

Transcatheter Cardiovascular Therapeutics 2012

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This year's TCT meeting, the world's largest gathering specializing in interventional cardiovascular medicine, presented cutting-edge educational content in Miami Beach, Fla., to nearly 11,800 attendees from 52 countries from October 21 to 25, 2012. This article reviews key sessions on antiplatelet and cell therapies.

Bivalirudin Reduces Cardiac Bleeding: The HORIZONS-AMI Trial

Gregg W. Stone, MD, Columbia University College of Physicians, New York, N.Y.

The HORIZONS-AMI trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) included 3,602 patients with ST-segment elevation myocardial infarction (STEMI) who had presented within 12 hours after the onset of symptoms and then underwent primary percutaneous intervention (PCI). They were then randomly assigned to receive unfractionated heparin (UFH) plus a glycoprotein IIb/IIIa inhibitor (GPI) or the direct thrombin inhibitor bivalirudin (Angiomax, The Medicines Company) alone.

The marked 44% reduced 3-year cardiac mortality rate reported in the bivalirudin group (2.9% vs. 5.1%; $P = 0.001$), Dr. Stone said, was usually attributed to decreased bleeding in that group. Three-year major bleeding was reported at 10.5% for the UFH + GPI group and at 6.9% for bivalirudin ($P < 0.001$). Further, comparing patients with and without major bleeding, respectively, significantly higher mortality rates for those without major bleeding were apparent in both groups (14.6% and 3.8% for UFH + GPI, 5.8% and 2.6% for bivalirudin).

"A fascinating observation," Dr. Stone commented, "is that even in patients with major bleeding, there's markedly reduced mortality between heparin plus GPI and bivalirudin (14.6%/5.8%), with a hazard ratio of 2.56."

After 3 years, the death rate was reduced by 61% with bivalirudin. Multivariable models showed bivalirudin, compared with UFH + GPI, to be an independent predictor of not dying ($P = 0.006$). Transfusion rates were similar between groups, suggesting that bleeding severity was not a factor. A significant cardiac mortality benefit persisted for bivalirudin even in patients without major bleeding (3.8% vs. 2.6% for UFH + GPI; $P = 0.046$).

Bivalirudin and the Impact on Thrombocytopenia

• Gregg W. Stone, MD, Columbia University College of Physicians, New York, N.Y.

Dr. Stone noted that bivalirudin is known to prevent thrombocytopenia (TTP). In-hospital acquired TTP occurred in 13.2% of patients in the UFH + GPI group and in 10.1% of the

bivalirudin group ($P = 0.004$). Cardiac mortality was higher in patients with acquired TTP (8.1% with TTP; 3.1% without TTP; $P < 0.001$). Looking separately at 3-year cardiac mortality for the two treatment groups with and without TTP showed a significant difference in the UFH + GPI groups (12.3% with TTP; 3.5% without TTP; $P < 0.0001$) but not in the bivalirudin groups (2.3% with TTP, 2.5% without TTP; $P = 0.51$), with a "very, very strong interaction P value ($P_{int} = 0.006$)."

Dr. Stone pointed out that 60.2% of cardiac deaths occurred in patients without TTP or major bleeding and that a multivariable model showed a 46% reduction in mortality rates for patients receiving bivalirudin rather than UFH + GPI ($P = 0.002$), independent of hematological complications.

He concluded, "In addition to reducing major bleeding, bivalirudin reduced the occurrence of thrombocytopenia, which contributed to the improved survival in patients with and without major bleeding."

He added, "Further studies are required to identify the non-hematologic benefits of bivalirudin."

30-Day Rehospitalization Rates for Clopidogrel and Prasugrel in Acute Myocardial Infarction

• Jay P. Bae, PhD, Eli Lilly, Indianapolis, Ind.

Although the stronger platelet inhibition of prasugrel (Effient, Daiichi Sankyo), compared with clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi), led to significant reductions in the primary endpoint (cardiovascular death, myocardial infarction [MI] or stroke) in the TRITON-TIMI 38 trial, this benefit was accompanied by increased TIMI major and minor bleeding and transfusions. TRITON-TIMI 38 included patients with moderate-to-high-risk acute coronary syndromes (ACS) who were scheduled for percutaneous coronary intervention (PCI).

Some earlier analyses of real-world prasugrel use, however, showed shorter hospital stays without differences in bleeding risk between the two thienopyridines. The current analysis, said Dr. Bae, compared prasugrel and clopidogrel 30- and 90-day acute myocardial infarction (MI) and bleeding-related hospitalization rates following discharge from the index hospitalization.

The analysis was based on the 5.5-million patient hospital discharge Premier database. Eligible patients included 74,163 receiving clopidogrel (30.5% women) and 9,404 in the prasugrel group (23.1% women). Because of known higher bleeding risks, few patients (1.1%) 75 years of age or older received prasugrel.

Observed 30-day rehospitalization rates were significantly higher for clopidogrel than for prasugrel (4.7% vs. 3.9%, respectively; $P < 0.001$), as were 90-day rates (6.3% vs. 5.1%). Rehospitalization rates for bleeding were also significantly higher ($P < 0.05$) for clopidogrel (30 days, 0.8% vs. 0.5%, respectively; 90 days, 1.4% vs. 0.8%, respectively).

After adjustments for clinical, demographic, and interventional factors, odds ratios (ORs) for 30- and 90-day rehospitalizations for acute MI significantly favored prasugrel (30 days:

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OR, 0.893; $P = 0.0466$; 90 days: OR, 0.901; $P = 0.0368$). At both 30 and 90 days, rehospitalization rates for bleeding were similar for clopidogrel and prasugrel.

Dr. Bae commented that the mitigated bleeding risk with prasugrel suggests that in real-world use, prescribers are targeting patients for different antiplatelet regimens, avoiding prasugrel in the presence of a higher bleeding risk. That finding was also suggested in Dr. Bae's separate cost-effectiveness analysis poster based on the same Premier hospital data set.

"Consistent with the index outcomes (including a significantly [$P < 0.05$] shorter length of stay with prasugrel), a cost analysis showed that prasugrel-treated patients used fewer health care resources compared to clopidogrel-treated patients," he commented.

In that analysis, observed mean hospital costs were \$17,647 \pm \$16,696 for clopidogrel and \$16,199 \pm \$10,054 for prasugrel—about a \$1,500 difference. After adjustments for the higher rates of baseline diabetes and renal insufficiency in the clopidogrel group, a propensity-adjusted cost regression revealed a savings of \$374.60 in the prasugrel group.

"The patient characteristics are very different, and I think what we are looking at is appropriate patient selection," Dr. Bae said.

Antiplatelet Regimen for Critical Limb Ischemia: The J-BEAT Registry

- Junichi Tazaki, MD, Kyoto University, Kyoto, Japan

Endovascular therapy has been shown to be effective in avoiding major amputation in patients with critical limb ischemia (CLI). What constitutes the optimal antiplatelet therapy for improving long-term outcomes, however, remains to be elucidated.

The multicenter Japanese J-BEAT (Japanese Below-the-knee Artery Treatment) trial Registry enrolled 884 consecutive patients (mean age, 71 years) (1,057 limbs) undergoing endovascular therapy for CLI that was caused by isolated infrapopliteal lesions. In this analysis, the endpoint was major adverse limb event (MALE), defined as a major amputation or any revascularization (endovascular therapy and bypass). Patients were stratified according to the antiplatelet therapy received:

- aspirin alone (185 limbs)
- dual therapy with either aspirin and a thienopyridine (209 limbs) or aspirin and cilostazol (Pletal, Otsuka) (319 limbs)
- triple antiplatelet therapy with aspirin, a thienopyridine, and cilostazol (105 limbs)

After 2 years, adjusted MALE-free survival rates were 45% for triple-antiplatelet therapy, 57% for aspirin plus cilostazol, 36% for aspirin/thienopyridine, and 41% for aspirin alone. The cumulative incidence of major amputations and any revascularization was lower with aspirin plus cilostazol (adjusted 40.2% log rank $P = 0.007$).

Dr. Tazaki noted that aspirin plus cilostazol was associated with a significantly lower incidence of MALEs (hazard ratio [HR] = 0.61; $P = 0.0053$) and major amputation (HR = 0.40; $P = 0.012$). For revascularization, the benefit for aspirin plus cilostazol achieved a strongly favorable trend (HR = 0.69; $P = 0.055$).

He concluded that the combination of aspirin and cilostazol

was associated with better outcomes in the CLI patient population with isolated infrapopliteal lesions.

Mobilized CD34+ Cells for Refractory Angina

- Thomas J. Povsic, MD, PhD, Duke University Medical Center, Chapel Hill, N.C., for the RENEW Investigators

As therapy for cardiovascular disease (CVD) improves through new pharmacology and interventional techniques, the population surviving with CVD continues to grow. Dr. Povsic said that from 10% to 15% of patients who undergo angiography are not candidates for conventional revascularization, percutaneous coronary intervention (PCI), or surgical bypass.

"Most studies show low mortality and incidence of heart attacks, about 3% to 5% per year. But these patients lead very debilitated lives," he continued.

Although various approaches for augmenting native reparative capacities and stimulating angiogenesis have generally been ineffective, some techniques using unselected bone marrow cells have demonstrated modest improvements in exercise capacity and ejection fraction. Dr. Povsic pointed out, however, that because harvesting unselected bone marrow cells leads to a very impure sample, with 95% to 98% not representing true progenitor cells, it seems likely that purifying the cell product to isolate the progenitor cell population might prove beneficial. Animal studies using isolated CD34+ cells, compared with nonpurified cells, led to better regional wall motion scores and ejection fraction.

In a phase 2 study, 167 patients with class III or IV angina who had not responded to best medical therapy and who were not candidates for PCI or surgical revascularization were randomly assigned to receive endomyocardial injections of one of two concentrations of autologous CD34+ cells as follows: 1×10^5 CD34+ cells/kg ($n = 55$), 5×10^5 CD34+ cells/kg ($n = 56$), or placebo ($n = 56$). At 6 and 12 months, there were 4 and 4.7 fewer mean weekly angina episodes for the lower and higher doses combined ($P = 0.02$ and $P = 0.035$, respectively) compared with placebo. Change in exercise duration at 6 and 12 months also favored the CD34+ injections, with time extensions of 70 seconds ($P = 0.014$) and 80 seconds ($P = 0.017$), respectively, compared with placebo.

Although the trial was not powered to assess major adverse events, there was a strongly favorable trend for lower rates of death and MI among patients receiving cell therapy ($P = 0.058$).

Dr. Povsic commented that the increase in exercise capacity with CD34+ cell therapy compared very favorably with other approved treatments, such as ranolazine (Ranexa, Gilead/CV Therapeutics) alone and in combination and enhanced external counterpulsation, which have ranged from 16 to 45.9 seconds. Similarly, the reduction in angina episodes was greater with the CD34+ regimen than with other strategies.

Dr. Povsic described the upcoming RENEW study, which he called "a definitive study to define the efficacy of this therapy for treating angina in this refractory population." The primary endpoint will be change in total exercise duration (modified Bruce protocol) at 12 months. The study is expected to enroll 400 patients, with 100 receiving unblinded standard-of-care remedies. He further noted that RENEW is the first trial of cell therapy for cardiovascular disease designed to fulfill requirements for FDA approval. ■