News and Views from the Literature

Patients at Risk

Recent Study Findings on Predicting and Improving Outcomes

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Evaluation of B-Type Natriuretic Peptide for Risk Assessment in Unstable Angina/Non-ST-Elevation Myocardial Infarction: B-Type Natriuretic Peptide and Prognosis in TACTICS-TIMI 18

Morrow DA, de Lemos JA, Sabatine MS, et al.

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Attempts to risk-stratify patients presenting with acute coronary syndromes including unstable angina and non–ST-elevation myocardial infarction (NSTEMI) have been greatly enhanced with the measurement of the myocardial necrosis biomarker troponin T. The CAPTURE trial revealed a 6-month incidence of the composite endpoint of death and myocardial infarction of more than 25% in the placebo population of patients with acute coronary syndromes presenting with troponin levels ≥ 0.2 ng/mL. In similar patients with troponin levels < 0.2 ng/mL, the incidence of the composite endpoint was only 10%.[1] The TACTICS trial clearly showed that an early, aggressive approach in patients with elevated troponin levels resulted in a 22% reduction of the composite endpoint of death, myocardial infarction, and rehospitalization at the 6-month endpoint.[2]

Morrow and associates have demonstrated the ability of brain natriuretic peptide (BNP) levels (Biosite Incorporated, San Diego, CA) > 80 pg/mL on presentation to identify short- and long-term mortality as well as new onset of congestive heart failure in patients presenting with unstable angina/NSTEMI. This prognostic ability was independent of troponin positivity on presentation. A stepwise increase in 6-month mortality rates was seen in patients with increasing levels of BNP. In patients with BNP levels < 40 pg/mL, 6-month mortality was 1.7%, versus 11.1% if presenting levels were > 160 pg/mL. In patients who had normal troponin and elevated BNP levels, 30-day mortality was 4.5%, versus 1.4% in patients who were troponin-positive and had normal BNP levels (Figure 1). In addition to mortality, BNP levels were able to add independent prognostic information in assessing risk of myocardial infarction and the development of congestive heart failure. In patients who were troponin$^-$ and BNP$^-$, the risk of CHF at 30 days was 0.2%, versus 4.5%

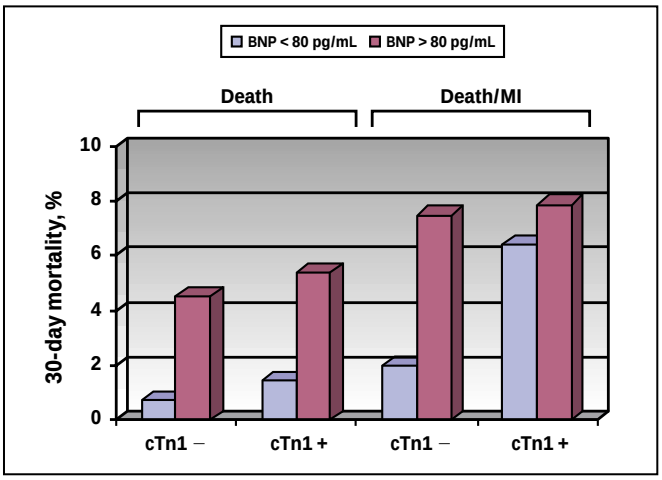

Figure 1. *Risk of death or myocardial infarction (MI) at 30 days, stratified by B-type natriuretic peptide (BNP) and cardiac troponin 1 (cTn1). Adapted with permission from Morrow et al.*

in patients who were troponin$^-$ and BNP$^+$.

The results of this trial showing the ability of BNP levels to assist in risk-stratifying patients presenting with an acute coronary syndrome are consistent with the results of Jernberg and coworkers, who used the N-terminal pro-BNP assay.[3] The results of this study indicate that BNP measurement can add to the ability of troponin testing to determine the risk of death, myocardial infarction, or congestive heart failure in patients presenting with unstable angina or NSTEMI. BNP levels in this trial did not seem to add to our ability to determine who would benefit from a conservative or early invasive management approach. However, being able to identify a group of patients previously believed to be at lower risk (the troponin$^-$/BNP$^+$ patients) as having an increased event rate could allow us to take a more aggressive treatment approach, including hospitalization and the use of ß-blockers, angiotensin-converting enzyme inhibitors, and antiplatelet therapy.

Effects of Ximelagatran, an Oral Direct Thrombin Inhibitor, r-Hirudin and Enoxaparin on Thrombin Generation and Platelet Activation in Healthy Male Subjects

Sarich TC, Wolzt M, Eriksson UG, et al.
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We are now witnessing in the field of anticoagulation the development of a compound that may have huge implications for the treatment or prevention of thromboemboli in patients with or at risk for atrial fibrillation, deep venous thrombosis, and prosthetic valve thrombosis. Upon oral administration, ximelagatran is rapidly absorbed and converted to melagatran, a potent and direct thrombin inhibitor. The purpose of this investigation was to determine whether ximelagatran exhibits similar effects on thrombin generation and platelet activation as seen with r-hirudin and enoxaparin, two compounds that have been found to be clinically effective in patients with acute coronary syndromes. Ximelagatran, 60 mg, was found to reduce the generation of prothrombin fragment 1+2 and thrombin-antithrombin complexes, both biomarkers of thrombin generation, more than enoxaparin at the 2-, 4- and 10-hour post-dose intervals, with less reduction of thrombin-antithrombin complexes at the 4-hour interval. Ximelagatran was found to reduce the levels of ß-thromboglobulin, a marker of platelet activation, more than did enoxaparin and to levels similar to those observed with r-hirudin. The ability of ximelagatran to induce the antithrombotic and antiplatelet effect was dose-related.

To assess the clinical implications of ximelagatran, the SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) III trial compared ximelagatran with warfarin in 3407 patients with atrial fibrillation. The preliminary results of this trial were presented at the American College of Cardiology's 2003 Scientific Session. A fixed dose of ximelagatran (36 mg b.i.d.) was compared with adjusted-dose warfarin with a goal international normalized ratio of 2 to 3. Patients studied included those with atrial fibrillation and at least one additional risk factor for stroke. The primary endpoint was the prevention of all strokes (ischemic or hemorrhagic) and systemic embolic events. Ximelagatran reduced the incidence of the primary endpoint from 2.3% to 1.6% over a mean treatment duration of 21 months. The incidence of major and minor bleeding events was 29.5% with warfarin and 25.5% with ximelagatran (P = .007). There was an increased incidence of liver function test elevation (alanine aminotransferase level > 3 times the upper limit of normal) from 0.7% with warfarin to 6.5% with ximelagatran (P < .001). Ximelagatran was not inferior to warfarin and was better tolerated.

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Nephrotoxic Effects in High-Risk Patients Undergoing Angiography

Aspelin P, Aubry P, Fransson SG, et al, for the NEPHRIC Study Investigators.

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Contrast-induced nephropathy (CIN) is a common complication of radiocontrast-requiring procedures that is associated with a significant increase in mortality, need for dialysis, and hospital resource allocation. The combination of renal insufficiency and diabetes characterizes the high-risk patient demographic. With the recent negative results of the CONTRAST trial, which showed no beneficial effect of fenoldopam in preventing CIN, and the mixed results with N-acetyl cysteine, the search continues for an optimal prevention strategy. The contemporary gold standard prevention strategy is aggressive periprocedural hydration. Whether the selection of an iso-osmolar contrast agent provides a renoprotective effect was assessed by these investigators. The NEPHRIC trial was a randomized, double-blind, prospective, multicenter study comparing the nephrotoxic effects of the iso-osmolar, dimeric, nonionic contrast medium iodixanol with those of the low-osmolar, nonionic, monomeric contrast medium iohexol.

It would be reasonable at the present time to consider iodixanol the contrast agent of choice in patients at high risk for contrast-induced nephropathy.

The study included 129 patients with diabetes and serum creatinine levels of 1.5 to 3.5 mg/dL undergoing coronary or aortofemoral angiography. The primary endpoint was the peak increase from baseline in the serum creatinine concentration during the three days following angiography. There was no difference between the patients receiving iodixanol or iohexol in mean age (71.1 y vs 70.6 y, respectively), weight (76.5 kg vs 77.2 kg), baseline mean serum creatinine level (1.49 mg/dL vs 1.60 mg/dL), baseline creatinine clearance rate (50.1 mL/min vs 47.3 mL/min), intravenous hydration volume (977 cc vs 934 cc), and volume of contrast exposure (163 cc vs 162 cc). At baseline, fewer patients in the iodixanol group than the iohexol group had urinary excretion of at least 50 mg of albumin per millimole of creatinine (10 vs 23).

Iodixanol induced a significantly smaller mean increase in serum creatinine level than was observed with iohexol (0.13 mg/dL vs 0.55 mg/dL). When CIN was defined as a 0.5 mg/dL increase in serum creatinine from baseline, the incidence of nephropathy was only 3% in the iodixanol group and 26% in the iohexol group ($P = .002$). These study results confirm the observations made in a previous unblinded trial comparing iodixanol to iohexol, in which a greater than 50% reduction in CIN was observed in the iodixanol group. There is no mention of the longer-term implications for those patients in whom CIN did develop, including rates of dialysis and mortality.

The authors provided potential explanations for the ability of an iso-osmolar contrast agent (iodixanol) to provide this benefit over a low-osmolar agent (iohexol). A possibility is that the greater osmotic diuresis induced by the low-osmolar agent may increase the work of the medullary tubules and create ischemic conditions within the renal medulla. In addition, the diuresis creates a state of volume depletion with activation of vasoregulatory hormones. The finding of a benefit of an iso-osmolar contrast agent over a low-osmolar agent runs in contradistinction to animal data showing no advantage of an iso-osmolar agent.

It would be reasonable based on the results of this clinical trial to consider iodixanol the contrast agent of choice in patients at high risk for CIN.

Ezetimibe Coadministered with Simvastatin in Patients with Primary Hypercholesterolemia

Davidson MH, McGarry T, Bettis R, et al.

J Am Coll Cardiol. 2002;40:2125-2134.

Attaining the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) goal for cholesterol level modification remains elusive, particularly in diabetic patients and those with apparent atherosclerotic cardiovascular disease. A variety of explanations for this include patient noncompliance, adverse events (particularly myalgias and liver function abnormalities as complications of statin therapy), and the need for combination therapy in patients with higher baseline levels of low-density lipoprotein cholesterol (LDL-C). The incidence of liver function abnormalities is a statin dose related phenomenon. These investigators evaluated the safety and efficacy of a cholesterol modification strategy using ezetimibe (E), a member of a new class of lipid-altering agents that inhibits the absorption of dietary and biliary cholesterol, in a 10-mg dose as monotherapy and in combination with simvastatin (S) in doses of 10, 20, 40, and 80 mg. The study was open to men and women aged 18 years and older with primary hypercholesterolemia

(LDL-C level of 145 mg/dL to 250 mg/dL). Six hundred sixty-eight patients were randomized to 12 weeks of active treatment in one of ten groups: placebo; E; S (10 mg); S (10 mg) + E; S (20 mg); S (20 mg) + E; S (40 mg); S (40 mg) + E; S (80 mg); and S (80 mg) + E.

Ezetimibe monotherapy resulted in an 18% reduction in LDL-C along with an 8% reduction in triglyceride levels and a 5% increase in high-density lipoprotein cholesterol (HDL-C). Coadministration of ezetimibe and simvastatin (pooled doses) was more effective than simvastatin alone (pooled doses) in reducing levels of LDL-C from baseline (49.9% vs 36.1%). Pooled analysis revealed that coadministration was also able to provide a 2.4% increase in HDL-C and 7.5% reduction in triglyceride levels over what was observed with simvastatin alone. Coadministration of 10 mg of ezetimibe plus 10 mg of simvastatin was able to effect a 44% reduction in LDL-C, equal to what was observed with 80 mg of simvastatin alone. A combination of 10 mg ezetimibe with 80 mg of simvastatin was observed to result in a 57% reduction in LDL-C. The coadministration of ezetimibe and simvastatin was well tolerated, with an observed overall safety profile similar to that of monotherapy with simvastatin and that of placebo.

In those patients who are intolerant of statins, ezetimibe provides an alternative monotherapy strategy or one that could be combined with other lipid therapies.

Coadministration of ezetimibe with a low(er)-dose statin provides a well-tolerated treatment option. Combination therapy also provides an opportunity to achieve NCEP ATP III target LDL-C concentrations in patients in whom monotherapy lacks sufficient potency or in patients who have adverse reactions to the higher statin doses. In those patients who are intolerant of statins, ezetimibe provides an alternative monotherapy strategy or one that could be combined with other lipid therapies, including niacin and fibric acid derivatives. ■

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Atherosclerosis

The Calcium Channel Blocker Lacidipine Slows the Progression of Carotid Atherosclerosis

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Calcium Antagonist Lacidipine Slows Down Progression of Asymptomatic Carotid Atherosclerosis: Principal Results of the European Lacidipine Study on Atherosclerosis (ELSA), a Randomized, Double-Blind Long-Term Trial

Zanchetti A, Bond MG, Hennig M, et al.
Circulation. 2002;106:2422–2427.

Hypertension contributes to cardiovascular events, in part by predisposing the patient to atherosclerosis and its progression. Antihypertensive drugs include calcium channel blockers; experimental data have suggested that these agents may also have antiatherogenic effects independent of their antihypertensive effects. The highly lipophilic, long-acting calcium channel blocker lacidipine has been shown to have antioxidant effects and is particularly effective in reducing atherosclerosis in animal models.

In this study, the investigators used B-mode carotid ultrasound to measure carotid intima-media thickness (IMT) as an index of carotid atherosclerosis in order to evaluate and compare the long-term effects of lacidipine and beta-blockers on atherosclerosis in hypertensive patients over a 4-year period. Several studies had previously documented the generally consistent relationship of carotid IMT to cardiovascular events, making it a useful surrogate marker for clinical events.

A total of 2035 hypertensive patients (systolic blood pressure, 150–210 mm Hg; diastolic blood pressure, 95–115 mm Hg) were recruited from 410 European centers and randomized to lacidipine (755 out of 1023 patients completed the trial) or atenolol (764 out of 1012 subjects completed the trial). At the end of the study, among those who completed the study, there was significantly