TRITON–TIMI 38: Clopidogrel and Prasugrel

Presenter: Elliott Antman, MD, Brigham and Women’s Hospital, Boston, Mass.
Discussant: Eric Topol, MD, Scripps Health, La Jolla, Calif.
Commentators:
- William B. Hillegass, MD, University of Alabama, Birmingham, Ala.
- Christoph Bode, MD, University of Freiburg, Germany

Clinicians treating patients with blocked coronary arteries are always poised over the twin abysses of thrombosis and platelet aggregation on one side and bleeding on the other. The Trial to Assess Improvement in Therapeutic Occurrences by Optimizing Platelet Inhibition with Prasugrel (TRITON–TIMI 38) compared prasugrel (CS-747, Daiichi Sankyo/Lilly), a thienopyridine, with aspirin against the standard of care—clopidogrel (Plavix, Sanofi-Aventis) plus aspirin—in patients undergoing percutaneous coronary intervention (PCI).

The hypothesis, stated lead investigator Dr. Antman, was that because prasugrel, a platelet receptor blocker, quickly produces higher and more consistent levels of inhibition of platelet aggregation (IPA), it would more successfully prevent clinical ischemic events in moderate-risk or high-risk patients with acute coronary syndrome (ACS) undergoing PCI. TRITON was presented as a late-breaking clinical trial.

Among the 13,608 patients (mean age, 61 years) from 707 centers and 30 countries, 26% were undergoing primary PCI for ST-segment elevation myocardial infarction (STEMI); the rest (74%) had already undergone angiography. In the latter group, patients had moderate-risk to high-risk unstable angina or non-STEMI or STEMI within the previous 14 days; they also had ischemia or were receiving drug therapy.

All patients received aspirin and were randomly assigned, in a double-blind fashion, to loading/maintenance doses of clopidogrel 30 mg/75 mg, respectively, or to loading/maintenance doses of prasugrel 60 mg/10 mg, respectively. The median duration of therapy was 12 months. The primary endpoint was a combination of death from cardiovascular disease, MI, and stroke. Safety endpoints were TIMI major bleeding episodes and life-threatening bleeding.

The clopidogrel group reached the primary endpoint more frequently (12.1% of the time) than the prasugrel group (9.3%); the hazard ratio (HR) was 0.81 \((P = 0.004)\). The benefit was significant in both loading and maintenance dose periods.

Stent thrombosis was significantly higher with clopidogrel (in 2.4% of the patients) than with prasugrel (in 1.1%) \((HR, 0.48; P < 0.0001)\). However, bleeding (TIMI major plus non-bleeding from coronary artery bypass grafting [CABG]) was more common with prasugrel (1.8% vs. 2.4%; \(HR, 1.32; P = 0.03)\). Life-threatening bleeding was also more common with prasugrel (1.4%) than with clopidogrel (0.9%) \((HR, 1.52; P = 0.01)\).

Bleeding risk was highest among patients with a history of stroke or transient ischemic attacks in those older than 75 years of age and weighing less than 60 kg.

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Dr. Antman concluded that with a 19% reduction in cardiovascular deaths, MI, and stroke, and a 52% reduction in stent thrombosis and a 32% increase in serious bleeding, the net clinical benefit significantly favored prasugrel. However, he cautioned that the regimen should be avoided in patients who have experienced a stroke.

While hailing TRITON’s expansion of the antiplatelet armamentarium with prasugrel, Dr. Topol voiced concern over patient selection in TRITON, which he termed “artificial,” in that it is not typical for patients to have angiograms prior to study entry. His main concern was over the heightened (HR, 4.73) bleeding in patients undergoing bypass graft surgery.

“There is already tremendous concern with clopidogrel,” he said.

Asked whether prasugrel should be approved in light of the TRITON results, most experts were affirmative, albeit with reservations. Dr. Bode indicated that he would approve prasugrel only for patients who had a history of problems, for instance, those who had experienced stent thrombosis.

Although in favor of approval, Dr. Hillegass said that until further studies show lower prasugrel doses to be safer, “a very good effort has to be made to educate clinicians to avoid prasugrel in prior stroke or low-weight patients.”

The author is a freelance medical writer living in New York City.
TRA–PCI: Thrombin Receptor Agonist and Percutaneous Coronary Intervention

Moderators:
- William B. Hillegass, MD, University of Alabama, Birmingham, Ala.
- Christoph Bode, MD, University of Freiburg, Germany

Presenter: Lisa K. Jennings, MD, University of Tennessee Health Science Center, Memphis, Tenn.

Both Drs. Bode and Hillegass were moderators of a session that included an investigative thrombin receptor antagonist (TRA) known as SCH 530348 (Schering-Plough), presented by Dr. Jennings. What was noteworthy in this early-phase trial among patients undergoing non-urgent PCI was a reduction in ischemic events but no increase in bleeding risk. Dr. Jennings said that the potential advantage might be explained by a TRA-PCI substudy showing that the TRA affected only one of four inducers of IPA:
- a thrombin receptor agonist peptide (TRAP)
- adenosine diphosphate (ADP)
- collagen
- arachidonic acid

Moderator Hillegass commented, “It’s an early-stage, underpowered trial, but it’s very encouraging to think that [SCH 530348] might reduce ischemic events without this inexorable trade-off between bleeding events and ischemic events.”

SEACOAST I and II: Niacin and Simvastatin

Study authors:
- Christie Ballantyne, MD, Baylor College of Medicine, Houston, Texas
- Richard Karas, MD, Tufts New England Medical Center, Boston, Mass.

In the SEACOAST study (Safety and Efficacy of A Combination Of niAcin ER and Simvastatin in PaTients with dyslipidemia), more than half of patients who had not attained their lipid target levels following statin monotherapy achieved these target levels with a combination of niacin (Niaspan, Abbott/Kos) and simvastatin (Zocor, Merck). In addition, the combination improved multiple clinically relevant lipid parameters among the high cardiovascular risk SEACOAST population, according to Dr. Ballantyne. Target levels, she noted, were high-density lipoprotein-cholesterol (HDL-C) of 40 mg/dL or more, triglycerides below 150 mg/dL, and National Cholesterol Education Program (NCEP) cardiovascular risk factor–adjusted goals for non–HDL-C and LDL-C.

Dr. Ballantyne explained that although the number of patients with multiple lipid disorders, obesity, diabetes, and metabolic syndrome has been increasing, aggressive treatment with high-dose statins does not appear to adequately lower cardiovascular risk. He noted also that niacin reduces apo-lipoprotein B–containing particles (non–HDL-C) and is the most potent agent available for improving HDL-C levels.

SEACOAST I and II compared low-dose and high-dose combinations of extended-release niacin/simvastatin (1,000/20 mg or 2,000/20 mg in SEACOAST I and 1,000/40 mg or 2,000/40 mg in II) against simvastatin alone (20 mg in SEA-

COAST I; 80 mg in II).

All patients in SEACOAST I had reached NCEP III Coronary Heart Disease risk-adjusted targets. Patients in SEACOAST II were at a higher risk and could have any LDL-C value. The primary endpoint of the double-blind, randomized trials was non–HDL-C values.

Co-investigator Dr. Karas reported that after 24 weeks, among 314 patients in SEACOAST I, the combination significantly improved non–HDL-C values by about 25%, LDL-C by about 15%, and triglycerides by approximately 35%; HDL-C increased by nearly 25%. Most flushing episodes were mild or moderate in intensity. Overall discontinuations resulting from flushing were modest (7.5%) for the two combination arms.

In SEACOAST II, with a total of 343 patients, among those receiving the higher-dose combination, more attained lipid target levels; 48.8% reached LDL, non–HDL, and triglyceride goals, compared with 18.7% for those receiving simvastatin 80 mg (P < 0.001). Sixty-one percent of patients receiving the combination achieved non–HDL-C goals, compared with 57.5% of those receiving simvastatin 80 mg (P = not significant). In that higher-dose group, 5% discontinued therapy because of flushing.

Dr. Karas commented that flushing is not a side effect of niacin; it is an effect. Both Drs. Karas and Ballantyne did emphasize, however, the value of instructing patients to take aspirin a half-hour before their dose, preferably at bedtime.

Dr. Ballantyne commented: “With good education and motivated patients, you can use this drug well and get better management of lipid disorders. Without spending the time on instruction, you may not see these numbers in practice. In our clinic, we take the extra time.”

Couma-Gen: Warfarin Studies

Presenter: Jeffrey Anderson, MD, Intermountain Healthcare and University of Utah, Salt Lake City, Utah

Experts agree that pharmacogenetics (PG) will become a cornerstone of a personalized medicine that abolishes “one-size-fits-all” health care and ushers in an age of treatments tailor-made according to individual genotypes. The Couma-Gen Trial, which was conducted among 200 adults and was presented by Dr. Anderson, compared genotype-guided versus standard dosing with warfarin (Coumadin, Bristol-Myers Squibb) in patients starting oral anticoagulation therapy.

Genotype variants, namely cytochrome P450 2C9 (CYP 2C9) and the VKORC1 haplotype (vitamin K epoxide reductase complex 1), plus a person’s age and weight, account for half of the 20-fold interindividual dose variability seen in more than two million patients receiving warfarin yearly. The impact of PG-guided warfarin dosing, however, has not been adequately tested in prospective trials, Dr. Anderson said.

The Couma-Gen trial prospectively evaluated a PG-guided warfarin dosing algorithm to assess its impact on International Normalized Ratio (INR)–based efficacy and safety endpoints. It was a prospective, blinded, randomized trial with standard-
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dose warfarin of 10 mg on days one and two, followed by 5 mg daily (i.e., 35 mg weekly, modified by INR results) as a comparator therapy to the PG-guided warfarin dosing.

The follow-up period lasted as long as three months. For PG-guided dosing, the investigators performed a genetics test using buccal swab samples and a rapid assay. Dosing was determined via a regression equation. Scores were categorized into 14 daily dose increments.

The primary endpoint was the percentage of out-of-range INRs (below 1.8 and above 3.2), with a subset analysis by genotype. The enrolled patients included those with an indication for oral anticoagulation (mean age, 61 years; 53% male). The target INR was 2 to 3.

The initial maintenance dose was scaled according to the number of variant alleles. Patients with the wild-type form (no variant alleles) received warfarin 44.7 mg/week; those with the maximum number of variants (four) received 8 mg/week.

Dr. Anderson reported that although PG modeling was good at predicting the observed warfarin stable maintenance dose, the primary endpoint of percentage out-of-range INRs was not significantly reduced in the PG-guided group (30.7%), compared with the standard-dosing group (33.1%) \( P = 0.47 \).

For the prespecified groups, the difference in the percentage of out-of-range INRs was significant only when patients with multivariant alleles were added to those with the wild-type form: 29.3% for PG modeling and 39.1% for standard-dose warfarin \( P = 0.03 \). Dr. Anderson called this analysis “exploratory” but suggested that although Couma-Gen demonstrated the feasibility of real-time genotyping, and PG-guidance was associated with a need for less INR monitoring and fewer dose adjustments, reduced percentages of out-of-range INRs were not achieved.

CLEAR PLATELETS: Clopidogrel, Eptifibatide, and Bivalirudin

Presenter: Paul Gurbel, MD, Sinai Hospital, Baltimore, Md.

Further promise toward highly individualized therapy was suggested in the setting of coronary artery disease for patients undergoing elective stenting. Dr. Gurbel presented the CLEAR PLATELETS 2 trial (Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets).

This study enrolled 200 individuals receiving clopidogrel (a loading dose of 600 mg for clopidogrel-naive patients and 75 mg/day for those already on clopidogrel maintenance doses) plus the standard dose of bivalirudin (Angiomax, The Medicines Company) with or without the standard dose of the glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitor eptifibatide (Integrilin, Millennium/Schering).

All patients received 325 mg of aspirin per day. The investigators evaluated the relationship between platelet aggregation and biochemical markers of myocardial necrosis, namely troponin and the creatine kinase-MB (CK-MB) isoenzyme. For the evaluations, platelet aggregation was induced with adenosine diphosphate (ADP), collagen, and the thrombin receptor agonist peptide (TRAP).

Dr. Gurbel pointed to two important findings from the platelet-aggregation study:

1. In the absence of eptifibatide, it took a loading dose of clopidogrel about six hours to achieve the level of reduced platelet aggregation observed in patients receiving the clopidogrel maintenance dose.

2. Inhibition of platelet aggregation (IPA) with eptifibatide was immediate and significantly greater than in the patients receiving bivalirudin alone, without variability in response.

Cardiac marker release was also higher in the non-epitifibatide patients.

Although the trial was not powered for clinical events, Dr. Gurbel noted lower rates of periprocedural myocardial infarction (MI) in the eptifibatide groups; however, there was some increase in major bleeding. He concluded that CLEAR PLATELETS 2 supported the link between platelet reactivity and post-stent MI.

He speculated further: “Selection of patients for adjunctive GP IIb/IIIa blockade may be facilitated in future studies by individualized platelet function measurements.”

EVA–AMI: Eptifibatide and Abciximab

Presenter: Uwe Zeymer, MD, Herzzentrum Ludwigshafen, Germany

EVA–AMI (Eptifibatide versus Abciximab in Primary PCI for Acute ST elevation Myocardial Infarction), another late-breaking trial, suggested that the antithrombin agent eptifibatide (Integrilin), given as a double bolus, might be an alternative to abciximab (ReoPro, Centocor/Lilly) in STEMI patients undergoing primary PCI. Both acquisition and hospitalization costs have been significantly lower with eptifibatide than with abciximab.1

Dr. Zeymer said that abciximab and eptifibatide, which are both GP IIb/IIIa inhibitors, reduce events in elective PCI patients, but they have not been compared directly.

The objective of EVA–AMI was to show non-inferiority for eptifibatide in patients scheduled for primary PCI who were receiving an abciximab bolus plus a 12-hour infusion or a double bolus of eptifibatide plus a 24-hour infusion. The primary endpoint was complete ST resolution at one hour after PCI, a marker of myocardial reperfusion that is closely linked to mortality after STEMI.

Among 429 patients (mean age, 61 years), complete reperfusion was similar between the groups (59.6% for abciximab, 63.1% for eptifibatide) \( P = \text{not significant} \), as were in-hospital events (death, re-infarction, heart failure, tricuspid valve replacement, and CABG).

Dr. Zeymeyer concluded: “Eptifibatide given as a double bolus is equally effective as abciximab as adjunct to primary PCI with respect to myocardial reperfusion. Also, there were no differences in preliminary clinical events.”

REFERENCE