APEX Trial Results: Pexelizumab Shows No Effect on Mortality and Morbidity

It is common knowledge that there is room for improvement in outcomes for patients that have had a heart attack and reperfusion therapy. Despite successful epicardial coronary reperfusion, microvascular and myocardial tissue perfusion often remains compromised due to reperfusion injury. Pexelizumab is a complement C5 inhibitor that had shown promise in reducing damage caused by heart attack and reperfusion injury. Paul W. Armstrong, MD, Professor of Medicine in the Division of Cardiology at the University of Alberta, Edmonton, Alberta, presented the results from the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX) trial that was conducted to determine whether treatment with pexelizumab would have an effect on all-cause mortality in this population.

Patients were randomized within six hours of heart attack onset to either pexelizumab 2 mg/kg bolus prior to PCI plus 0.05 mg/kg/hour for 24 hours or placebo. The trial did not meet its primary endpoint: there was no reduction in 30-day or 90 day cumulative risk of death after treatment with pexelizumab. There were 113 deaths (3.92%) out of 2,885 placebo patients and 116 deaths (4.06%) out of 2,860 pexelizumab-treated patients (HR=1.04; 95% CI[0.80-1.35]). There was also no difference between groups in 30-day cumulative risk of death, shock, re-infarction or congestive heart failure (HR=0.98; 95% CI [0.83-1.16]).

Outcomes at 30 days in APEX-AMI (revised end points and time frame)

End point	Pexelizumab, n= 2,860 (%)	Placebo, n=2,885 (%)
All-cause mortality*	4.06	3.92
Death, shock, or HF	8.99	9.19

*Primary end point, revised from 90-day all-cause mortality in original protocol.
No significant differences.

"The result was not what we expected", commented Dr. Armstrong. The projected mortality in the placebo group was 6.5 %, but turned out to be much lower (3.92%), which was very surprising to the investigators. "There was no effect of pexelizumab on mortality or morbidity despite earlier evidence to the contrary" said Dr. Armstrong.

He concluded by saying that Phase 2 data are sometimes overly optimistic in predicting what will occur. The therapies for reperfusion injury, especially those aimed at decreasing the degree of inflammation, have been disappointing possibly because of the multiple pathways involved in the reperfusion injury cascade.

Results of the TOSCA-2 Trial: PCI Maintains Patency but has no Effect on LVEF

Vladimir Dzavík, MD
Photo courtesy of the American Heart Association

Vladimir Dzavík, MD, presented the results of the Total Occlusion Study of Canada (TOSCA)-2, which was a mechanistic sub-study of the Occluded Artery Trial (OAT) funded by the National Institutes of Health. Observational studies have suggested beneficial effects of opening a persistently occluded infarct related artery so called "open artery hypothesis", and the TOSCA-2 study set out to determine the effects of stent-based interventions 3 to 28 days post-myocardial infarction. The co-primary endpoints were the change in the heart's pumping ability as measured by left ventricular ejection fraction (LVEF) and the number of arteries which were still open after one year (patency). Secondary endpoints included the changes in left

ventricular end-systolic volume index (LVESVI) and left ventricular end-diastolic volume index (LVEDVI).

In this sub-study, 381 patients were enrolled between May 2000 and July 2005 in eight countries, 195 to percutaneous coronary intervention plus optimal medical therapy (PCI), and 186 to optimal medical therapy alone (MED). The participants were similar in baseline characteristics except for a history of diabetes which was more frequent in MED (25 % vs. 16% in PCI). The arterial occlusion at baseline was 99% in PCI and 100% in MED. The majority of patients in both groups (>80%) took beta-blockers, ace inhibitors, and statins during the trial.

After one year, patency was significantly greater in the PCI group (83% vs. 25%, respectively; p<0.0001). More surprising was the finding that the LVEF significantly improved in both groups, with no statistically significant difference between the two treatment arms (p=0.47). "Assignment to PCI was not predictive of improvement in LVEF" said Dr. Dzavík. There was, however, a trend favoring PCI in the secondary measures of volume (LVESVI percent change p=0.07, LVEDVI percent change p=0.09), especially when LAD was the infarct-related artery. The investigators have therefore concluded that PCI establishes and sustains coronary artery patency but does not result in improved LVEF. One explanation is that although the epicardial artery is opened during PCI, the downstream microvasculature remains obstructed. It is also possible that the follow-up period was not long enough to illustrate a benefit of PCI, so the investigators plan to continue following the patients for a longer period of time. The results of the TOSCA-2 study were published online on November 14, 2006 in *Circulation* (www.circulationaha.org; DOI 10.1161 CIRCULATIONAHA.106.669432).

Are Open Arteries Beneficial in Late Reperfusion? Results of the OAT Trial

Judith S. Hochman, MD

Photo courtesy of the American Heart Association

The Occluded Artery Trial (OAT) was presented by study chair Judith S. Hochman, MD, on behalf of all investigators. This large multicenter trial was conducted at 217 sites around the world in 27 countries. There is no question that early reperfusion enhances left ventricular function and survival in patients with ST-segment elevation myocardial infarction (STEMI). This trial, however, set out to answer the question of whether or not late reperfusion would reduce by 25% the occurrence of a composite endpoint of death, reinfarction, or heart failure (NYHA class IV). The investigators hypothesized that opening arteries later (3 to 28 days post-MI) would decrease adverse remodeling, increase the electrical stability of the heart, and increase collateral development.

This trial was designed to study stable patients, therefore those with shock, rest or low threshold angina, class III-IV congestive heart failure, significant left main or 3 vessel coronary artery disease, hemodynamic/electrical instability or a creatinine level greater than 2.5 mg/dL were excluded. Patients had to have a proximal occlusion or an ejection fraction less than 50% to participate in the study. Eligible patients were randomized to one of two treatment arms: percutaneous coronary intervention with stenting and optimal medical therapy (PCI group) or optimal medical therapy alone (MED). A total of 2,166 of patients were randomized from 2000 to 2005, 1,082 in the