Late-Breaking Clinical Trial Abstracts From the American Heart Association’s Scientific Sessions 2008

Featuring: Late-Breaking Clinical Trials—Plenary Sessions I–IV; and other Clinical Trials to include—Translational Trials and Strategies: First in Man, Clinical Trials in ACS and Interventional Cardiology, and New Trials in Electrophysiology and Pacing
Rosuvastatin in the Prevention of Cardiovascular Events Among 17,802 Men and Women with Elevated Levels of C-Reactive Protein: The JUPITER Trial

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Background: Increased levels of the inflammatory biomarker high sensitivity C-reactive protein (hsCRP) predict cardiovascular events, even when cholesterol levels are low. As statins lower hsCRP as well as cholesterol, we hypothesized that individuals with elevated hsCRP but without hyperlipidemia might benefit from statin therapy. Methods: In an investigator-initiated, multi-national, randomized, double-blind, placebo-controlled trial conducted at 1,300 sites in 26 countries, 17,982 apparently healthy men and women with LDL < 130 mg/dL, and hsCRP > 2 mg/L were randomly allocated to rosuvastatin 20 mg daily or to placebo and then followed for the occurrence of a first major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or cardiovascular death). Median levels of LDL, HDL, TG, and hsCRP at entry into JUPITER were 108 mg/dL, 49 mg/dL, 118 mg/dL, and 4.3 mg/L, respectively. The JUPITER trial included 6,801 women and 25 percent of the randomized cohort are of minority background. Results: Based on a range of expected event rates in the placebo group, power calculations for the JUPITER trial suggested that a sample size between 15,000 and 19,000 participants would be needed to detect a relative risk reduction of 25 percent, assuming an average follow-up period of 3 to 4 years and a 5 percent drop-out rate. However, on March 29, 2008, the Independent Data and Safety Monitoring Board of the JUPITER trial unanimously recommended early termination after a mean follow-up of only 2 years due to the emergence of an unacceptable benefit of rosuvastatin on the trial primary endpoint in the absence of any substantive safety hazard. Conclusions: Formal presentation of the JUPITER trial results will be made for the first time at the AHA meeting in November 2008.

Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Trial (JPAD trial)

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Background: Previous large trials have investigated the effects of low-dose aspirin on primary prevention of cardiovascular events in healthy individuals or in patients with hypertension or cardiovascular risk factors, but not in type 2 diabetes. We intended to examine the efficacy of low-dose aspirin for primary prevention of cardiovascular events in type 2 diabetic patients. Methods: The JPAD trial was a multi-center prospective randomized open-label blinded-endpoint study started in December 2002. The study population was patients with type 2 diabetes mellitus without history of atherosclerotic disease, who were randomly assigned to the aspirin group (81 or 100 mg / day) or the non-aspirin group. Primary endpoint was atherothrombotic events including fatal or nonfatal coronary heart disease, fatal or nonfatal cerebrovascular disease, and peripheral arterial disease. Secondary endpoint included each and combinations of primary endpoints as well as death from any cause. We also analyzed hemorrhagic, and gastrointestinal events. Results: We recruited 2539 patients (mean age: 65.10 years, and 1262 and 1277 patients were assigned to aspirin and non-aspirin group, respectively. Median follow up period was 4.37 (95%CI:4.35–4.39) years. 154 atherothrombotic events occurred (13 fatal); 68 in the aspirin group and 86 in the non-aspirin group (RR = 0.80, 95% CI, 0.50–1.10, log-rank test, p = 0.2). There were 11 fatal coronary and cerebrovascular events (in 1 in the aspirin group, 10 in the non-aspirin group). The incidence of fatal coronary and cerebrovascular events was significantly lower in the aspirin group than in the non-aspirin group (RR = 0.30, 95%CI = 0.01–0.79, p = 0.004). In 1363 patients age 65 years or older, the incidence of atherothrombotic events was significantly lower in the aspirin group than in the non-aspirin group (RR = 0.68, 95%CI = 0.46–0.98, p = 0.047). There was an increased risk of hemorrhagic strokes in the aspirin group. Conclusion: Aspirin was associated with a nonsignificant reduction in total atherothrombotic events and a significant reduction in fatal coronary and cerebrovascular events in patients with type 2 diabetes mellitus. This trial also indicated that diabetic patients aged 65 years or older would benefit from aspirin.

SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine): Randomized Comparison of Folic Acid 2 mg Plus Vitamin B1 1 mg Daily versus Placebo for 7 Years in 12,064 Myocardial Infarction Survivors

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Background: In observational studies, 3–4 μmol/L lower blood homocysteine is associated with 10% proportionally lower risk of CHD and 20% lower risk of stroke. Randomized trials have not yet provided convincing evidence that lowering blood homocysteine levels with folic acid reduces cardiovascular events. Large long-term randomized trials of folic acid supplementation are needed to assess the balance of efficacy and safety reliably. Methods and Results: Between Sept 1998 and Oct 2001, 12,064 MI survivors from 88 UK hospitals were randomly allocated folic acid 2mg plus vitamin B1 1mg daily versus matching placebo. Follow-up was at 2, 4, 8 and 12 months, and then 6-monthly, for a mean of 6.7 (SD 1.5) years. Allocation to folic acid and vitamin B1 yielded reductions in homocysteine levels of 3.2μmol/L at 1 year and of 3.6μmol/L over the whole trial period. The prespecified primary outcome was MVE, which was defined as non-fatal MI, coronary death or coronary revascularisation (major coronary event: MCE), any type of stroke, or any non-coronary revascularisation. MVEs were recorded among 1537 (25.5%) patients allocated folic acid and vitamin B1 versus 1492 (24.7%) allocated placebo corresponding to a risk ratio of 1.04 (95%CI 0.97–1.12). MCEs were recorded among 20.4% vs 19.6% of the participants; stroke among 4.5% vs 4.4% and non-coronary revascularisation among 3.0% vs 2.5%. No significant differences were observed in vascular (9.5% vs 9.0%) or non-vascular (6.8% vs 6.7%) mortality, or in cancer incidence overall (11.2% vs 10.5%) or at any particular site. As well as considering other serious adverse events, the effects on cognitive function and hearing were assessed. SEARCH is the largest randomized trial to assess the effects of homocysteine-lowering treatment. Despite maintaining a 3–4μmol/L lower homocysteine levels for 7 years, there were no significant effects on the incidence of any type of vascular event, cancer or other major outcome. These results are consistent with previous results recorded previously from smaller and less proactive trials. They indicate that widespread folic acid supplementation (in order to avoid neural tube defects) through fortification of flour is safe, but will not materially affect vascular disease or cancer.

SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine): Randomized Comparison of Simvastatin 80 mg versus 20 mg Daily for 7 Years in 12,064 Myocardial Infarction Survivors

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Background: Previous studies have shown that statin therapy reduces the incidence of major vascular events by about one-fifth per 40mg/dL LDL-cholesterol reduction. Higher statin doses may produce larger reductions in vascular events, but large long-term randomized comparisons of different doses are needed to assess the balance of efficacy and safety reliably. Methods: Between September 1998 and October 2001, 12,064 myocardial infarction (MI) survivors from 88 UK hospitals were randomly allocated simvastatin 80mg versus 20mg daily. There were...
10,012 men and 2052 women; average age 64 (SD 9) years. At randomization, 33% reported coronary revascularization, 7% cerebrovascular disease, 11% diabetes and 42% treated hypertension. Allocation to simvastatin 80mg daily yielded further LDL-reductions of 0.5 mmol/L at 2 months and 0.3 mmol/L at 5 years. Primary outcome is major vascular event (MVE), which is defined as non-fatal MI or coronary death, any stroke, or any arterial revascularization. During median follow-up of 7 years, about 3000 participants have had MVEs (1500 non-fatal MI or coronary death; 500 strokes;1000 revascularisations), 1300 have developed cancer and 2000 have died (1000 vascular and 1000 non-vascular). 

Conclusion: SEARCH is the largest randomized trial to assess the effects of more intensive statin therapy directly. The large numbers of vascular and non-vascular events during the prolonged treatment period provide good statistical power to detect plausible further reductions in major vascular events, while also providing a reliable assessment of the safety of more intensive LDL-lowering. 

Final results of SEARCH would be presented during the AHA meeting and discussed in the context of the other randomized evidence. The implications of these findings are important because they will help to resolve the existing uncertainty about the value of more intensive cholesterol-lowering therapy.

Late-Breaking Clinical Trials II
Subspecialty: General
Hall F
Abstracts 1309–1315

Randomized Comparison of Rivaroxaban, an Oral Direct Factor Xa Inhibitor, with Placebo in Patients with Acute Coronary Syndromes: The ATLAS ACS-TIMI 46 Trial
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Background: Rivaroxaban is a novel oral direct Factor Xa inhibitor that has been effective in preventing venous thromboembolism after major orthopedic surgery. The efficacy and safety of rivaroxaban than following acute coronary syndromes (ACS) has not previously been evaluated.

Methods: ATLAS ACS-TIMI 46 is a phase II, international, randomized, double-blind, placebo-controlled, dose-escalation study conducted in post-ACS patients to evaluate the efficacy and safety of rivaroxaban in combination with aspirin (Stratum 1) or aspirin + thienopyridine (Stratum 2). Patients received rivaroxaban (total daily dose: 5, 10, 15, or 20 mg as a once-daily or twice-daily regimen) or placebo and were followed for 6 months.

Results: A total of 3,491 subjects (760 in Stratum 1; 2,731 in Stratum 2) were randomized at 297 sites in 27 countries. The final visit for the last patient will be conducted by September 21, 2008. The mean age at 57 years (range: 24–89); 77% are male; 19% have diabetes; and 21% had a prior MI. On presentation, 52% had a STEM; 65% of subjects underwent PCI for their index event. Subjects are being followed for efficacy (death, MI, stroke, and severe recurrent ischemia requiring revascularization) and safety (TIMI major and minor bleeding and bleeding requiring any medical attention) events. An independent clinical events committee is adjudicating all components of the endpoints. Efficacy and safety results will be presented.

Conclusion: ATLAS ACS-TIMI 46 is a randomized clinical trial investigating the relative risks and benefits of the addition of the novel anticoagulant rivaroxaban to either single or dual antiplatelet therapy in a contemporary cohort of post-ACS patients.

Drug-Eluting and Bare Metal Stenting in Patients with Diabetes Mellitus: Results from the Mass-DCR Age

Background: Patients with diabetes mellitus (DM) are at high risk of restenosis, myocardial infarction (MI) and cardiac mortality following coronary stenting and the long-term safety of drug-eluting stents (DES) relative to bare metal stents (BMS) in DM is uncertain. We report on a large consecutive series of patients with DM followed for 3 years after DES and BMS from a regional contemporary US practice with mandatory reporting.

Methods: All adults with DM undergoing percutaneous coronary intervention (PCI) with stenting between April 1, 2003 and September 30, 2004 at all acute care non-federal hospitals in Massachusetts (MA) were identified from a mandatory state database. According to index admission stent type, patients were classified as DES treated if all stents were drug-eluting and BMS-treated if all stents were bare metal; patients treated with both types of stents were excluded from the primary analyses. Mortality was derived from vital statistics records with complete 3 year follow up, and MI and revascularization rates, from the state database with 2 years follow up on the entire cohort. Risk-adjusted mortality, MI, and revascularization differences (DES-BMS) were estimated using propensity score matching, based on clinical, procedural, hospital, and insurance information collected at the index admission. Results: DM was present in 50% of the population (treated with DES or BMS during the study. Patients with DM were more likely to receive DES than BMS (66.1% vs. 33.9%, p<0.001). The unadjusted cumulative incidence of mortality at 3 years was 14.4% in DES vs. 22.2% in BMS (p<0.001). Based on propensity score analysis of 1:1 matched DES vs. BMS patients (1476 DES:1476 BMS), the risk-adjusted mortality at 3 years was 17.5% vs. 20.7% risk difference -3.2% [-6.0%, -0.4%], p=0.02) and MI and target vessel revascularization rates at 2 years were 10.8% vs. 14.1% [-3.3% [-5.7%, -1.0%], p=0.062) and 12.7% vs. 17.1% [-5.4% [-8.1%, -2.6%], p<0.001 respectively. 

Conclusion: In a real-world diabetic patient population with mandatory reporting and follow-up, DES were associated with reduced mortality, MI, and revascularization rates at long-term follow-up compared with BMS.

Randomized Comparison of Early vs. Delayed Invasive Strategies in High-Risk Patients with Non-ST-Segment Elevation Acute Coronary Syndromes: Main Results of the TIMING of intervention in Acute Coronary Syndrome (TIMACS) Trial
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Background: Randomized trials have trials have demonstrated a benefit of an invasive management strategy in patients with non-ST segment elevation acute coronary syndromes (ACS). However, the optimal timing of when to intervene in these patients has not been determined.

Study Design: A prospective, multi-center, multi-national, randomized trial comparing early versus delayed invasive strategies in patients with high risk ACS.

Hypothesis: An early invasive strategy will be superior to a delayed invasive strategy in reducing death, MI or stroke.

Inclusion Criteria: Patients presenting with symptoms/signs compatible with UA/NSTEMI and within 24 hours from symptom onset and at least two of the following 3 criteria: Age ≥60, Elevated Troponin T or I or CKMB or ischemic ECG changes.

Sample Size: Approximately 3000 patients from 100 centers in 30 countries

Randomized Treatments: Early Invasive Strategy defined as coronary angiography as soon as possible (and no later than 24 hours) followed by anatomy-driven intervention (PCI or CABG). Delayed Invasive Strategy defined as coronary angiography after 36 hours followed by anatomy-driven intervention (PCI or CABG).

Primary Outcome: Composite of Death, Myocardial Infarction or Stroke at 6 months

Study Power: Assuming a control event rate of 12% in the delayed invasive group, the study will have 80% power to detect a 27% relative risk reduction. Progress: The last patient will be included in early July 2008. Will the last followup visit will be in mid October and we will finalize the data in early November for presentation at the AHA meeting.

Tailored Clopidogrel Loading Dose According to Platelet Reactivity Monitoring to Prevent Stent Thrombosis
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Background: Stent thrombosis represents a major pitfall of percutaneous coronary revascularization. Enhanced platelet reactivity inhibition has been associated with a reduction in thrombotic events in patients undergoing percutaneous coronary intervention (PCI). We aimed to investigate the impact of tailored clopidogrel loading dose (LD) according to platelet reactivity monitoring, using the VASP index, on definite stent thrombosis (DST) in patients undergoing PCI. 

Methods: A multicenter prospective randomized study included all consecutive patients included with clopidogrel low response after a 600mg LD of clopidogrel undergoing PCI. The control group included 214 patients and the VASP guided group 215 patients who received up-to 3 additional 600mg clopidogrel LD to obtain a VASP index <50% before PCI. The primary end-point was the rate of DST at one month. Secondary end-points were the rate of major adverse cardiovascular events (MACE) and of bleeding.

Results: Despite 2400 mg LD of clopidogrel 8% of the patients randomized to the VASP-guided group remained low-responders. The rate of definite stent thrombosis was significantly lower in the VASP-guided group compared to the control group (5.5 vs 4.2 %, p<0.01). Fifty five percent of patients who had stent thrombosis had GP IIb/IIIa inhibitors at the time of the index procedure. The rate of MACE was also significantly reduced.

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lower in the VASP-guided group (0.5% vs 8.9%; p < 0.001). There was no difference in the rate of bleeding (control vs VASP-guided group 2.8% vs 3.7%; p = 0.8). Conclusion: Tailored clopidogrel loading dose according to platelet reactivity monitoring decreased the rate of early definite stent thrombosis after PCI without increased bleeding.

Late-Breaking Clinical Trials III 
Subspecialty: General 
Hall F

Abstracts 3318–3324

Morbidity and Mortality Outcomes from Aerobic Exercise Training in Heart Failure: Results of the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) Study
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Background: Aerobic exercise training in heart failure (HF) patients (pts) improves symptoms, exercise capacity, and quality of life (QOL). HF guidelines recommend exercise training for stable outpts. Prior studies have not been powered to evaluate exercise training and clinical outcomes. HF-ACTION tested the hypothesis that aerobic exercise training in HF pts will improve clinical outcomes. Methods: HF-ACTION was a multicenter, randomized (1:1) controlled trial of usual care + exercise training vs. usual care alone in stable pts with LVEF ≤35% and NYHA class II-IV HF. Key exclusions were regular exercise, cardiac devices limiting target heart rate, and exercise test results indicating training may be unsafe. The intervention included 36 supervised training sessions (goal 3 times/week). Exercise intensity was increased based on heart rate reserve and rate of perceived exertion. Pts were then provided with home equipment and encouraged to exercise at home 5 times/week. The usual care arm received the ACC/AHA recommendation to perform 30 minutes of moderate intensity activity most days of the week, but no additional instructions for exercise were given. Adherence was measured for the exercise training arm, and physical activity was recorded for the usual care group. Pts were followed for at least 1 year. The primary endpoint was the composite of all-cause mortality and all-cause hospitalization. The study was designed to achieve 90% power to detect an 11% reduction in the 2 year primary event rate, accounting for nonadherence and crossover. Secondary endpoints included individual components of the primary endpoint, cause-specific mortality/morbidity, cardiopulmonary fitness measures, QOL, and cost. Results: Between 4/03 and 2/07, 2331 pts were enrolled. Median age was 59 years, 28% were women, and 40% were minorities. Mean LVEF was 25%, and 51% had an ischemic etiology. Baseline treatments included ACE-inhibitor or angiotensin receptor blocker, 94%, beta blocker, 55%; ICD or bi-ventricular pacemaker, 45% overall and 53% in ischemic pts. Median follow-up was 2.5 years. Primary endpoint data will be presented. Conclusions: HF-ACTION will reveal the effect of exercise training on important clinical outcomes, including survival, in pts with systolic HF.

The Effect of Subcutaneous Treatment with Interferon-Beta-1b Over 24 Weeks on Safety, Virus Elimination and Clinical Outcome in Patients with Chronic Viral Cardiomyopathy
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Thirty-one centers from 7 European countries participated in this randomized, double-blinded, placebo-controlled, parallel group, multicenter phase II study evaluating the safety and efficacy of two doses of interferon beta-1b (IFNβ-1b) versus placebo in patients with biopsy-proven chronic viral cardiomyopathy (CVC). The diagnosis of CVC for the target population was based on the presence of chronic inflammation and the presence of viral (adenovirus, parvovirus) and/or enterovirus and/or reduction in parvovirus in endomyocardial biopsies taken 12 weeks after randomization. In the three treatment arms, patients received 2 different doses of IFNβ-1b or placebo, given subcutaneously every other day for 24 weeks. The primary variable was the presence of adenovirus, enterovirus and/or reduction in parvovirus in endomyocardial biopsies taken 12 weeks after the end of treatment. For the parvovirus group, virus-elimination or load reduction was assessed using a quantitative assay by defining a suitable threshold value. Secondary efficacy variables were change in NYHA functional class, 6-minute walking test, single cardiac symtoms and quality of life. The occurrence of clinical events (CVC) was the primary endpoint. Secondary endpoints were clearance or reduction of virus load with favorable effects on quality of life, NYHA functional class and patient global assessment in patients with CVC.

Midirolateral pro-Antedromenil (proADM) vs BNP and NTproBNP as Prognosticator in Heart Failure Patients: Results of the BACH Multinational Trial
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Background: Natriuretic peptides have well established prognostic value in acute heart failure (AHF). NTproADM is a marker of endothelial function and previous studies suggest it to be a primary composite endpoint of death, non-fatal MI, or stroke, hospitalization for HF, unstable angina, or cardiac arrhythmia. Secondary endpoints include HF mortality or hospitalization, all-cause and cardiovascular mortality, non-fatal MI or stroke, and quality of life. Methods: I-PRESERVE is a randomized, double-blind, placebo-controlled trial. It was continued until 1,440 primary events occurred, providing 90% power to detect a 14.5% relative risk reduction of the primary endpoint with a 2-sided α = 0.05 in an intention to treat analysis of time to first event. Pts with LVEF ≤45% and ≥60 years with NYHA class II-IV CHF symptoms and a HF admission within 6 months or NYHA III-IV symptoms and supportive evidence for HFPEF were eligible for enrolment. Major exclusions were prior LVEF <40%, primary valvular or cardiomyopathic disease, uncontrolled conditions that might limit patient life expectancy to <5 years or cause symptoms that mimic HF. Patients taking an ARB were excluded, and only 1/3 Pts could be on an ACE inhibitor at entry. Ibaseran or matching placebo was initiated at 75 mg daily and uptitrated to 150 mg and 300 mg at 2 week intervals as tolerated. Results: Commencing in June 2002, 4,129 Pts (mean EF 59±9%; mean age 72 years; 60% women) were randomized. 88% had a history of hypertension (mean entry BP 136/89, 29% atrial fibrillation, 27% diabetes, 23% prior MI, and 10% stroke or TIA. Baseline medications included diuretics (84%), beta-blockers (59%), calcium blockers (40%), ACE inhibitors (25%), spironolactone (15%). The study ended on April 17, 2008, when an estimated 1,440 primary endpoints had occurred. The I-PRESERVE results are being presented for the first time at this meeting. Conclusion: I-PRESERVE is the largest trial conducted in Pts with HFPEF. It will determine whether ibaseran is effective in reducing the major cardiovascular events that affect this population and provide novel insight into the clinical course of this syndrome.
strong prognosticator in AHF patients. Methods: The BACH Multinational Trial was a prospective, 1.25-center multiple international serum biomarker study of 1641 patients presenting to the emergency department (ED) with shortness of breath (SoB). The primary endpoint was to test for superiority of mProADM vs BNP to predict 90-day mortality. Secondary endpoints included to test for superiority in NTproBNP, and to perform these tests in all patients presenting with SoB to the ED. Physicians were blinded to mProADM values. The gold standard diagnoses of HF were established by 2–3 cardiologists. Clinical lab troponin values (Tnl or Tnt) were judged as elevated if above the local normal range. Results: Of 1641 BACH patients, 568 (34.6%) had a diagnosis of HF. Of these, 65 (11.4%) died within 90 days. The prognostic accuracy of mProADM (73.1% correct) was superior to BNP (60.8%, p < 0.001) and NTproBNP (63.0%, p < 0.001). These findings held true for all 1641 enrolled patients (130 deaths) and for the 477 AHF patients admitted to the hospital (all p < 0.001), satisfying the primary and secondary prognostic endpoints of the BACH Multinational Trial. The hazard ratios (HRs) comparing the 2nd, 3rd, and 4th ADM quartiles to the first in all 1641 patients were 7.4 (95% CI 2.2–24.8, p < 0.001), 10.7 (3.3–35.0, p < 0.001), and 26.8 (9.5–85.1, p < 0.001), respectively. Troponin values were available in 511 of 568 HF patients, and in 107 (20.9%) patients they were elevated. As shown below, mProADM significantly predicted 90-day mortality in Cox analyses independently of either BNP or NTproBNP in models both with and without troponin. Conclusions: mProADM is superior to BNP and NTproBNP, regardless of troponin levels, for predicting 90-day mortality in patients with shortness of breath and acute heart failure. 

Late-Breaking Clinical Trials IV

Subspecialty: General

Hall F

Abstracts 5217–5223

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A Prospective Randomized Controlled Trial of the Impact of Home INR Testing on Clinical Outcomes: The Home INR Study (THINRS), VA Cooperative Study #481

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Background: Warfarin anticoagulation reduces thromboembolic complications in patients with atrial fibrillation and mechanical heart valves but effective management is complex and it is common for patients to be above or below target INR range. Point-of-care INR devices can be used by patients in their homes. By allowing greater testing frequency and patient involvement, such home testing has the potential to improve clinical outcomes. We tested whether weekly home INR testing would reduce the risk of stroke, major bleed and death compared to monthly clinic testing. Methods: Patients on warfarin due to mechanical heart valves or atrial fibrillation were trained in the use of the iTec ProTome® POC-INR device and tested for competency after 2 to 4 weeks. Subjects competent in device use were randomized to either weekly home testing or monthly clinic testing. In a substudy about 100 subjects home tested twice a week and about 100 home tested once a month. The primary endpoint was time to first event: stroke, major bleed, or death. Sample size was based on an estimated composite annual event rate of 3.5% in the clinic testing arm, which would result in 375 individuals in the home testing arm. Secondary outcomes included time in target range, major cardiac infections, non-stroke thromboembolisms, minor bleeds, patient satisfaction, competence and compliance with PST, anticoagulation related quality of life, and cost effectiveness. Results: 3,745 subjects at 28 VA Medical Centers were enrolled in Part 1 and 2,922 subjects (78%) were randomized into Part 2. Informed consent was obtained from all subjects. The primary endpoint arm had 672 patients (665 subjects randomized), and the monthly clinic testing arm had 673 patients (666 subjects randomized). Subjects were followed for 2.0 to 4.7 years, with 8,730 patient-years (PY) of follow-up: 4,495 PY in the home testing arm and 4,235 PY in the clinic arm. Time to first reported event was not significantly improved in the home testing arm (hazard ratio = 0.875 with 95% confidence interval of 0.761 to 1.033; p = 0.11 by log-rank test) for the primary endpoint or any of its three components (stroke, major bleed, death). Similar analyses to be conducted on adjudicated endpoints may indicate different findings. Time in target range was higher in the home testing group (95.9% vs. 62.2%, p < 0.001), as was patient satisfaction (47.7 vs. 49.1, p = 0.002). Conclusions: Weekly home INR monitoring may not improve the aggregate outcome of stroke, major bleed, or death, to the extent previously suggested. However, such monitoring does appear to improve time in target range and patient satisfaction with anticoagulation therapy. The study supports the notion that home testing is an acceptable alternative to routine care, and may be preferable when patient access to routine care is difficult (e.g., due to disability or geographic distance).

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Effect of Exercise Training on Health-related Quality of Life in Patients with Chronic Heart Failure: An HF-ACTION Substudy

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Background: Patients with heart failure have reduced exercise tolerance, resulting in lowered health-related quality of life. Exercise training may improve physical functioning, reduce symptoms, and improve health-related quality of life, but in previous studies effects of exercise training on health-related quality of life have been inconsistent. The NHLBI-funded Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study was designed to test the hypothesis that exercise training in heart failure patients will improve clinical outcomes. A secondary outcome was exercise training on health-related quality of life endpoints. Methods: The HF-ACTION ICT was a large multicenter, randomized (1:1), controlled trial (RCT) in medically stable patients with LVEF ≤ 35% and NYHA class II-IV heart failure. Patients were randomized to either usual care plus aerobic exercise training, consisting of 3 months of supervised aerobic exercise training followed by instruction on home-based training, or to usual care alone. The primary health-related quality of life endpoint was patient-reported health status, measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The KCCQ was administered at baseline, at 3 month intervals during clinic visits for the first year, and annually thereafter for up to 4 years. We will compare the treatment groups to determine mean differences in the KCCQ Overall Summary Scale and key subscales (Physical Limitations, Symptoms, Social Limitations, and Health-related Quality of Life) using linear mixed models following the intent-to-treat principle. Results: 2331 patients were enrolled. Median age was 59 years, 28% were women, and 40% were minorities. Mean LVEF was 25%, and 51% had an ischemic etiology. Median follow-up was approximately 2.5 years. Baseline clinical characteristics (peak VO2) and KCCQ scores will be presented, as will results from the analysis of change in overall KCCQ and its subscales by treatment arm. Conclusions: The HF-ACTION ICT results from a large number of patients will address the effect of aerobic exercise training on health status in patients with systolic heart failure, an outcome of primary importance from patients’ perspectives.

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Results of the APPROACH Trial: Assessment on the Prevention of Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History

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Background: Rosiglitazone (RSG), a member of the thiazolidinedione class of peroxisome proliferator-activated receptor-γ agonists, has effects on insulin resistance and other cardiovascular risk factors that may favorably affect progression of coronary atherosclerosis. Study Design: The APPROACH trial is a prospective, double-blind, placebo, randomized, active-controlled clinical trial comparing the effects of the insulin sensitizer RSG with an insulin secretagogue, glipizide, on the progression of coronary atherosclerosis. Patients with type 2 diabetes and coronary artery disease undergoing clinically indicated coronary angiography or percutaneous coronary intervention are randomized to receive RSG or glipizide for 18 months using a glycemic titration algorithm designed to provide comparable glycemic control between treatment groups. The primary endpoint is the change in percent atheroma volume from baseline to study completion in a non-intervened coronary artery, as measured by intravascular ultrasound (IVUS). Cardiovascular events are adjudicated by an Endpoint Committee and patient safety monitored by an Independent Data Monitoring Committee. Results: A total of 672 patients were randomized to double-blind treatment at 92 centers in 19 countries. At baseline, mean age was 61 years, HbA1c 7.2%, body mass index 29.5 kg/m², and median duration of diabetes 4.8 years. The majority of patients were receiving oral antidiabetic monotherapy (53.3%) at baseline, with 27.5% receiving dual-combination therapy and 17.9% treated with diet and exercise alone. Sixty-eight percent of patients had dyslipidemia, 79.9% hypertension, and 24% had a prior myocardial infarction. Follow-up IVUS examinations are expected to be completed in Summer 2008, with study results available for presentation at AHA Scientific Sessions. Conclusions: The APPROACH trial is the largest cohort of type 2 diabetic patients with type 2 diabetes of any IVUS study. APPROACH will compare the glucose-independent effects of RSG with glipizide on the progression of coronary atherosclerosis and provide additional data on the cardiovascular safety of RSG in patients with type 2 diabetes and coronary artery disease.

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A Novel Family-Based Intervention Trial to Improve Heart Health (FIT): Results of a Randomized Controlled Trial

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Family members of patients with CVD may be at increased risk due to shared genes and lifestyle. We hypothesized that hospitalization for CVD may represent a “motivational moment” for family members to take action for lifestyle change. The question is whether a Nicotine诫gated randomization controlled trial was to test the effectiveness of a novel systems approach to screen
and educate family members about lifestyle at the time of hospitalization for CVD to improve adherence to prevention goals. Methods: Participants were adult family members (N = 501, 66% female, 36% non-white, mean age 48 yrs) of patients admitted with atherosclerotic CVD. Subjects were eligible for the primary prevention of CVD and were excluded if they were diabetic or pregnant. Individuals were randomized to a special intervention (SI) that received personalized risk factor screening, lifestyle change counseling by a registered dietitian, nurse-non health educators at regular intervals for 1 yr or to the control intervention (C) that received a general health message at baseline and only critical values for risk factors. Standardized CVD risk factors were obtained on all subjects at baseline and 1 yr by research assistants blind to group assignment (80% follow-up). Lipids were measured in the Columbia University CTSA Biomarker Laboratory. Diet was assessed by the validated Block 98 and MEDFICTS Questionnaires. Results: There was significant improvement in the SI vs C group in the mean % change in MEDFICTS diet score from baseline to 1 yr (p = .04, difference = 13.4%) and both groups showed significant improvements in HDL-C, saturate fat, dietary cholesterol, trans fat intake, LDL-C, and physical activity. HDL-C decreased in the SI group but not the SI group, and the mean % change in 3D-LC from baseline to 1 yr was significantly increased in the SI vs C group (p = .01, difference 3.5%). The SI subjects were more likely to exercise >3 days per week compared to controls at 1 yr (p < .0001). Conclusion: A family based, low cost intervention that focused on improving lifestyle and HDL-C beyond several lifestyle improvements made in controls. Hospitalization of a family member with CVD is a unique and motivational educational opportunity to lower individual CVD risk.

Translational Trials and Strategies: First in Man

I. Myocardial Delivery of AAV1/SERCA2a in Subjects with Advanced Heart Failure: A First-In-Human Clinical Trial

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Objectives: Deficiency of the cardiac sarcoplasmic reticulum ATPase pump (SERCA2a) represents a common abnormality in the decline of cardiac contractility and relaxation function in HF. Preclinical studies, restoration of this enzyme in a gene transfer utilizing a AAV1 viral vector (AAV1/SERCA2a) was well tolerated and resulted in significant improvement in cardiac function and energetics. The present study is designed to investigate safety and efficacy of AAV1/SERCA2a on cardiac performance, LV remodeling and functional status in subjects with advanced HF. Methods: 9 class A/B HF subjects (EF <50%) on maximal medical therapy with baseline anti-AAV1 neutralizing antibody (NAb) titers of <1:12 received intra coronary artery infusion of AAV1/SERCA2a. One of the following single doses was administered in an open-label dose-escalation manner: 1.4 x 1011, 6 x 1011, or 3 x 1012 DNase Resistant Particles. Subjects had ICDS (and CTR if indicated). Safety and efficacy assessments were scheduled at 3, 6, 9 & 12 months. Results: We present 6-month follow-up data for subjects in Cohorts 1 & 2 in the table (clinically meaningful changes are underlined). AAV1/SERCA2a demonstrated an acceptable safety profile in these advanced HF subjects. The subject in Cohort 1 with baseline NAB>1.2 failed to improve and went on to receive heart transplant. In contrast, significant improvement was observed in all NAB negative (<1:2) subjects of 4 with having a decrease of 1 NYHA Class, as well as improvement in number of other functional parameters. Conclusions: AAV1/SERCA2a resulted in an acceptable safety profile in subjects with advanced HF. Clinically meaningful improvements in functional status and/or cardiac function were observed in the majority of subjects receiving AAV1/SERCA2a. Although the number of subjects in each cohort is too small to conduct statistical analyses, qualitative evidence of biological activity could be detected in a number of subjects following gene transfer.

II. Three Months of Treatment with 5-Lipoxygenase Inhibitor VIA-2291 in Patients with Recent Acute Coronary Syndrome

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Background: There are currently no medications available to directly treat underlying inflammation of the blood vessel wall that can lead to plaque rupture and MI, ACS and stroke. Production of leukotrienes by 5-Lipoxygenase (5-LO) has been linked to atherosclerosis and plaque instability in humans and animal models. VIA-2291 is a potent 5-LO inhibitor that was approximately 1100 patients in clinical trials for asthma. The purpose of this study was to test whether inhibition of 5-LO by VIA 2291 in a dose ranging, double blind study in ACS patients would demonstrate safety and efficacy in inhibiting 5-LO, and provide some insight into VIA 2291 effect on inflammatory biomarkers related to CAD. Methods: 191 patients 3 weeks after ACS event were randomized to receive 25, 50, 100 mg VIA-2291 or placebo for 3 months. The primary endpoint was whole blood LTE4 (a measure of leukotriene biosynthesis) measured at trough drug level; secondary endpoints were urine LTE4 and serum hsCRP; and tertiary endpoints were other serum inflammatory biomarkers. Biomarkers were assessed by treatment group at baseline and weeks 2, 6, and 12. Results: Based on still blinded study population, baseline characteristics included age 37 - 79 years (med 57, SD 9.7); 84% male / 16% female; BMI range 17.2 - 46 (med 23.7); 79% <65; 21% 65-79; 66% <12; 33% 12-24; 11% >24. This study in post-ACS patients was designed to test the ability of VIA-2291 to inhibit leukotriene production in a dose-related fashion, and provide initial insight into the ability of VIA-2291 to reduce CAD associated inflammatory serum biomarkers such as hsCRP.

Three Months of Treatment with 5-Lipoxygenase Inhibitor VIA-2291 in Patients Selected for Elective Carotid Endarterectomy Surgery

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Production of leukotrienes by 5-Lipoxygenase (5-LO) has been linked to atherosclerosis and plaque instability in humans and animal models. VIA-2291 is a potent 5-LO inhibitor that was
previously studied in 1100 patients. The purpose of this study was to test whether inhibition of S-LO would demonstrate anti-inflammatory effects in plaque tissue surgically removed from patients undergoing carotid endarterectomy (CEA), assess safety, mechanism of action and inflammatory biomarkers in this target population. **Methods:** 50 patients with significant carotid artery stenosis (60–90%) were treated for three months with 100 mg qd of VA-2291 or placebo in a Phase 2, double blind, randomized study. Patients were clinically stable and asymptomatic at randomization. The primary endpoint was plaque macrophage density (CD68); secondary endpoints included plaque S-LO, whole blood LTB4, urine LTE4 and serum hCRP. **Results:** Baseline characteristics were well balanced between treatment groups in the evaluable population with a median age of 68 (60 – 72), 57% diabetes and 49% with systolic blood pressure (SBP) >2.0 mmHg. VA-2291 was generally well-tolerated. There were no serious or unexpected drug-related adverse events. Carotid plaques from patients treated with VA-2291 100mg qd for 12 weeks showed no difference in the mean % area of macrophages (Placebo: 7.83 ± 1.7, VA-2291: 7.18 ± 3.99, p=0.42, n=25) when compared to placebo. Infusions were 2 hrs in length and treated with stable HF medication. In Cohorts 1– 4, patients received 3 escalating i.v. doses of CK-452 and 1 placebo treatment, randomized into the dosing sequence. Infusions were 2 hrs in length and regular dose for two months. Total study period was ten months. The cut-off blood level was 10mmHg at the control period, and three drugs significantly reduced BP similarly (p<0.01). **Conclusion:** This first Phase II trial may support translation of this novel mechanism into populations with more advanced heart failure.

**Clinical Trials in ACS and Intervventional Cardiology**

**Subspecialty: Interventional cardiology**

**Auditorium B**

**Abstracts 2017–2020**

**3017 Long-Term Strut Coverage of Paclitaxel Eluting Stents Compared with Bare-Metal Stents Implanted During Primary PCI in Acute Myocardial Infarction: A Prospective, Randomized, Controlled Study Performed with Optical Coherence Tomography.**

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**Background:** The use of drug eluting stents in acute ST-segment elevation myocardial infarction (STEMI) remains controversial. The underlying necrotic core and intracoronary thrombus may increase the number of uncovered stent struts and subsequent late stent thrombosis (LST). **Purpose:** This study was designed to assess the long-term stent strut coverage in consecutive STEMI patients randomly treated with paclitaxel eluting stents (PES, TAXUS Express, Boston Scientific) or otherwise identical bare-metal stents (BMS, Express) at micro-scale level by Optical Coherence Tomography (OCT). **Methods:** HORIZONS-AMI was a prospective, open-label, multicenter trial that randomized 3602 patients with STEMI undergoing primary PCI to PES vs BMS, in a 1:1 ratio. In a formal single-center substudy we performed OCT at 13 months follow-up in 122 consecutive patients (200 successfully implanted stents) enrolled in HORIZONS-AMI. Images were acquired during automated pullback (1 mm/sec), with low pressure balloon occlusion and constant intracoronary inflow. Quantitative strut level analysis was performed at every 0.3 mm interval by an independent blinded core-laboratory. Lumen, stent and strut contours were semi-automatically delineated and neointimal stent coverage, thickness and wall apposition were determined for 360 chords (1 degree increments). Standard QCA and IVUS measures were also assed at blinded core laboratory. **Results:** Mean age was 62 yrs, 75% were male, 15% had diabetes, the LAD was the infarct-related artery in 49% and 69% had baseline TIMI 0–1 flow pre PCI. Thrombus aspiration was used in 11% of all pts. The number of stents implanted per patient was 1.75 ± 0.9 (median total stent length: 29 mm, 25°-75° percentile 20–49). OCT imaging at 13 months follow-up ended on May 2008. To date 40 stents and 16.737 stent struts have been analyzed. Clinical follow-up will be ongoing to 5 years. **Conclusions:** This study is the first large-scale prospective, randomized, controlled OCT study that will provide in vivo assessment of late stent strut coverage of PES implanted during primary PCI in STEMI, in comparison to BMS. Complete unblinded OCT, QCA and IVUS analysis will be available in November for presentation.

**3018 FrRace - Randomized Intra-Individual Comparison of Sirolimus-Eluting Cypher® Stent and Paclitaxel-Eluting Taxus® Stent for Coronary Revascularization.**

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**Background:** Sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES), as compared with bare-metal stents, reduce the risk of restenosis. It is unclear whether there are differences in safety and efficacy between the two types of drug-eluting stents by intra-individual analysis. **Methods:** We conducted a randomized, controlled single-blind trial comparing sirolimus-eluting and paclitaxel-eluting stents intra-individually in 112 patients with at least two de novo lesions undergoing percutaneous coronary intervention. The two stenoses were randomized either to SES (Cypher®) or PES (Taxus®). The primary endpoint was angiographic restenosis...
peripheral blood (33%), and 65 to standard therapy (32%). Mean age was 56.9 ± 9.7 years, 170 patients were male (85%), median ischemic time was 3.3 (2.3–4.5) hours, and there was TIMI 3 flow grade post PCI in 179 patients (90%). Details of the cell infusion, the occurrence of clinical events, and the outcomes for LV function will be presented at the AHA meeting.

Conclusion: Intracoronary cell therapy is safe and feasible in a multicenter setting. The primary endpoint of improvement in regional LV function will be reported at the AHA meeting.

New Trials in Electrophysiology and Pacing

Subspecialty: Clinical Electrophysiology/Pacing

La Nouvelle C

Abstracts 4078–4084

Evaluation of Efficacy and Safety of Remote Monitoring for ICD Follow-Up: The TRUST Trial

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Background: Remote monitoring (RM) of ICDs may provide daily, automatic device and patient status data and cardiac event notifications. TRUST tested the hypothesis that RM was safe and effective for ICD follow-up for 1 year in a prospective, randomized controlled clinical trial.

Methods: 1282 patients were randomized 2:1 to RM or to conventional (RM disabled) groups. Follow up checks occurred at 3, 6, 9, 12 and 15 months post-implant. In the RM arm, RM was used before office visits (OVs) at 3 and 15 months. At 6, 9, and 12 months, RM only was used but followed by ICDs if necessary. Conventional patients were evaluated with ICDs only. Follow up was “actionable” if system reprogramming/review or change in anti-arrhythmic therapy occurred. Scheduled and unscheduled ICDs (including responses to event notifications in RM) were quantified for each individual patient year (pt yr) of follow up. Incidence of death, strokes and surgical interventions (morbidity) was tracked in both groups.

Results: RM and conventional patients were similar in age (63.3 ± 12.9 vs. 64.1 ± 12.0 yrs, p = 0.30), gender (71.9% vs 72.4% male, p = 0.89), pathology (LVEF 29.1 ± 12.9 vs. 28.6 ± 9.8%, p = 0.47), coronary artery disease 64.5% vs 71.4%, p = 0.02, medications (β blockers 79.5% vs 75.8%, ACE inhibitors 42.4% vs 46.8%, statins 70.5% vs 68.8%, p = AD), indication (primary prevention 72.3% vs 74.2%, p = 0.50, and dual chamber implants 57.9% vs 50.7%, p = 0.76). RM reduced scheduled OVs by 54% and total OVs by 42% without affecting morbidity. Event notifications were managed using RM alone in 92% of cases. Of the remainder resulting in unscheduled OVs, 52.2% were actionable. RM follow up was “actionable” if system reprogramming/review or change in anti-arrhythmic therapy occurred. TRUST demonstrated that remote monitoring is safe, decreases the need for in-office visits, provides early detection of significant problems, and improves ICD surveillance without increasing unscheduled office visits. Remote monitoring is a safe alternative to conventional care.
symptoms were performed weekly for the first 8 weeks and monthly thereafter. The primary endpoint was freedom from documented symptomatic AF episodes. Secondary endpoints included AF frequency, total AF recurrence, and quality of life assessed by standardized SF-36 questionnaire. Results: Of 528 screened pts, 167 met criteria for enrollment, gave informed consent, and were randomized (106 CA: 61 AA). Mean age was 56 ± 11 yrs and 56 pts (34%) were female. Hypertension was present in 81 pts (49%), diabetes in 17 (10%), and structural heart disease in 14 (8%). Mean left atrial diameter was 40 ± 5 mm. A prior history of atrial flutter was present in 28%. The mean number of symptomatic AF episodes in the 6 mo prior to randomization was 63 ± 55 (range 3–720). There were no significant differences between groups. The final pt was enrolled October 11, 2007. Conclusions: The baseline characteristics of treatment groups in the Thermocool AF Trial were balanced. The final outcomes of the trial will be presented.

Microwave Ablation in Mitral Valve Surgery for Atrial Fibrillation (MAMA)

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Background: Microwave ablation in conjunction with open heart surgery is effective in restoring sinus rhythm (SR) in patients with atrial fibrillation (AF). However, no prospective randomized trial has reported its efficacy in patients assigned for isolated mitral valve surgery. Objective: To evaluate if complementary microwave ablation of permanent AF in concomitant mitral valve surgery will lead to a significant increase in restoration of SR compared to mitral valve surgery alone. Methods: 70 patients with permanent AF were included from 5 different centres in Sweden and Finland. They were randomly assigned to mitral valve surgery and left + right atrial microwave ablation or mitral valve surgery alone. The cardiologist responsible for follow-up and the patient were unaware if additional ablation was performed until the study was completed, i.e. double-blinded design. The primary endpoint was the presence of SR at 6 and 12 months. Secondary endpoints were the occurrence of predefined serious adverse events (SAE) and the use of antiarrhythmic drugs (Class I, II, III). Results: The mean duration of permanent AF before surgery was 52 ± 83 months (median = 12) in the ablation group compared to 34 ± 49 months (median = 11) in the control group (p = 0.44). Out of 70 randomized, 66 and 64 patients where available for evaluation at 6 and 12 months, respectively. At 12 months SR was restored in 81% in the ablation group vs. 36% in the control group (p = 0.001), corresponding figures at 6 months was 78% vs. 41% (p = 0.001). The overall 30-day mortality rate was 2.6%, with two deaths in the ablation group vs. zero deaths in the control group (p = 0.15). At 12 months the mortality rate was 7.1% (Ablation n = 3 vs. control n = 2; p = 0.04). No significant differences existed between the groups with regard to SAE during the in-hospital period and at the end of the study. Sixteen percent of patients randomized to ablation were on antiarrhythmic drugs compared to 6% in the control group after 1 year (p = 0.22). Conclusion: Microwave ablation of left and right atrium in conjunction with mitral valve surgery is safe and effectively restores sinus rhythm in patients with long-lasting permanent AF as compared to mitral valve surgery alone.

Clinical Impact of Pacing during the Onset of Revascularization after Acute Myocardial Infarction

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Background: Animal studies have shown that intermittent dysynchrony induced by ventricular pacing during early reperfusion reduces infarct size. This pacing postconditioning (PPC) also opens new possibilities for cardioprotection in the clinical setting. The Pacing duRing the OnseT of rEvasCularizaTion (PROTECT) study is the first clinical trial evaluating the cardioprotective effect of PPC on patients with acute ST-segment elevation myocardial infarction (STEMI). Methods: The PROTECT study is a randomized, controlled, single-center, first-in-man study. Patients with their first STEMI eligible for treatment with primary percutaneous coronary intervention (PCI) were enrolled in the study. Enrolled patients were randomized to the therapy arm (PPC + PCI, n = 25) or to the control arm (PCI only, n = 28). In the therapy arm, PPC consisted of 10 short bursts of intermittent pacing in the right ventricular apex during early reperfusion. The impact of PPC on the infarct size was measured by the area under the curve of creatine kinase collected during 72 hours from admission as well as by contrast-enhanced MRI. For assessment of arrhythmias and safety analysis 24-hour Holter analysis was used. Results and Conclusions: Primary endpoint of this first-in-man study is defined as infarct size as measured by the area under the curve of creatine kinase (CK). The secondary endpoint is defined as safety and is measured by arrhythmia incidence post procedure as assessed by 24-hour Holter monitoring. Additional analysis will include data on contrast enhanced MRI, myocardial function and remodeling measured by cine-MRI, ST segment analysis and clinical follow-up.