Late Breaking Science: Linking Genes to Function in the Heart and Vasculature

CLINICAL ABSTRACTS

Results of the Treat Angina With Aggrastat and Determine the Cost of Therapy With an Invasive or Conservative Strategy (TACTICS-TIMI 18) Trial: A Comparison of Invasive Versus Conservative Strategy in Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

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Background: In the treatment of patients with unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI), debate exists as to whether an early invasive vs. a conservative strategy is optimal therapy. Methods: In the international TACTICS-TIMI 18 trial, 22220 patients with UA/NSTEMI who had either electrocardiographic changes, elevated cardiac markers or a history of prior coronary artery disease, were immediately treated with aspirin, heparin and the glycoprotein (GP) IIb/IIIa inhibitor tirofiban. They were randomized to an early invasive strategy with routine catheterization and revascularization as appropriate within 4–48 hours, or to a conservative, “selective invasive” strategy, with catheterization performed only if the patient had objective evidence of recurrent ischemia or a positive stress test. The primary endpoint was a composite of death, myocardial infarction or rehospitalization for acute coronary syndromes at 6 months. Results: The rate of the primary endpoint was significantly reduced with the invasive strategy compared to the conservative strategy, 15.9% vs. 19.4%, odds ratio (OR) 0.76, p = 0.025. The rate of death or MI at 6 months was also significantly reduced (9.5% vs. 7.3% respectively, OR 0.74; p < 0.001). Conclusions: In patients with UA/NSTEMI treated with the GP IIb/IIIa inhibitor tirofiban, an early invasive strategy resulted in a significant reduction in major cardiac events. These data suggest a need to update the ACC/AHA Unstable angina guidelines, and to modify the clinical approach to managing unstable angina with broader use of an early invasive strategy with upstream GP IIb/IIIa inhibition.

Effect of the Angiotensin Receptor Blocker Valsartan on Morbidity and Mortality in Heart Failure: the Valsartan Heart Failure Trial (Val-HeFT)

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In order to assess the efficacy of the angiotensin receptor blocker valsartan in the treatment of heart failure (HF), 5010 patients were studied in 16 countries on 4 continents. Patients with chronic HF [NYHA II (62%), III (36%) and IV (2%)], ejection fraction (EF) <40% and left ventricular diastolic transverse diameter (LVDD) >2.9 cm/m2 were randomly assigned to receive placebo (P) or valsartan (V) (titrated to 160 mg BD) in addition to all other appropriate therapy including ACE inhibitors (93%), beta blockers (68%), diuretics (88%) and digoxin (67%). Primary end-points were all-cause mortality (M) and mortality plus morbidity (M+M), which included hospitalization for heart failure (adjudicated), cardiac arrest with resuscitation, or need for intravenous support for worsening heart failure. Time to death was similar in the two groups but time to first M+M event was significantly reduced by 13.3% by V (32.1% in P, 28.8% in V; p = 0.01). HF hospitalization was significantly reduced by 27.5% by V (18.5% in P, 13.9% in V; p < 0.001). The benefit of V on M+M was particularly prominent in patients not taking a beta blocker (37% to 30.8%, p = 0.001) and in those taking a blocking and ACE inhibitor (42.5% to 24.9%, p < 0.001). The benefit on M+M was accompanied by significant improvements in NYHA class, quality of life, and EF. These data demonstrate clinical efficacy of valsartan in heart failure in patients already receiving standard HF therapy.

The Department of Veterans Affairs Aneurysm Detection and Management (ADAM) Study.

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Aortic aneurysm is the 13th leading cause of death in the US, and most of these deaths are due to rupture or elective repair of abdominal aortic aneurysm (AAA). Because AAA diameter is the strongest predictor of patient AAA rupture, a principal question in AAA management is the appropriate AAA diameter at which to offer elective repair to both prevent rupture and minimize deaths from elective surgery. The Surgery versus Surveillance (SVS) study enrolled 1136 veterans aged 50–79 years with AAA 4.0–5.4 cm. Of these, 99% were male, 94% were white, and 42% had coronary artery disease. Mean follow-up was 4.8 years. AAA repair was performed in 92% of the Surgery group and 61% of the Surveillance group (8.8% against protocol) by the end of the 8-year study. Operative mortality at 30 days was 1.8% overall (Surgery 2.1%, Surveillance 1.5%). There was no significant difference between the two groups in the primary outcome of long-term death. Deaths occurred in 141 of 569 Surgery patients and in 121 of 567 Surveillance patients (RR 1.20, 95% CI 0.94, 1.53, p = 0.14). This non-significant trend toward increased mortality in the Surgery group was strongest in patients with the smallest AAA at entry (4.0–4.4 cm, RR 1.43, 95% CI: 0.89, 2.30, p = 0.14), although the operative mortality in this Surgery subgroup was only 0.7%. This observation is consistent with a previous VA Cooperative Study finding that late survival may be reduced after major peripheral vascular surgery. Nine Surveillance patients (0.5% per year at risk) had AAA rupture, of which two were incidental findings at elective repair and five resulted in death. In the Surgery group, one patient who delayed elective repair had non-fatal AAA rupture, and another died of thoricacic aortic aneurysm rupture after AAA repair. In addition to 30-day post-operative deaths and known rupture deaths, there were 25 sudden deaths in the Surveillance group and 23 in the Surgery group. We conclude that long-term survival is not improved by repair of AAA smaller than 5.5 cm even when operative mortality is very low, that delaying repair until the AAA has enlarged to 5.5 cm does not increase operative mortality, and that rupture is rare in this population.

Fluvastatin in Acute Myocardial Infarction: Effects on Early and Late Ischemia and Events: the FLORIDA Trial

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In post-myocardial infarction (MI) patients, residual ischemia is related to an adverse cardiac outcome. Thus, early initiation of statin treatment may be particularly beneficial after MI. The “Fluvastatin On Risk Diminishing after Acute myocardial infarction” (FLORIDA) trial is a prospective, placebo-controlled multicenter trial, designed to study the effect of Fluvastatin 80 mg per day, on new-onset ambulatory ECG monitoring (AECG) and major adverse cardiac events (MACE). Included were 540 patients (83% male, age 61 ± 11 yrs) with an acute myocardial infarction (43% anterior) and a cholesterol value <6.5 mmol/L (mean 5.4 ± 0.7). AECGs were performed during admission for MI, after 6 weeks and 12 months. Fluvastatin 80 mg/day or placebo were administered during admission and for one year. Events were adjudicated by a blinded monitoring committee. After 12 months treatment, fluvastatin lowered LDL cholesterol from 3.5 to 2.7 mmol/L and placebo from 3.6 to 3.9 mmol/L (p < 0.001). At baseline, 6 weeks and 12 months ischemia on AECG was present in 12%, 8% and 6% of the patients on fluvastatin and on 13%, 6% and 10% of the patients on placebo (p > 0.14). On fluvastatin the ischemic burden (in sem) was 19.4 ± 5.2 and ± 2.1 mm–min on placebo 16.6 ± 5.3 ± 3.1 ± mm–min (p = 0.14). At baseline, 12 months and 1 year after MI on AECG was highly predictive for adverse outcome after one year. Fluvastatin had no beneficial effect on post-MI ischemia after 6 weeks or 12 months. Although not powered for this purpose, this study showed no effect of fluvastatin on MACE. A positive trend though, was observed in patients with severe ischemia at baseline.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Trial: Effects of Intensive Atorvastatin Treatment on Early Recurrent Events After an Acute Coronary Syndrome

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Background: Previous trials have demonstrated that treatment with conventional doses of statins, initiated in patients with stable coronary heart disease, reduces death and non-fatal ischemic events over periods of years. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial tested the hypothesis that intensive treatment with atorvastatin, initiated immediately after an acute coronary syndrome, reduces death and non-fatal ischemic events in the ensuing 16 weeks. Methods: We conducted a randomized, double-blind trial comparing atorvastatin (80 mg daily) with placebo in 3086 patients with unstable angina or non-Q-wave acute myocardial infarction. Treatment was initiated 24 to 96 hours after hospitalization and continued for 16 weeks. The primary combined endpoint was death, non-fatal acute myocardial infarction, cardiac arrest with resuscitation, or worsening angina with new objective evidence of ischemia requiring emergency rehospitalization, analyzed by time to first event. Secondary endpoints included the components of the primary endpoint as well as stroke, coronary revascularization, worsening congestive heart failure, and worsening angina without new objective evidence of ischemia. Results: A primary endpoint event occurred in 228 patients in the atorvastatin group (14.8%) and 269 patients in the placebo group (17.4%) (relative risk 0.84; 95% confidence interval 0.70 to 1.00; P = 0.048). The greatest effect of atorvastatin was on worsening angina with new objective evidence of ischemia requiring emergency rehospitalization (relative risk 0.74; 95% confidence interval 0.57 to 0.95; P = 0.02). Death, non-fatal myocardial infarction, and cardiac arrest were less frequent in the atorvastatin group than in the placebo group, but the differences were not statistically significant. Of the other secondary endpoints, there were significantly fewer strokes in the atorvastatin group than in the placebo group (12 versus 24 events). In the atorvastatin group, mean LDL cholesterol declined from 123 to 72 mg/dl (3.2 to 1.9 mmol/L). Abnormal liver transaminases (>3 times upper limit of normal) occurred in 2.5% and 0.6% of patients in atorvastatin and placebo groups, respectively. Conclusion: Early, intensive lipid-lowering with atorvastatin reduces recurrent ischemic events in the first 16 weeks after an acute coronary syndrome.
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