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2008 Late-Breaking Clinical Trial Abstracts

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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



2008 Late-Breaking Clinical Trial Abstracts

Late-Breaking Clinical Trials I

Subspecialty: General

Hall F

Abstracts 161–167

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SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine): Randomized Comparison of Folic Acid 2 mg Plus Vitamin B₁₂ 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 B₁₂ 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 B₁₂ yielded reductions in homocysteine levels of 3.9 μmol/L at 1 year and of 3.6 μmol/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 B₁₂ 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. **Conclusion:** SEARCH is the largest randomized trial to assess the effects of homocysteine-lowering treatment. Despite maintaining a 3–4 μmol/L lower homocysteine levels for 6.7 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 results reported previously from smaller and less prolonged 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.

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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, 17,802 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 study entry into JUPITER were 108 mg/dL, 49 mg/dL, 118 mg/dL, and 4.3 mg/L, respectively. The JUPITER trial includes 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 18,000 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 unequivocal 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.

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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 aimed 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 end points were atherosclerotic events including fatal or nonfatal coronary heart disease, fatal or nonfatal cerebrovascular disease, and peripheral arterial disease. Secondary end points 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 atherosclerotic events occurred (13 fatal): 68 in the aspirin group and 86 in the non-aspirin group (RR= 0.80; 95% CI, 0.58–1.10; log-rank test, p=0.2). There were 11 fatal coronary and cerebrovascular events (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= 0.10, 95%CI= 0.01–0.79, p=0.004). In 1363 patients age 65 years or older, the incidence of atherosclerotic events was significantly lower in the aspirin group than in the non-aspirin group (RR= 0.68, 95%CI= 0.46–0.998, p=0.047). There was no increased risk of hemorrhagic strokes in the aspirin group. **Conclusion:** Aspirin was associated with a nonsignificant reduction in total atherosclerotic 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 who were randomized to aspirin 81mg daily had a lower risk of cardiovascular events compared with placebo. Downloaded from circ.ahajournals.org/ by guest on July 30, 2015

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A Randomized Factorial Trial of Vitamins E and C in the Prevention of Cardiovascular Disease and Mortality in Men: The Physicians' Health Study II

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Background: Basic science and observational studies support a potential role of antioxidants, including vitamins E and C, in the prevention of cardiovascular disease. Some secondary prevention trials of vitamin E have seen potential reductions in cardiovascular disease, whereas primary prevention trials have mostly been negative, with only some including men at initially low or usual risk. Few long-term trials have evaluated vitamin C alone in the prevention of cardiovascular disease. Despite uncertainty regarding long-term effects, use of vitamin supplementation remains highly prevalent in the US. **Methods:** The Physicians' Health Study II (PHS II) tested vitamin E (400 IU every other day) and vitamin C (500 mg daily) supplementation on risk of cardiovascular disease from 1997 through August 31, 2007, in a randomized, double-blind, placebo-controlled trial of 14,641 U.S. male physicians initially aged ≥50 years. The trial included 754 (5.1%) men with prevalent cardiovascular disease at randomization. We identified major cardiovascular events (including nonfatal myocardial infarction, nonfatal stroke, and fatal cardiovascular disease) that occurred prior to termination of the vitamin E and C components. All endpoints are reviewed and confirmed by an Endpoints Committee of physicians blinded to randomized treatment assignment. High rates of morbidity and mortality follow-up have been maintained in the PHS II. **Results:** During a mean follow-up of 8.0 years among men with a mean baseline age of 64.3 years, there have been 1,240 major cardiovascular events and 1,660 deaths. We will present analyses of major cardiovascular events according to randomized vitamin E and vitamin C treatment assignments, as well as the effects of compliance, effect modification by coronary risk factors and baseline cardiovascular disease, and potential side effects. **Conclusion:** These data from a large prevention trial of long duration will inform clinical and public health recommendations regarding whether vitamin E or vitamin C supplementation has any benefits or harm on the risk of cardiovascular disease.

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

Rory E Collins, On behalf of the SEARCH Study Collaborative Group; Univ of Oxford, Oxford, United Kingdom

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 revascularisation, 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 revascularisation. 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

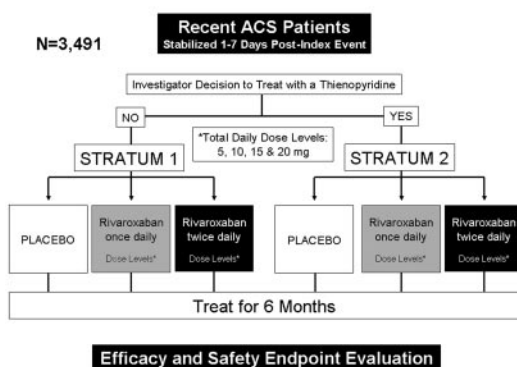
Abstracts 1309–1315

1309

Randomized Comparison of Rivaroxaban, an Oral Direct Factor Xa Inhibitor, with Placebo in Patients with Acute Coronary Syndromes: The ATLAS ACS-TIMI 46 Trial

C. Michael Gibson, Beth Israel Deaconess Med Cntr, Boston, MA; Jessica L. Mega, Brigham and Women's Hosp, Boston, MA; Christopher J Hammett, Royal Brisbane and Women's Hosp, Brisbane, Australia; Vasil Hricak, The National Institute of Cardiovascular Diseases, Bratislava, Slovakia; Pascual Bordes, Hosp General Univiro de Alicante, Alicante, Spain; Adam Witkowski, Institute of Cardiology, Warsaw, Poland; Valentin Markov, Tomsk Cardiology Scientific and Rsch Institute, Tomsk, Russian Federation; Paul Burton, Johnson & Johnson Pharmaceutical Rsch and Development, Raritan, NJ; Eugene Braunwald; Brigham and Women's Hosp, Boston, MA

Background: Rivaroxaban is a novel oral direct Factor Xa inhibitor that has been effective in prevention of venous thromboembolism after major orthopedic surgery. The efficacy and safety of rivaroxaban 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 is 57 years (range: 24–88), 77% are male, 19% have diabetes, and 21% had a prior MI. On presentation, 52% had a STEMI; 63% 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.



1311 Drug-Eluting and Bare Metal Stenting in Patients with Diabetes Mellitus: Results from the Mass-DAC Registry

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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 analysis. Mortality rates were obtained 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 5051 patients (29% 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%], $p = 0.006$) 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.

1313

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 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.

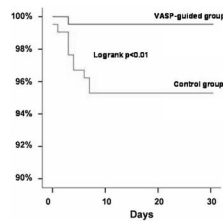
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Tailored Clopidogrel Loading Dose According to Platelet Reactivity Monitoring to Prevent Stent Thrombosis

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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 patients 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 (0.5 vs 4.2%; $p < 0.01$). Fifty percent of patients who had stent thrombosis had a low response to clopidogrel at the index procedure. The rate of MACE was also significantly

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

3318 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 outpatients. 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 $\leq 35\%$ 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, 95%; 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.

3320 The I-PRESERVE Trial: A Randomized Double-Blind Placebo-Controlled Trial of Irbesartan in the Treatment of Heart Failure in Patients with Preserved Ejection Fraction

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Background: 50% of heart failure (HF) patients (Pts) have preserved ejection fractions (HFPEF), yet no treatment has improved their clinical outcomes. **Hypothesis:** I-PRESERVE tested the hypothesis that the angiotensin receptor blocker (ARB) irbesartan would improve 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 $\alpha = 0.05$ in an intention to treat analysis of time to first event. Pts with LVEF $\geq 45\%$ 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 enrollment. Major exclusions were prior LVEF $< 40\%$, primary valvular or cardiomyopathic disease, uncontrolled hypertension, and comorbid conditions that might limit 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. Irbesartan 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, 4,128 Pts (mean EF $59 \pm 9\%$; mean age 72 years; 60% women) were randomized. 88% had a history of hypertension (mean arterial 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 irbesartan is effective in reducing the major cardiovascular events that affect this population and provide novel insight into the clinical course of this syndrome.

3322 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 efficacy and safety of two doses of interferon beta-1b (IFNB-1b) versus placebo in patients with biopsy-proven chronic viral cardiomyopathy (CVC). The diagnosis of CVC for the target population was based on the existence of chronic heart failure and the presence of adenovirus, enterovirus, and/or parvovirus in endomyocardial specimens obtained by endomyocardial biopsy. In the three treatment arms, patients received 2 different doses of IFNB-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 \pm 14 days 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 clinical symptoms, quality of life, left ventricular ejection fraction (LVEF) at rest and on exertion, echocardiographic parameters, inflammatory state in endomyocardial biopsies, composite clinical endpoint, wedge pressure and mean pulmonary artery pressure. 368 patients were screened for enrollment and 143 patients were randomized to treatment. 131 patients completed the study. Compared to placebo, virus elimination and/or virus load reduction were significantly higher in the IFNB-1b groups as compared with Placebo (odds ratio 2.33, 2-sided $p = 0.049$), without significant differences between both interferon groups. IFNB-1b treatment was associated with beneficial effects on NYHA functional class ($p = 0.013$ at follow-up week 12), improvement in quality of life (Minnesota total score) ($p = 0.032$ at follow-up week 24) and patient global assessment (follow-up week 12 to follow-up week 24) ($p = 0.039$). There were no safety concerns. The results demonstrate that IFNB-1b treatment leads to an effective virus clearance or reduction of virus load with favorable effects on quality of life, NYHA functional class and patient global assessment in patients with CVC.

3324 Midregional pro-Adrenomedullin (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). Midregional pro-Adrenomedullin (proADM) has been shown to be a novel marker of endothelial function and previous studies suggest it to be a

strong prognosticator in AHF patients. **Methods:** The BACH Multinational Trial was a prospective, 15-center international multiple 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 MRproADM vs BNP to predict 90-day mortality. Secondary endpoints included to test for superiority vs NTproBNP, and to perform these tests in all patients presenting with SoB to the ED. Physicians were blinded to MRproADM values. The gold standard diagnoses of HF were established by 2–3 cardiologists. Clinical lab troponin values (TnI 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 MRproADM (73.1% correct) was superior to BNP (60.6%, $p < 0.001$) 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, MRproADM significantly predicted 90-day mortality in Cox analyses independently of either BNP or NTproBNP in models both with and without troponin. **Conclusions:** MRproADM 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.

Model with BNP					Model with NT-proBNP				
	Wald	HR	95% CI	P		Wald	HR	95% CI	P
log BNP	0.01	1.04	0.54-2.00	0.906	log NTproBNP	1.10	1.39	0.75-2.56	0.295
log MRproADM	24.87	13.99	4.96-39.44	<0.001	log MRproADM	15.92	10.38	3.29-32.75	<0.001
Model with BNP and Troponin					Model with NTproBNP and Troponin				
log BNP	0.06	0.92	0.45-1.88	0.812	log NTproBNP	0.09	1.11	0.57-2.16	0.764
log MRproADM	13.59	8.50	2.72-26.51	<0.001	log MRproADM	9.87	7.50	2.13-26.37	0.002
elevated Tn	10.93	2.56	1.47-4.48	<0.001	elevated Tn	11.04	2.55	1.47-4.43	<0.001

All analyses were made on binary variables defined using ROC cut-points.
Cut-points: MRproADM (1.9935 pg/mL), BNP (993 pg/mL), NTproBNP (6307 pg/mL).

Late-Breaking Clinical Trials IV

Subspecialty: General

Hall F

Abstracts 5217–5223

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 will 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 ITC ProTime® 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 5.5% in the clinic testing arm, which would be reduced to 3.75% in the home testing arm. Secondary outcomes included time in target range, myocardial infarctions, 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. Indications for warfarin were mechanical heart valve (23%) and atrial fibrillation (83%). Subjects were followed for 2.0 to 4.75 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 0.741 to 1.033; $p = 0.11$ by log-rank test) for the primary endpoint nor 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 (65.9% vs. 62.2%, $p < 0.001$), as was patient satisfaction (47.7 vs. 49.1, $p < 0.02$; lower score means higher satisfaction). **Conclusions:** Compared with monthly clinic INR testing, 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 results support 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 distance).

5217

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, the 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 goal was to examine the impact of exercise training on health-related quality of life. **Methods:** HF-ACTION was a large multicenter, randomized (1:1), controlled trial (RCT) in medically stable patients with LVEF $\leq 35\%$ 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 instructed 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 examine treatment group effects and estimate 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 VO_2) 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 RCT 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.

5219

Results of the APPROACH Trial: Assessment on the Prevention of Progression by 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, multicenter, double-blind, 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-interventive 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 (53.9%) 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 has enrolled the largest cohort of high-risk 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.

5221

A Novel Family-Based Intervention Trial to Improve Heart Health (FIT Heart): 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 preventive action. The purpose of this NHLBI sponsored 1yr randomized controlled trial was to test the effectiveness of a novel systems approach to screen

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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 and therapeutic lifestyle change (TLC) diet/exercise counseling by non-physician, non-nurse health educators at regular intervals for 1yr or to the control intervention (CI) 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 1yr by research assistants blind to group assignment (94% 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 CI group in the mean % change in MEDFICTS diet score from baseline to 1 year (p=.04, difference = 13.4%) and both groups showed significant improvements in saturated fat, dietary cholesterol, trans fat intake, LDL-C, and physical activity. HDL-C significantly decreased in the CI group but not the SI group, and the mean % change in HDL-C from baseline to 1 yr was significantly increased in the SI vs CI group (p=.01, difference 3.5%). The SI subjects were more likely to exercise >3 days per week compared to controls at 1yr (p=.04). **Conclusion:** A timely, targeted, low cost educational intervention was successful in improving lifestyle and HDL-C beyond several lifestyle improvements made in controls. Hospitalization of a family member with CVD is a unique motivational and educational opportunity to lower individual CVD risk.

Translational Trials and Strategies: First in Man

Subspecialty: Health Policy and Outcomes Research
 Room 275-277
 Abstracts 1258-1263

1258

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 contractile and relaxation function in HF. In preclinical studies, restoration of this enzyme via gene transfer utilizing a rAAV1 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 effects of AAV1/SERCA2a on cardiac performance, LV remodeling and functional status in subjects with advanced HF. **Methods:** 9 class III/IV HF subjects (EF ≤30%) on maximal medical therapy with baseline anti-AAV1 neutralizing antibody (NAB) titers of ≤1:2 received intracoronary 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 CRTs 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 with 4 of 5 having a decrease of 1 NYHA Class, as well as improvement in a 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 most subjects receiving AAV1/SERCA2a. Although the number of subjects in each cohort is too small to conduct statistical analyses, quantitative evidence of biological activity could be detected in a number of subjects following gene transfer.

Cohort/ Subj. #	BL NAB	BL Visit	MLWHFQ		VO2 max (mL/kg/ min)		6MWT (m)		NYHA Class		NT-Pro BNP (pg/mL)		LVESV (mL)		LVEF (%)	
			Obs	Chg	Obs	Chg	Obs	Chg	Obs	Chg	Obs	% Chg	Obs	Chg	Obs	Chg
1/#1	<1:2	BL	54	17.3	408	3	315	158	23							
	M6	39	<u>-15</u>	<u>19.3</u>	<u>+2</u>	549	<u>+141</u>	3	0	326	+3.5	198	<u>-20</u>	30	<u>+7</u>	
1/#2	1:2	BL	73	12.3	372	3	2329	233	18							
	M6	79	+6	10.8	<u>-1.5</u>	366	-6	3	0	1640	-29.6	237	+4	16	-2	
1/#3	<1:2	BL	11	14.3	350	3	2928	245	25							
	M6	12	+1	14.0	-0.3	439	<u>+89</u>	2	-1	1161	<u>-60.4</u>	178	<u>-67</u>	31	<u>+6</u>	
2/#4	<1:2	BL	34	13.0	466	3	1420	200	21							
	M6	22	<u>-12</u>	<u>14.7</u>	<u>+1.7</u>	456	-10	2	-1	874	<u>-38.5</u>	229	<u>+29</u>	24	<u>+3</u>	
2/#5	<1:2	BL	35	10.2	276	3	5236	352	16							
	M6*	22	<u>-13</u>	ND	NA	276	0	2	-1	6061	+15.8	354	+2	13	-3	
2/#6	<1:2	BL	70	15.8	523	3	2596	137	29							
	M6	45	<u>-25</u>	<u>21.7</u>	<u>+5.9</u>	627	<u>+104</u>	2	-1	2186	-15.8	139	+2	30	+1	

BL=Baseline or Screening value; M6=Month 6; Obs=observed; Chg=change; ND=not done; NA=not available; clinically meaningful changes are underlined. * Data are available through Month 2 or 3 for Subject #5 who died on Day 96; sudden death was assessed as unlikely related to investigational product. Month 6 data are not available for Subject #5.

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The Safety and Efficacy of Recombinant Activated Factor VII for the Treatment of Bleeding Following Cardiac Surgery: A Multinational Randomized, Placebo-Controlled Trial

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Introduction: There is evidence to suggest that recombinant activated factor VII (rFVIIa) can reduce intractable bleeding following cardiac surgery for patients who do not respond to standard treatment. We hypothesize that rFVIIa is safe and beneficial for use in patients undergoing cardiac surgery at high risk of bleeding. **Methods:** In a global trial, 172 patients who had undergone cardiac surgery and were bleeding were randomized to receive placebo (N=68), 40 mcg/kg rFVIIa (N=35), or 80 mcg/kg rFVIIa (N=69) as a single bolus in an ICU setting. The primary endpoint was the number of patients suffering critical serious adverse events (cSAEs) at 30 days. Secondary endpoints included rates of re-operation, blood loss volumes and transfusion of allogeneic blood. **Results:** There were numerically more cSAEs in the rFVIIa groups (40 mcg/kg 14%, p=0.25; 80 mcg/kg:12%, p=0.43) than in placebo group (7%). Despite the numerical increase of cSAEs in the rFVIIa groups, the unadjusted and adjusted log Odds Ratios for cSAEs were statistically similar to the placebo group. Age (P<0.05), cardio-pulmonary bypass duration (P<0.05) and type of surgery (emergent/urgent) (P<0.001) were statistically significant predictors of cSAEs. Significantly fewer patients in the rFVIIa group underwent re-operations for bleeding (placebo:25%; 40 mcg/kg rFVIIa:14% [P=0.21]; 80mcg/kg rFVIIa:12% [p=0.04]) and had smaller allogeneic blood transfusion volumes { placebo:825 mL [25%-75% IQR: 326.5-1893]; 40 mcg/kg rFVIIa:640 mL, P=0.047 [25%-75% IQR: 0-1920] ; 80mcg/kg rFVIIa: 500 mL, P=0.042 [25%-75% IQR: 0-1750]}. Four hours after randomization and drug administration the median drainage rate in the 80mcg/kg rFVIIa was significantly slower (24 mL/hr, P=0.018; 25%-75% IQR: 13.3-32.0) than in the placebo (51 mL/hr; 25%-75% IQR: 21.3-82.7) and 40mcg/kg rFVIIa treatment groups (35 mL/hr, P=0.763; 25%-75% IQR: 26.7-85.3). There was an approximately 50% reduction in the drainage volume within the 4 hours after treatment with 80mcg/kg rFVIIa (P<0.001) compared with placebo. **Conclusions:** On the basis of this preliminary prospective randomized trial it may be cautiously concluded that rFVIIa is probably safe and may be beneficial to treat bleeding after cardiac surgery.

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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 previously studied in 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 an ACS event were randomized to receive 25, 50, 100 mg VIA-2291 qd or placebo qd for 3 months. The primary endpoint was whole blood LTB4 (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 30, SD 4.8); presenting ACS event 45% STEMI/ 31% non-STEMI/ 24% UA; 90% PCI for presenting ACS event. Risk factors included 54% with history of hypertension; 17% prior MI; 20% prior PCI; 17% diabetic. Concomitant medications: 95% HMGCoA reductase inhibitors; 97% platelet inhibitors (91% ASA / 91% clopidogrel); 84% beta blocker; 65% ace inhibitor; 17% A-II antagonist. VIA-2291 was generally well-tolerated. ~11% of patients had SAEs, of these ~50% were cardiovascular, none of which were considered related to study drug. TEAEs were generally mild to moderate, the majority considered unrelated to treatment. hsCRP was elevated at baseline to 3-5 mg/L consistent with a post-ACS population. **Conclusion:** 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.

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Three Months of Treatment with 5-Lipoxygenase Inhibitor VIA-2291 in Patients Scheduled 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 5-LO would demonstrate anti-inflammatory effects in plaque tissue surgically removed from patients undergoing carotid endarterectomy (CEA), assess safety, mechanism of action and serum 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 VIA-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 5-LO, whole blood LTB4, urine LTE4 and serum hsCRP. **Results:** Baseline characteristics were well balanced between treatment groups in the evaluable population with a median age of 68 (56 - 82), 57% diabetics and 49% with hsCRP >2.0 mg/L. VIA-2291 was generally well-tolerated. There were no serious or unexpected drug-related adverse events. Carotid plaques from patients treated with VIA-2291 100mg qd for 12 weeks showed no difference in the mean % area of macrophages (Placebo: 7.63 +/- 7.1%; VIA-2291: 8.17 +/- 5.96 %; p=0.84, n=25) and 5-LO immunostaining (Placebo: 0.84 +/- 1.26; VIA-2291: 1.79 +/- 3.27; p=0.35, n=25) when compared to placebo. A significant reduction from baseline was observed for whole blood LTB4 production (p<0.001) and hsCRP (p=0.008) measured at 12 weeks. Urine LTE4 was significantly lower during the entire treatment phase in the group receiving 100mg VIA-2291 (Baseline p=0.42, p<0.0017 at Week 2, 6 & 12). **Conclusions:** Administration of 100mg daily of VIA-2291 for 12-weeks significantly reduces systemic inflammatory biomarkers including hsCRP in patients undergoing CEA, while exhibiting a good safety profile. Significant changes in plaque inflammatory markers might not be observed for a number of reasons including: small sample size, high variability in plaque type and the high number of relatively stable plaques expected and subsequently found in these asymptomatic patients.

1262

Gene Evaluation for ANThypertensive Effect of drugs (GEANE): A Multicenter Trial

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Aim: Prediction of antihypertensive effect of drugs based on genetic variation is supposed to be most desirable in individualized treatment of hypertension. The aims of this study are to clarify susceptible single nucleotide polymorphisms (SNPs) to angiotensin II receptor blockade (ARB; Valsartan), calcium channel blockade (CCB; Amlodipine) and thiazide type diuretics (DU; Indapamide) and to establish the way to predict the most effective drug based on these SNPs information in each individual. **Methods:** This study is a multi-center trial with the prospective randomized crossover design. Patients with untreated mild to moderate essential hypertension were recruited. After a control period for one month, each of antihypertensive three drugs was administered. In each drug period, subjects took a half dose of ARB or CCB or DU for one month and regular dose for two months. Total study period was ten months. The cut-off definition of drug responder was investigated by several values including <140/90mmHg, systolic blood pressure (SBP) <-10 or -20mmHg and treated BP adjusted by baseline BP. DNA analysis was performed by Affymetrix 500K DNA micro-array chips. **Results:** Finally, 134 subjects (Male: 73) completed all study protocol and genetic analysis. Averaged BP was 156 ± 13/94 ± 10mmHg at the control period, and three drugs significantly reduced BP similarly (ARB: 135 ± 14/84 ± 10, CCB: 133 ± 12/83 ± 9, DU: 134 ± 14/84 ± 10). 39 subjects had obtained target BP (<140/90mmHg) by all three drugs, however, 21 subjects did not obtain target BP by any drugs. Nine had below target BP only by ARB, 10 had it only by CCB and 9 had below target BP only by DU. 386506 SNPs selected by HWE ≥0.01 and MAF ≥0.01 were analyzed. There were 18000–20000 statistical significant SNPs (p<0.05) for each single drug using several cut-off values, and 2000–3000 SNPs associated with two drug response and 300–400 SNPs associated with all three drug response. Minimum p value range was about 10⁻⁸-10⁻⁶. **Conclusion:** There are some susceptible SNPs to BP response of three important antihypertensive drugs. Although the validation of reproducibility of these SNPs is necessary, our strategy would be useful to establish prediction of the best drug based on SNPs information in individualized treatment of hypertension.

1263

The Selective Cardiac Myosin Activator, CK-1827452, Increases Systolic Function in a Concentration-Dependent Manner in Patients with Stable Heart Failure

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Background: CK-1827452 (CK-452) increases systolic function by activating cardiac myosin. In healthy subjects CK-452 increases systolic ejection time (SET), stroke volume (SV), fractional shortening (FS), and ejection fraction (EF). We sought to extend these findings in 2 - 72 hr infusions in stable heart failure (HF) patients. **Methods:** This first Phase II trial of CK-452 is a multi-center, double-blind, randomized, placebo-controlled study in patients with EF < 40% 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 Cohorts 1&2 and 24 hrs in Cohorts 3&4. Cohort 5 investigates 72 hr infusions as a two-period placebo-controlled crossover with a target plasma concentration of 650 ng/ml. **Results:** In analyses of data from 28 completed patients in Cohorts 1 to 4, echocardiographic data were paired with coincident plasma concentrations of CK-452 to perform a PK/PD analysis. Statistically significant concentration dependence was observed for increases in EF and decreases in heart rate and left ventricular end systolic volume. The significance of increases in EF differed between methods of calculation. Treatments were well tolerated at pre-specified dosages. Results from Cohorts 1 to 4 and initial results from the 72 hr exposure will be available at the time of presentation. **Conclusions:** CK-452 appears to be well tolerated and increases systolic function in stable HF patients during intravenous infusion. <http://www.cytokinetics.com>

this first Phase II trial may support translation of this novel mechanism into populations with more advanced heart failure.

Placebo Corrected Changes from Baseline

[CK-452] (ng/mL) (n per bin)	Baseline	1–100 (69)	>100–200 (50)	>200–300 (32)	>300–400 (19)	>400–500 (30)	>500–883 (20)	Correlation vs [CK-452]
SET (ms)	318	3 ± 4	24 ± 5*	54 ± 5*	65 ± 7*	72 ± 8*	98 ± 7*	‡
LVOT SV (mL)	68	1 ± 2	1 ± 2	6 ± 2*	12 ± 3*	14 ± 3*	14 ± 3*	‡
FS (%)	17	1 ± 1	2 ± 1*	3 ± 1†	4 ± 1†	3 ± 1#	4 ± 1‡	‡
EF (%) ^A	32	0 ± 1	0 ± 1	1 ± 1	1 ± 1	1 ± 1	2 ± 1	#
EF (%) ^B	30	1 ± 1	1 ± 1	1 ± 2	7 ± 2†	7 ± 2†	5 ± 2#	‡

p < 0.05 * p ≤ 0.01 † p < 0.001 ‡ p < 0.0001 ^AEF = (LVEDV-LVESV)/LVEDV*100 (Bipl MOD) ^BEF = (LVOT SV/LVEDV)*100 (Doppler, Bipl MOD) Increases in SET, SV, and FS were statistically significant at > 200 ng/mL and concentration dependent.

Clinical Trials in ACS and Interventional Cardiology

Subspecialty: Interventional cardiology
Auditorium B
Abstracts 3017–3020

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. HORIZONS-OCT

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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. **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 micron-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 3:1 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 flush. 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 strut coverage, thickness and wall apposition were determined for 360 chords (1 degree increments). Standard QCA and IVUS measures were also assessed at blinded core laboratories. **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 mean number of stents implanted per patient was 1.75 ± 0.9 (median total stent length: 28 mm, 25th-75th percentile 20–48). 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

FreRace - 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 intraindividual 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 stenosis were randomized to SES or PES (1:1 ratio). **Conclusions:** The primary endpoint was angiographic restenosis

by 8 months. The secondary endpoint was a composite of major adverse cardiac events (myocardial infarction, and ischemia-driven revascularization of the target lesion) by 12 months. **Results:** The clinical and angiographic baseline characteristics were similar in both examined groups. At 8 months angiographic follow up the minimal luminal diameter in stent was significant larger with SES as compared to PES (2.58±0.04 mm vs. 2.45±0.04 mm, p=0.025). The rates of angiographic restenosis were 9.2±1.3% using SES as compared to 14.1±1.3% of the PES (p=0.011). Late luminal loss in stent was significantly less using SES as compared to PES (0.13±0.03 mm vs. 0.26±0.04 mm, p=0.011). At 12 months, clinical event were not different in the two groups with regard to the secondary endpoint (SES group: 5 events, PES group: 3 events). By intra-individual comparison three different patterns were present: (1) patients with comparing restenosis in both stents, (2) patients with restenosis predominantly within the SES, and (3) patients with restenosis predominantly within the PES. **Conclusion:** In this first intra-individual comparison the use of SES resulted in a lower rate of angiographic in stent restenosis as compared with the PES. Clinical course was found not to be different at 12 months.

3019

Association Between Migraine Headaches and Patent Foramen Ovale: A Large Case-Control Study

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Background: Both migraine headaches and patent foramen ovale (PFO) are highly prevalent. While some observational studies have suggested an association between the two conditions, recent randomized trials of PFO closure in migraine patients have been negative. We sought to evaluate the association between migraine headaches and the presence of PFO in a large case-control study. **Methods:** We conducted a case-control study with prospective data collection to assess the prevalence of PFO in subjects with and without migraine. Cases (N=158) were those with a history of migraine (diagnosed by neurologists at a headache clinic in a major academic hospital). Controls (N=156), healthy volunteers without migraine, were 1:1 matched on age and sex with cases. To avoid enrollment of subjects with risk for PFO other than migraine alone, subjects with known history of cerebrovascular disease, paradoxical embolism or decompression illness were excluded. Presence of PFO was determined using transthoracic echocardiogram with second harmonic imaging and transcranial Doppler ultrasonography, both using agitated saline contrast ± Valsalva maneuver, and performed and reported with blinding to case-control status. PFO was considered to be present if both studies were positive. Odds ratios (OR) were calculated using conditional logistic regression in the matched cohort (N=288). **Results:** Cases (N=144) and controls (N=144) were well balanced with respect to matching factors (mean age, 41.6 vs. 41.4; females, 83% both cohorts). Migraine with aura was present in 39% of cases. In the matched analysis, the prevalence of PFO was similar in cases and controls (26.4% vs. 25.7%; OR 1.04, 95% CI: 0.62–1.74, p=0.90). There was no difference in PFO prevalence in those with migraine with aura or those without (26.8% vs. 26.1%; OR 1.03, 95% CI: 0.48–2.21, p=0.93). Multivariable analysis identified family history of migraine as the strongest independent predictor of migraine (OR 21.16, 95% CI: 7.4–60.5, p<0.001) followed by family history of cerebrovascular disease (OR 2.78, 95% CI 1.19–6.49, p=0.02). PFO was not predictive of migraine (p=0.18). **Conclusion:** We found no association between migraine headaches and the presence of patent foramen ovale in this large case-control study.

3020

Intracoronary Infusion of Mononuclear Cells After Primary Percutaneous Coronary Intervention: The HEBE Trial

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Background: Studies reporting the effect of intracoronary infusion of bone marrow-derived mononuclear cells (MNC) on improvement of left ventricular (LV) function in patients with acute myocardial infarction (AMI) have shown conflicting results. The primary objective is to determine whether intracoronary infusion of autologous MNC from bone marrow or peripheral blood provides improved recovery of regional LV function after AMI treated by percutaneous coronary intervention (PCI), compared to conventional therapy. **Methods:** Two-hundred patients with first AMI treated with primary PCI and stenting were prospectively enrolled in 8 centers. Patients were randomized to (1) intracoronary infusion of bone marrow-derived MNC, (2) intracoronary infusion of peripheral blood-derived MNC or (3) conventional therapy, as previously described (Hirsch et al, Am Heart J 2006;152:434–441). Between 3 and 8 days post MI, bone marrow or venous blood was collected. MNC were infused into the infarct-related artery through an over-the-wire balloon catheter during 3 balloon inflations. Global and regional LV function was measured by cardiovascular magnetic resonance before randomization and at 4 four months. The primary endpoint of the study was the change in regional LV function. The HEBE trial has been assigned the International Standard Randomized Control Trial Number 95796863. **Results:** Of the 200 patients, 69 were randomized to the MNC group and 131 to the control group. Mean age was 56±9 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.

peripheral blood (33%), and 65 to standard therapy (32%). Mean age was 56±9 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

4078

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 & 12 months, RM only was used but followed by OVs if necessary. Conventional patients were evaluated with OVs only. Follow up was "actionable" if system reprogramming/revision or change in anti-arrhythmic therapy occurred. Scheduled and unscheduled OVs (including responses to event notifications in RM) were quantified for each individual patient per 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 ± 10.8% 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 75.9%, ACE inhibitors 42.4% vs 46.8%, ARBs 7.8% vs 9.9%, p = NS), indication (primary prevention 72.3% vs 74.2%, p = 0.50), and dual chamber implants (57.9% vs 57.0%, 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 improved adherence to follow-up. **Conclusions:** 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. In conclusion, remote monitoring is a safe alternative to conventional care.

	n	Office Follow-up Visits			Adherence to Scheduled Follow-up Checks	Morbidity
		Scheduled	Unscheduled	Total		
RM	867	n = 934 1.3 ± 1.0 per pt yr 13.9% actionable	n = 396 0.6 ± 1.6 per pt yr 29.5% actionable	1.9 ± 1.8 per pt yr	86.0% ± 23.0%	8.5%
Conventional	395	n = 1009 2.8 ± 1.2 per pt yr 29.9% actionable	n = 118 0.5 ± 1.5 per pt yr 30.6% actionable	1.8 ± 1.8 per pt yr	78.6% ± 25.8%	7.6%
p value		< 0.001*	0.104*	< 0.001	< 0.001	0.660

4080

Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients with Paroxysmal Atrial Fibrillation: The ThermoCool AF Trial

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Background: The role of catheter ablation (CA) for treatment of paroxysmal atrial fibrillation (AF) remains incompletely defined. A prospective multicenter randomized trial (NCT 00116428) was designed to test the effectiveness of the Navistar Thermocoil Radiofrequency Ablation Catheter (Biosense Webster, Diamond Bar CA) compared to antiarrhythmic drug (AAD) therapy in this population. **Methods:** The trial was conducted in 19 centers. Enrollment criteria included ≥ 3 symptomatic episodes of paroxysmal AF (at least one ECG verified) within the 6 mo prior to randomization, and failure with at least one AAD or AV nodal blocking agent. Pts with AF > 30 days in duration, age < 18, or ejection fraction < 40% were excluded. Pts were randomized 2:1 to CA or a previously untested class I or III AAD, and were followed for one year. CA included pulmonary vein isolation with electrophysiologically confirmed entrance block as the endpoint in all pts. In pts randomized to CA, chronic efficacy was evaluated after a 3 mo blanking period. In pts randomized to AAD, chronic efficacy was evaluated after a 2 week dose titration period. All pts underwent transtelephonic monitoring via an independent core laboratory. **Results:** 200 patients were randomized to the CA group and 131 to the control group. Mean age was 56±9 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.

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 5298 screened pts, 167 met criteria for enrollment, gave informed consent, and were randomized (106 CA, 61 AAD). 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 ± 93 (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.

4082

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 where 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-blind 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, III). **Results:** The mean duration of permanent AF before surgery was 52 ± 82 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 2,8 %, 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=2; $p=0,64$). 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.

4084

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

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Background: Animal studies have shown that intermittent dyssynchrony 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.