acids docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA) to reduce cardiovascular risk in patients with established coronary disease, and at least 2 g/day to treat hypertriglyceridemia. It's tough to get that much by eating fish. Besides, there is growing concern regarding the adverse health effects of eating large quantities of fish possibly contaminated by mercury, polychlorinated biphenyls (PCBs), and other toxins.

In nature, fish obtain omega-3 fatty acids by consuming large quantities of DHA/EPA-producing algae and plankton. When cost isn't an issue, Dr. Merenich's preferred source of omega-3 fatty acids is the DHA oil capsules produced by Martek Biosciences Corp. Martek has developed proprietary technology to grow large quantities of a DHA-rich microalgae, bypassing the middleman—that is, the fish—altogether.

"You don't have to kill the fish, you don't have to worry about the organic solvents, the mercury, dioxins, whatever. The PETA [People for the Ethical Treatment of Animals] people are happy. Everybody's happy," he said.

It's a very well-tolerated product. The downside is it's quite expensive, at a cost of about $2/day.

Fish oil capsules are much cheaper. But it's important to understand that a 1-g capsule of fish oil typically contains only 300 mg of DHA/EPA. So to obtain 2 g of the triglyceride-lowering active ingredients, a patient has to swallow 6 or 7 capsules per day. Still, Dr. Merenich has found most patients are much more willing to do that than to take conventional, side-effect-laden niacin for triglyceride lowering.

"Niacin is a pain in the rear end," he declared, noting that he is successful in keeping patients on long-term niacin therapy only about 60% of the time.

Fish oil supplements are distilled to achieve purity. Concerns about contamination by mercury, PCBs, or dioxin haven't been borne out in lab studies conducted by Consumer Reports and ConsumerLab.com.

Consumer Reports evaluated 16 brands of fish oil supplements in its July 2003 issue. None were contaminated. All contained the claimed quantities of omega-3 fatty acids. The review concluded it's reasonable to choose a product based upon low cost and listed two as "best buys": Kirkland Signature Natural Fish Oil, available at Costco, and Member's Mark Omega-3 Fish Oil, sold at Sam's Club.

More recently, ConsumerLab.com tested 41 commercially available fish oil products. Again, none were contaminated by the environmental toxins that are increasingly concentrated in many fish species.

"The GNC and Vitamin Cottage products are very, very good and priced reasonably. I refer patients there," said Dr. Merenich, who disclaimed financial interest in the products he discussed.

He added that the omega-3 fatty acids lend themselves particularly well to combination lipid-lowering therapy with statins. Many patients like the idea of taking a nonprescription 'natural' product along with their prescription drug. While statins primarily target LDL, in higher dosages they can also lower elevated triglycerides by 25%-35%.

Another reason to consider combination therapy is that a patient's LDL level often increases after initiating triglyceride-lowering therapy. "That's a common clinical situation. I probably get this question more than any other," he said.

Even if the LDL does go up, the cardiovascular risk as reflected in the non-HDL cholesterol level is often reduced by effective triglyceride lowering. And non-HDL cholesterol is an even better indicator of risk than LDL, particularly in patients with metabolic syndrome.

Consider, for example, a patient with metabolic syndrome who has a baseline total cholesterol of 186 mg/dL, a triglyceride level of 258 mg/dL, an LDL level of 98 mg/dL, and an HDL level of 36 mg/dL. After 3 months of triglyceride lowering, total cholesterol is 179, triglyceride is 142, LDL is 113, and HDL is 38 mg/dL. That patient's baseline non-HDL cholesterol was 150 mg/dL; after treatment, it has dropped to 141 mg/dL. ■

1 in 12 MIs Present With Life-Threatening Noncardiac Condition

BY BRUCE JANCIN
Denver Bureau

ORLANDO, FLA. — One in 12 patients with acute MI presents with a concomitant acute potentially life-threatening noncardiac condition, Judith H. Lichtman, Ph.D., reported at the annual meeting of the American College of Cardiology.

None of the current risk-adjustment models for MI patients that are widely used to guide clinical care and benchmark hospital and physician performance take account of these life-threatening noncardiac conditions.

Instead, the prognostic models are restricted to variables directly related to the patient's cardiovascular disease. That's largely because the models were developed using data from randomized clinical trials from which patients with significant comorbidities are generally excluded. As a consequence, the risk-adjustment models fail to account for much of the variation in short-term outcomes in MI patients, explained Dr. Lichtman of Yale University, New Haven.

This is a glaring oversight, she stressed, because those one in 12 MI patients who have a dueling potentially life-threatening acute noncardiac condition account for a disproportionate share of total inpatient deaths. Indeed, in the Prospective Registry Evaluating Outcomes After Myocardial Infarction: Events and Recovery (PREMIER) study, they had an in-hospital mortality of 20%, compared with 3% in MI patients without such comorbidities.

"We feel that in this study we've identified a very important subgroup of acute MI patients at increased risk for mortality that have really not been previously described in the literature," she added.

The PREMIER registry involved 3,948 acute MI patients prospectively enrolled at 19 participating U.S. medical centers during 2003-2004. Chart review showed 8% had an acute potentially life-threatening noncardiac condition at the time of admission. These were not chronic conditions such as arthritis or seizure disorders. The most common of these conditions included severe pneumonia requiring intubation, trauma, stroke, sepsis, severe GI bleeding, and hip fracture. Patients who present with one of these conditions in addition to an acute MI typically require care from multiple specialists, both cardiovascular and noncardiovascular.

The MI patients with acute potentially life-threatening noncardiac conditions in PREMIER presented differently from those with MI alone. They were older—a mean age of 62 years compared with 56—and more likely to be women and nonwhite. They also were more likely to have diabetes and hypertension and less likely to present with ST-elevation MI.

After adjustment for the lesser use of guideline-based initial therapies for MI in the patients with potentially life-threatening comorbid conditions, along with differences in demographics, prior history, and clinical presentation, the study showed the patients still had a 4.9-fold increased risk of in-hospital mortality.

"I think this underscores a strong need to adopt a broader perspective of the clinical factors that contribute to the initial assessment, process of care, and outcomes for acute MI patients. … These factors need to be put on the radar of these risk-adjustment models," Dr. Lichtman concluded.

Session cochair Eric D. Peterson, M.D., of Duke University, Durham, N.C., who was a coinvestigator in the PREMIER registry, said that while most MI patients with an acute potentially life-threatening noncardiac condition are routinely admitted to coronary care units, it might make more sense for them to go directly to the intensive care unit, where caregivers are experienced in managing a wider array of very serious medical conditions. ■