Late-Breaking Clinical Trial Abstracts

Late-Breaking Clinical Trials I

Subspecialty:
West Hall D2

Abstracts -

Evaluation of Prasugrel Compared With Clopidogrel in Patients With Acute Coronary Syndromes and Planned Percutaneous Coronary Intervention: The TRITON–TIMI 38 Study
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Background: Dual antiplatelet therapy with aspirin and a thienopyridine is standard for reduction of ischemic complications of acute coronary syndromes (ACS) and following percutaneous coronary intervention (PCI). Prasugrel is a novel thienopyridine that has been shown to be more potent, more rapid in onset, and to have more consistent antiplatelet effects than standard, approved doses of clopidogrel. TRITON–TIMI 38 compared prasugrel to clopidogrel in patients with moderate to high risk unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) or ST-elevation myocardial infarction (STEMI) undergoing planned PCI.

Methods: TRITON–TIMI 38 is an international, double-blind, double-dummy Phase 3 trial. It tests the hypothesis that prasugrel (60 mg loading dose and 10 mg maintenance dose) compared to clopidogrel (300 mg loading dose and 75 mg maintenance dose) for up to 15 months reduces the composite end point of cardiovascular (CV) death, myocardial infarction (MI) or stroke. Analyses are performed first in the UA/NSTEMI cohort, and, conditionally on the whole ACS population. An exploratory noninferiority boundary of 1.15 was prespecified. Major safety end points include TIMI major and minor bleeding not related to coronary artery bypass surgery. Results: 13,610 subjects were randomized (1:1) at 771 sites in 31 countries, including 10,075 with UA/NSTEMI and 3535 with STEMI. 99% of subjects had a PCI with 94% receiving at least one coronary stent, and 40% received a GP IIb/IIIa receptor antagonist. Demographics closely matched contemporary phase 3 trials; 13% were older than 75 years, and 23% were diabetic. Last patient visit is scheduled for July 13, 2007. Conclusions: Approximately 950 primary end point events will be accrued, resulting in greater than 90% power to detect a 20% relative reduction in CV death/MI/stroke in the UA/NSTEMI cohort. The sample size and contemporary management will allow for a comprehensive assessment of the safety and efficacy of prasugrel vs clopidogrel. This is the first large-scale clinical assessment of whether any agent that achieves higher levels of inhibition of platelet aggregation than the standard, approved thienopyridine therapy will translate into improved clinical outcomes.

Differential Improvement in Stress Myocardial Perfusion Ischemia Following Percutaneous Coronary Intervention as Compared With Optimal Medical Therapy Alone: Nuclear Substudy Results From the Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE) Trial
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Background: While there were no clinical outcome differences for percutaneous coronary intervention (PCI) with optimal medical therapy (OMT) vs OMT in the main COURAGE trial, the role of myocardial perfusion SPECT (MPS) in identifying subsets of stable CAD patients (pts) with inducible ischemia and changes in ischemic burden following treatment has not been explored. Methods: 313 of 2,287 COURAGE pts underwent serial rest/stress MPS (Tc-99m sestamibi or Tl-201) performed at baseline and 6–18 months following randomization. MPS was analyzed by a blinded core laboratory using quantitation of stress–rest total perfusion ischemia. A clinically meaningful reduction in ischemia at baseline. These data support MPS as an effective guide to identify pts likely to benefit from PCI.

Eptifibatide Versus Abciximab in Primary PCI for Acute ST Elevation Myocardial Infarction. The Randomized EVA-AMI Study
Uwe Zeymer, Herzzentrum Ludwigshafen, Ludwigshafen, Germany; Emmanuel TeigerChl Henri Mondor, Paris, France; Chl Mondor, Paris, France

In primary PCI the additional stent implantation does not improve early reperfusion in AMI, but decreases the incidence of reinventions. In contrast the adjunctive therapy with the GP IIb/IIIa receptor abciximab improved myocardial reperfusion, LV function and clinical outcome. There are no placebo-controlled trials available with the use of the small molecule GP IIb/IIIa inhibitors eptifibatide and tirofiban. In the ESPRIT trial eptifibatide, a synthetic specific GP IIb/IIIa inhibitor, reduced the rate of thrombotic complications in patients with non-urgent stent implantation. This reduction is similar to the reduction observed in EPISPECT with abciximab. Eptifibatide is less expensive than abciximab and has the advantage of reversible receptor occupation. Therefore it seems necessary to compare the efficacy and safety of these two GP IIb/IIIa inhibitors in primary PCI. Objective(s): To demonstrate non-inferiority of eptifibatide as compared to abciximab as adjunct in patients undergoing primary PCI for STEMI. Endpoint(s): Primary endpoint is the incidence of complete ST resolution (>70%) 60 (range 45–75) minutes after PCI, as assessed by a core ECG laboratory. Secondary endpoints include TIMI flow grades, myocardial blush grade following PCI (TMPG), final infarct size, death, re-MI and urgent target vessel revascularisation (UTVR), stroke and bleeding complications at several time points. Study Design: International, multicentre, randomised, prospective, open parallel group comparison of eptifibatide, clopidogrel, ASA, heparin or enoxaparin vs abciximab, clopidogrel. ASA and heparin or enoxaparin in patients with STEMI <12 h undergoing primary PCI. Study Population: Male and female subjects at least 18 years of age with acute myocardial infarction (less than 12 h prior to randomization) defined as: (a) Angina or equivalent symptoms >20 min, and (b) ST elevation >2 contiguous leads (≥2 mm precordial lead, ≥1 mm limb lead). Results: A total of 430 patients were included in the EVA-AMI Study in France and Germany between November 2006 and May 2007. The final results for the primary endpoint and 30 day outcomes will be available in November.

Brief Infusion of Eptifibatide Following Successful Percutaneous Coronary Intervention (BRIEF-PCI)
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Background: The recommended regimen for eptifibatide given at the time of percutaneous coronary intervention is a double bolus followed by an infusion for 18 hours. We hypothesized that the post-procedural infusion can be shortened if the intervention is uncomplicated. Methods and Results: We randomized 624 patients with stable angina, acute coronary syndrome or recent ST elevation myocardial infarction (MI, >46 hours) who underwent successful non-emergent coronary stenting and who received intravenous eptifibatide during the procedure to either a standard 18-hour infusion (standard group, n=312) or to an abbreviated infusion of less than 2 hours (brief group, n=312). The primary end-point was the incidence of peri-procedural ischemic myocardial injury defined as post-procedure troponin-I elevation greater than 0.26 mcg/L measured in a core laboratory. The abbreviated regimen was compared with the 18-hour regimen using a pre-specified non-inferiority analysis. Secondary
Outcomes Research: Implications for Clinical Practice

Subspecialty: W Chapin Theater

Abstracts -

The Reperfusion of Acute MI in Carolina Emergency Departments (RACE) Systems Improvement Program: Primary Results

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Long-term clinical outcomes following drug-eluting and bare metal stenting in Massachusetts

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Background: Observational studies of drug eluting stents (DES) have yielded conflicting results regarding late mortality relative to bare metal stents (BMS). We report on the largest consecutive series of patients followed after DES and BMS from a regional contemporary US practice with mandatory reporting. Methods: All adults undergoing percutaneous coronary intervention (PCI) with stenting between January 1, 2003, and September 30, 2004, at all acute care non-US government hospitals in Massachusetts (MA) were identified from a state database that monitors the quality of cardiac care. According to the stent types used from the index admission, patients were classified as DES-treated if all stents were drug-eluting and BMS-treated if all stents were bare metal. Crude mortality risk differences (DES - BMS) were determined from vital statistics records of those patients with 2 year follow-up, and risk-adjusted mortality differences were estimated using matched pairs constructed from propensity scores that included prospectively collected demographic, clinical, and procedural information. Results: The analysis cohort consisted of 11517 DES and 6210 BMS patients. LAD location (<0.0001), multivessel PCI (<0.0001), and diabetes (<0.004) were associated with increased DES use. Age >65 (<0.0001), STEMI (<0.0001), saphenous vein graft location (<0.0001), history of smoking (<0.0001) or CHF (p<0.004) were associated with increased BMS use. The unadjusted cumulative incidence of mortality at 2 years was 6.7% for DES and 12.4% for BMS (p<0.001). After adjusting for patient baseline characteristics and procedure indication, STEMI (p=0.025), female gender (p<0.001) and tobacco use (p=0.004) were associated with increased mortality post DES. Further adjustment for door to balloon time, type of stent used, and the PCI operator decreased this association (p=0.08, 0.84, and 0.86). Conclusion: In this contemporary US practice, treatment with DES was not associated with a higher rate of adjusted 2-year mortality than treatment with BMS. 2-year risk-adjusted rates of MI and revascularization will be available at presentation.

Impact of Patient Self-Management Skills Training on Death and Hospitalization in Patients With Heart Failure: Results From the Heart Failure Adherence and Retention Trial

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Heart failure (HF) is one of the few cardiovascular conditions that is increasing in prevalence. Drug therapies and lifestyle changes can slow progression, but only if patients adhere to them. HART was a randomized behavioral clinical trial aimed at reducing death and repeat hospitalizations by offering patients one year of small group counseling to assist them with their adherence to evidence-based treatment through training in self-management skills. Treatment was compared to an educational control delivered over one year by mail and phone. The HART cohort was recruited from the Chicago metropolitan area and followed for an average of 34 months. It consisted of 902 patients with NYHA class II (66%) or class III (32%). The baseline age was 63.6 years and 23% had diabetic dysfunction, 47% were women, and 40% were ethnic minorities. This diversity makes it generalizable to current clinical practice. Description of the cohort at baseline revealed challenges to adherence and areas in need of intervention. Patients had an average of 3.2 co-morbidities, including hypertension (70%), diabetes (40%), previous MI (45%), and depression (30%), translating into an average of 6.8 medications per patient. Using data from electronic pill caps, 37% of the patients were not taking medications as prescribed and the average daily intake of sodium was 3338 mg/day, 67% higher than the recommended intake of 2000 mg/day. Average relative weight was in the obese range (BMI ≥31.2) and 32.5% watched TV more than 4 hours/day. Ethnic minorities, relative to Caucasians, were more non-adherent to medications (49.8% vs 29.3%), had higher salt intake (3530 mg/day vs 3148 mg/day), and had higher BMI (32.6 vs 30.1), all comparisons p<0.001. These data suggest that better understanding of factors influencing adherence to evidence-based care is needed in HF, particularly in the ethnic minorities. The HART investigators will become unblinded to outcome data during the summer. This presentation will determine whether treatment improved adherence and, if so, benefited the clinical outcomes of death, HF hospitalization, all-cause hospitalization, and the composite of death or HF hospitalization. Implications bear on the value of patient skills training, as an adjunct to standard health education, in clinical practice for HF patients.

The Simplified Treatment Intervention to Control Hypertension (STITCH) Trial: A Cluster Randomized Controlled Trial of a Step-Care Algorithm Using Initial Fixed Dose Combination Therapy for the Management of Hypertension

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Context: Notwithstanding the availability of antihypertensive drugs and practice guidelines, blood pressure control rates remain suboptimal. The complexity of current treatment guidelines may contribute to this problem. To simplify this treatment algorithm, we chose a new fixed dose combination containing low dose angiotensin converting enzyme inhibitor (ACE-I)/diuretic or angiotensin receptor blocker (ARB)/diuretic combinations which is more effective than guideline-based management. Design and Setting: Cluster randomization trial conducted at 45 family practices in Southwestern Ontario, Canada. Within each practice, up to 50 patients with uncontrolled hypertension were evaluated. Practices randomized to GUIDELINE-cares were provided with the implementation materials from the Canadian Hypertension Education Program. Practices assigned to STITCH-care were treated according to the following algorithm: (1) initiation of therapy with a low-dose ACE-I/diuretic or ARB/diuretic combination, (2) up-titration combination therapy to the highest dose, (3) addition of a calcium channel blocker and up-titration, (4) addition of a non-first line antihypertensive agent. Main Outcome Measure: The proportion of patients treated to target blood pressure (systolic blood pressure [SBP] less than 140 mmHg and diastolic blood pressure [DBP] less than 90 mmHg for patients with no diabetes) or SBP less than 130 mmHg and DBP less than 80 mmHg for patients with diabetes) at 6 months analyzed at the level of the practice. Results: The proportion of patients achieving target blood pressure was significantly higher in the STITCH-care group compared with the GUIDELINE-care group (64.7% vs 52.7%, Absolute difference 12.0%, 95% CI 1.5% to 22.4%, p = 0.026). Multivariate analysis of patient-level data showed that assignment to the intervention arm increased the possibility of reaching the blood pressure prevention target by

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Late-Breaking Clinical Trials II

Subspecialty: West Hall D2

Abstracts -

Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)—Results of an Outcomes Trial in Patients With Ischemic Heart Disease and Heart Failure

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Background: Because patients with symptomatic heart failure (HF) were excluded from past placebo-controlled trials with statins, the benefit–risk of statins in the treatment of HF remains uncertain. Placebo-controlled trials with statins have been conducted in patients with ischemic heart disease and systolic HF. The primary objective is to determine whether rosuvastatin (10 mg daily) reduces the number of patients suffering from the combined endpoint of cardiovascular mortality or non-fatal myocardial infarction or non-fatal stroke (time to first event). The secondary endpoint is all-cause mortality.

Methods: Men and women aged ≥60 years with chronic symptomatic systolic HF of ischemic etiology and ejection fraction ≤0.40 (NYHA class II-IV) or ≤0.35 (NYHA class II) were eligible if they were not using or in need of cholesterol-lowering drugs. CORONA was event driven aiming for 1422 patients suffering from a primary endpoint (given >90% power to detect a mean relative risk reduction versus placebo of 16.1%, intention to treat); and 1319 deaths. Results: Mean age 73 years (n=5011; 24% women); 57% in NYHA II and 62% in NYHA III; ejection fraction 0.31; total cholesterol 5.2 mmol/L (200 mg/dL). 60% have a history of myocardial infarction, 63% hypertension, and 30% diabetes. Patients are well treated for heart failure with 87% on loop or thiazide diuretics, 39% aldosterone antagonists, 91% ACE inhibitor or AT-1 blocker, 75% beta-blocker, and 33% digitalis; also 51% on ASA and 36% on anticoagulants. The study was closed May 20, 2007 (mean follow-up time 2.5 years). The results of CORONA will be presented for the first time. Conclusions: The CORONA trial will determine the efficacy and safety of adding rosuvastatin 10 mg to optimal therapy in patients with ischemic heart disease and systolic HF.

Torcetrapib—Final Results of the ILLUMINATE Trial

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Hypothesis and Purpose: Torcetrapib (T), a CETP inhibitor, increases HDL cholesterol (HDL-C). High levels of HDL-C have been shown consistently to be associated with decreased risks of cardiovascular disease (CVD). The ILLUMINATE trial was designed to test whether or not T in combination with atorvastatin (A) reduces major cardiovascular disease events (MCE), when compared to A alone. Study Design and Methods: A randomized, double-blind, trial comparing T plus A (T/A) with A alone. Patients were randomized between August 2004 and December 2005. An independent endpoint committee masked to treatment adjudicated all reported events. Ethics committees of each of the 260 participating clinical sites in 7 countries approved the trial. Sample Size: 15,067 subjects. Population Studied: Adult males and females aged 45–75 at high risk for CVD events [prior coronary heart disease (CHD), peripheral vascular disease, symptomatic carotid artery disease, or type 2 diabetes] and eligible for statin treatment.

Intervention: Torcetrapib. Power Calculations: Estimated power of 0.9 for a 15% reduction in the hazard of a MCE. Primary End Point: Time to first occurrence of a MCE defined as CHD death, nonfatal myocardial infarction, stroke or unstable angina. Secondary End Points: Time to first occurrence of each individual MCE component, all-cause mortality and change from baseline in LDL-C and HDL-C. Outcome(s): In December, 2006, the independent and multidisciplinary Data and Safety Monitoring Board unanimously recommended early termination based on a totality of evidence that included an increase in all-cause mortality [T group 82/7533 vs A group 51/7534; HR=1.61 (p=0.007)]. The sponsor immediately discontinued the development program for T. The adjudication of events will complete in July/August 2007. The presentation will be the first disclosure of the final treatment comparisons including, primary and secondary CVD endpoints and their predictors. The presentation will also include baseline characteristics as well as lipid/ lipoprotein and safety parameter changes. These data should provide further insight as to whether the observed results are specific to this particular molecule or to CETP inhibition.

Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography (COR-64): Results of a Multicenter, International Trial to Assess Diagnostic Accuracy Compared With Conventional Coronary Angiography

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Background: Multidetector Computed Tomography Angiography (MDCTA) has been proposed as a non-invasive alternative to determine the presence of obstructive stenoses in patients with suspected coronary artery disease (CAD). However, prior single-center studies have reported highly variable diagnostic accuracy results and have not compared MDCTA to conventional coronary angiography (CCA) in predicting revascularization (RV). Methods: COR-64 is the first prospective, multicenter study to compare 64-row 0.5mm MDCT with CCA. Nine centers enrolled 316 pts with calcium scores ≤600 and 291 who completed MDCTA followed by CCA were available for analysis by independent core laboratories each consisting of 2 readers blinded to all clinical and cross-sectional data. All non-normal segments with ≥50% stenoses were analyzed. Stenoses were assessed visually and quantitatively by both methods. CCA lesions ≤50% were quantified by coronary angiographic (QCA) were considered significant. Pts were followed for 30 day and 6 month clinical events including RV (angioplasty and bypass surgery). Results: Of 291 pts (26% female), the median (interquartile range) age was 59 (52–66). BMI = 27 (25; 30), calcium score =80 (1, 244). The prevalence of significant CAD was 56%. Quantitative analysis of stenosis by MDCTA in comparison with QCA revealed an area under the ROC curve of 0.92 and 0.91 for QCA thresholds of 50% and 70% respectively. MDCTA visual analysis compared to QCA yielded specificity =91% [86–96] and sensitivity =83% [78–89], with PPV =92% [86–92] and NPV =61% [74–87]. Assuming non-normal segments (NES) had CAD versus excluding NES made no difference in this pt based analysis. Most importantly, quantitative MDCT had similar ability to QCA in predicting subsequent revascularization with AUC =0.80 for MDCT vs AUC =0.79 for QCA. Conclusion: In pts with suspected CAD and calcium score ≤600, 64 MDCTA can be used to assess the presence of significant CAD and the potential need for coronary revascularization. The strong performance of quantitative MDCTA analysis (AUC =0.92) was superior to visual analysis. The combination of both methods is recommended. Per segment, per vessel analyses along with 6 months clinical follow-up will be available at the time of presentation.

PCI in the OAT Trial: Lots of Bucks, Not Much Bang

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Background: The Occluded Artery Trial (OAT) compared primarily assigned percutaneous coronary intervention (PCI) with stenting vs medical therapy alone in post-MI patients (up to 28 days) with a totally occluded infarct artery and increased risk (EF <50%) and/or proximal occlusion of a major coronary artery). The primary endpoint comparison (death, MI, hospitalization for class IV heart failure) showed no evidence from PCI. Quality of life (QOL) and costs were secondary endpoints of OAT. Methods: The OAT GOL battery included the Duke Activity Status Index (DASI), emotional and social roles and function from the Short Form-36, and cardiac symptoms from the Rose Dyspnea and Angina scales. The QOL substudy included 951 patients (46% of those enrolled 2000–2004). Data were collected at baseline (median = 0, post-MI), and at 4, 12, and 24 months post randomization with 98% of forms completed. Costs were calculated on all US patients using medical billing data. Results: The OAT GOL sample was representative of the total clinical OAT cohort (median age 59 years, 83% Caucasian, 78% male). Over the first 2 years of OAT follow-up, cardiac-specific physical functioning, as reflected by the DASI, was preserved in the PCI arm while declining modestly in the medical arm. The OAT GOL subscale magnitudes of the compared arms were significant (p≤0.001) at 4 months post-MI and at 24 months post-MI (p≤0.001). The magnitude of the comparison was 92% (4 years DASI points, lowest clinically significant difference), and not clinically significant thereafter. In contrast, there was no effect of PCI on psychological well-being, as measured by the SF-36 Mental Health Inventory (MH-5). At 4 months post-MI, Rose angina rates were higher in the medical arm than in the PCI arm (16.5% vs 10.3%, p<0.049), but differences were smaller and not significant at 24 months post-MI. In the medical arm, medical costs were about $9000 higher in the PCI arm than the medical arm (p<0.0001). Follow-up medical costs for the 2 arms were similar. The cost to produce a slightly Adjusted Life Year (QALY) with PCI exceeded $100,000. Conclusions: In OAT, PCI with stenting was associated with marginally better physical functioning and less angina at 4 months but not subsequently. PCI as used in the OAT Trial is not an economically efficient way to improve health outcomes.
Late-Breaking Clinical Trials III

Subspecialty:
West Hall D-2

Abstracts

The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) Trial
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Purpose: To determine whether restoring and maintaining sinus rhythm significantly reduces cardiovascular mortality compared with a rate-control strategy in patients with both atrial fibrillation (AF) and congestive heart failure (CHF). Design: A prospective multicenter (123 sites in Canada, Brazil, Argentina, Europe and Israel) randomized clinical trial. The primary endpoint is cardiovascular mortality. Secondary endpoints include total mortality, worsening CHF events, 133 ventricular tachyarrhythmias, and 77 strokes/emboli. Follow-up is planned for 27 months. Other major clinical events noted during the trial include 832 deaths from any cause, 35% and at least one ischemic cardiovascular event in 48% of patients and the mean left ventricular ejection fraction is 27 ± 6%. Intervention(s): Patients randomized to the rhythm-control group underwent electrical cardioversion combined with amiodarone as the initial drug of choice and sotalol or dofetilide in selected cases. Patients in the rate-control arm received titrated doses of beta blockers and digoxin or both and were randomized to atrial fibrillation prophylaxis. Follow-up: The last patients are being followed-up and the study 1-year results will be available in August 2007.

Results: Current indications for CRT include patients (Pts) with QRS duration > 120ms, LVEF ≤ 35% and NYHA Class III-IV. However, some patients with narrow QRS demonstrate mechanical dyssynchrony (MD) and therefore may benefit from CRT. Methods: Pts eligible for the Resynchronization Therapy in Normal QRS (RethinQ) Study had an LVEF > 35% and NYHA Class II-III, CRT OFF (mean ± SD: 57.2 ± 14.6) compared to CRT OFF (mean ± SD: 59.3 ± 14.2), improved ≥1.0 m/kg/min/N=31, 39.7%). Conclusion: This randomized controlled trial, CRT did not improve peak VO2 in Pts with NYHA Class III heart failure, QRS duration < 130 ms and EF < 35%. Further data analysis will be critical in our understanding of CRT in this patient population.

Table 1 Demographic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N=241)</th>
<th>CRT ON (N=97)</th>
<th>CRT OFF (N=144)</th>
<th>p-value (CRT ON vs OFF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68 ± 11</td>
<td>66 ± 11</td>
<td>69 ± 11</td>
<td>0.03</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>54%</td>
<td>50%</td>
<td>57%</td>
<td>0.21</td>
</tr>
<tr>
<td>Male</td>
<td>159 (66%)</td>
<td>73 (76%)</td>
<td>86 (60%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Female</td>
<td>82 (34%)</td>
<td>24 (24%)</td>
<td>58 (38%)</td>
<td>0.42</td>
</tr>
<tr>
<td>LVEF (SD) (mm)</td>
<td>59 ± 13</td>
<td>57 ± 12</td>
<td>60 ± 14</td>
<td>0.21</td>
</tr>
<tr>
<td>Ischemic Cardiomyopathy, n (%)</td>
<td>130 (49%)</td>
<td>47 (49%)</td>
<td>83 (58%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Primary Results From the Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients (MASTER I) Trial
Theodore Chow, Dean J Kienaikas, Lindner Ctr at The Christ Hosp, Cincinnati, OH; John Onufrow, Cardiovascular Associates, LTD, Chesapeake, VA; Alan Wolfel, West Michigan Heart, Grand Rapids, MI; Srin Gurney, Naples Community Hosp, Naples, FL; Brett J Peterson, Mark L Brown, Wenji Pu, Medtronic, Inc., Minneapolis, MN; David G Benditt, Univ of Minnesota, Minneapolis, MN

Purpose: The objective was to determine if MTWA predicts LTVTE in QRS subgroups. Methods: This prospective trial was conducted at 50 US centers. Patients were eligible if they met Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) indication for device implant, and were not in atrial fibrillation. At enrollment, all patients underwent MTWA testing, with classification according to standard criteria. The protocol required that all indeterminate tests be repeated. Following MTWA testing patients underwent ICD implant, with pre-specified programming to minimize the likelihood of therapies for non-LTVTE. Minimally discordant follow-up was 2 years. Results: The analyses were conducted on 575 patients (84% male; avg. age ± SD = 65 ± 11; avg. LVEF ± SD = 24.0 ± 5.4). The final distribution of MTWA results were: MTAI = in 293 (51%), MTAI- in 214 (37%), and indeterminate in 68 (12%). Repeat testing of initially indeterminate MTWA tests resulted in a determinate test for 41 of 69 cases (59%). Over an average follow-up of 2.1 ± 0.9 years, there were 70 LTVTE (7 arrhythmic deaths and 63 appropriate device therapies). A LTVTE occurred in 48 of 361 (13%, 6.3%/yr) MTAI non-negative and 22 of 214 (10%, 5.0%/yr) MTAI negative patients. A non-negative MTWA test result was not associated with having a LTVTE (HR=1.16, 95% CI (0.76, 2.09), p=0.60). Conclusions: In MADIT II-type ICD treated patients, the risk of LTVTE does not differ according to MTWA classification.

Resynchronization Therapy in Patients With Narrow QRS (RethinQ)
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Background: Current indications for CRT include patients (Pts) with QRS duration > 120ms, LVEF ≤ 35% and NYHA Class III-IV. However, some patients with narrow QRS demonstrate mechanical dyssynchrony (MD) and therefore may benefit from CRT. Methods: Pts eligible for the Resynchronization Therapy in Normal QRS (RethinQ) Study had an LVEF > 35% and NYHA Class II-III, CRT OFF (mean ± SD: 57.2 ± 14.6) compared to CRT OFF (mean ± SD: 59.3 ± 14.2), improved ≥1.0 m/kg/min/N=31, 39.7%). Conclusion: This randomized controlled trial, CRT did not improve peak VO2 in Pts with NYHA Class III heart failure, QRS duration < 130 ms and EF < 35%. Further data analysis will be critical in our understanding of CRT in this patient population.

Table 1 Demographic Data
Late-Breaking Clinical Trials IV
Subspecialty: West Hall D2
Abstracts -

The Perioperative Ischemic Evaluation (POISE) Trial: A Randomized Controlled Trial of Metoprolol Versus Placebo in Patients Undergoing Noncardiac Surgery

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Introduction: Noncardiac surgery is associated with substantial cardiovascular mortality, morbidity, and cost. Small trials of beta-blockers suggest that they may prevent cardiovascular events in patients undergoing noncardiac surgery, but trial results are inconclusive. Objective: We undertook the PeriOperative Schemic Evaluation (POISE) Trial to determine the impact of perioperative administration of metoprolol on the 30-day risk of major cardiovascular events in patients undergoing noncardiac surgery. Methods: The POISE Trial is a blinded randomized controlled trial of metoprolol CR versus placebo in 8,000–8,500 patients undergoing noncardiac surgery who were at risk of a perioperative cardiovascular event. Patients received study drug starting 2 to 4 hours before surgery and subsequently for 30 days. The primary outcome is a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest at 30 days after surgery. Results: To date the POISE Trial has recruited over 8,000 patients in 186 centers in 23 countries. The POSE Trial will finish recruitment at the end of July 2007 and we will complete the 30-day follow-up at the end of August 2007. We will complete the trial analyses in September and early October 2007. Conclusions: The POISE Trial is the first large international perioperative cardiac trial that will provide a reliable assessment of the effects of beta-blocker therapy in patients undergoing noncardiac surgery.

A Double-Blind, Randomized Trial of Genotype-Guided Versus Standard Warfarin Dosage in Patients Initiated on Oral Anticoagulation: The Couma-Gen Study

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Background: Personalized medicine is a goal of pharmacogenetics (PG). PG-guidance of warfarin (W) dosing is a promising concept that has not been adequately tested. We performed a Couma-Gen, a prospective, randomized trial to compare PG-guided W dosing versus standard (STD) care. Methods: Patients (pts) being initiated on W with a target prothrombin time (PTT) ratio of 2.0 were enrolled and randomized double blind to a PG-guided or a STD W dosing regimen. Buccal swab DNA was genotyped for CYP2C9 *2 and *3 and VKORC1-2173G>A, using a rapid (median, 1 h) assay, STD arm initial (10 mg/d, 2 mg/d, then 5 mg/d) and subsequent dosing followed a standard protocol (after Kovacs), whereas PG arm doses were determined by a regression equation incorporating the 3 genetic variants, age, sex, and weight. Study INRs were routinely measured on days 0, 3, 5, 8, 21, 60, and 90. An un-blinded research pharmacist managed all dose adjustments using separate STD and PG algorithms. Pts were followed up to 3 mo. Endpoints included % of out-of-range (OOR) INRs (primary), time to first above range, INR, time in therapeutic range, number of INRs and dose adjustments required, and clinical and laboratory (INR >4) adverse events. Subset analysis by genotype also was performed. A study enrollment of 200 pts was planned to give 80% power to detect a reduction in %OOR INRs from 40% to 20%. Results: Study enrollment (N=200) is complete. Pt age averages 61 y, weight 93.4 kg; 53% are male. Reasons for OAC were: 11.4%; 1) MI, 1.7%; 2) VTE, 28%; 3) atrial fibrillation, 11%; 4) adverse events. Subset analysis by genotype showed that patients with the CYP2C9 *2/*2 genotype had a significantly lower rate of OOR INRs compared to the CYP2C9 *1/*1 genotype (32.9 vs 44.5%, p=0.021).

A Randomized Trial of ARB-Based Versus Non-ARB Standard Therapy in Patients With Coronary Artery Disease and Hypertension: HIJ-CREATE Study

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Hypothesis and Purpose: It remains uncertain whether Angiotensin II receptor blockers (ARBs) reduce the risk of coronary disease events. The primary hypothesis is that the ARB-based pharmacotherapy would reduce the cardiovascular events observed in angiographically documented coronary artery disease (CAD) patients with hypertension. Study Design and Methods: A multicenter, prospective, randomized, open-label, blinded-endpoint trial was performed. The incidence of any endpoint events as well as drug safety concerns was determined during the scheduled 6-, 12-, 24-, 36-, and 60-month outpatient visits. Sample Size: A total of 2,049 patients were randomly assigned to candesartan-based therapy without any angiotensin-converting enzyme inhibitors (ACEIs) or non-ARB based standard therapy at 14 sites throughout Japan between June 2001 and April 2004. Population Studied: The study population included patients with acute coronary syndrome (35.3%), and prior myocardial infarction (38.9%), respectively. Intervention(s): The eligible patients were placed into either the candesartan-based treatment arm or non-ARB-based treatment arm according to a computer-generated, stratified, permuted-block randomization code. Power Calculations: The primary endpoint event rate for approximately 100 events/1000 person-years in the control group was estimated to be 2% at a 90% power of significance with an 8% power, 1015 patients per group were required during the enrollment and a follow-up period of at least 3 years. Primary End Points: The primary endpoint of the present study was the time to the first major adverse cardiovascular event. Secondary End Points: The major secondary endpoints included the incidence of coronary revascularization and new-onset diabetes. Outcome(s)/Statistical Plan or Main Results: There were 552 primary events during a mean follow-up of 4.2 years: 264 (25.6%) in the candesartan group and 288 (28.1%) in the non-ARB group (relative risk 0.89 [95% CI 0.76–1.08], p=0.04). However, candesartan significantly reduced the incidence of the primary end points at 3–6 months after randomization (HR=0.55–0.59, 95% CI 0.34–0.91, p<0.021).

Propective Evaluation of Rifalazil Effect on Vascular Symptoms of Intermittent Claudication (IC) and Other Endpoints in Chlamydia Seropositive Patients (The PROVINCIE-1 Trial)

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Background: Chlamydia pneumoniae may promote atherosclerosis, and antibiotics with activity against C. pneumoniae may have clinical benefit in peripheral arterial disease (PAD). Rifalazil is a fumaric acid derivative that is a particularly potent anti-Chlamydia agent. PROVINCIE-1 is a prospective double blind multicenter international trial that tested the hypothesis that rifalazil improves exercise performance in patients with PAD and intermittent claudication. Methods: Subjects with intermittent claudication due to PAD from 3 countries and 44 centers were prospectively randomized to receive rifalazil or placebo every 8 weeks or matching placebo. Inclusion criteria included hemodynamic tests confirming PAD and subjects with antibody titers of C. pneumoniae >1:128. The primary endpoint was change in peak walking time (PWT) as measured by a graded treadmill test six months following initiation of treatment. Of the 297 randomized patients, 292 (94.9%) had at least one post-baseline treadmill test assessment and qualified for the intent-to-treat (ITT) population. Safety and quality of life assessments also were evaluated at 3, 6 and 12 months. Results: At baseline, the mean (min-max) age of patients in the ITT population (n=257) was 66 (42–83) years; 86% were males; 20% had diabetes mellitus; and 36% were current tobacco users. The mean (min-max) PWT and claudication onset time (COT) from the average of two baseline exercise treadmill tests was 252 (71–692), and 107 (24–523) seconds, respectively. The median (min-max) baseline ankle-brachial index (ABI) was 0.62 (0.24–4.16); upper range of the ABI reflects values ≤0.90 where patients met enrollment criteria based on other hemodynamic tests, n=281. Results above are from the open clinical database as of June 15, 2007. The final results of the trial will be presented at the annual meeting. Conclusions: Antibiotic treatment for C. pneumoniae is a novel approach for the treatment of PAD. This study will determine whether rifalazil is an effective therapy for treating intermittent claudication in patients with PAD.

Cell Stem Cell Therapy in Humans: The Next Steps
Subspecialty: Translational Science Room W414bdc
Abstracts -

Final One-Year Results of the CAUSMIC Trial: First United States Randomized Controlled Trial Utilizing 3-Dimensional Guided, Catheter-Based Delivery of Autologous Skeletal Myoblasts for Ischemic Cardiomyopathy

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Background: Previous Phase I clinical trials have used epicardial injection of myoblasts. This study was designed to assess the safety and feasibility of using 3-D guided catheter based injection of myoblasts to the endocardium. Methods and Results: Twenty-three subjects, who had previous myocardial infarction and symptoms of congestive heart failure, NYHA Class II–IV were enrolled. All 23 subjects received autologous skeletal myoblasts in addition to medical therapy (MMT). Subjects were followed for 12 months. Safety evaluations included clinical examination, ECG, echocardiography, device interrogation and laboratory tests. Effects on cardiac perfor-
myocardial viability as measured by electromechanical voltage mapping. Conclusions: This Phase I trial showed favorable outcomes at all myocardial sites, including the highest dose of 600 million cells. Importantly, at 12 months follow-up, there were no differences in control versus treated patients concerning occurrence of arrhythmias. Patients treated with myoblasts showed improved measures of quality of life, ventricular viability, and echocardiographic measures of ventricular dimensions. Control patients showed declines in these same measures. These data demonstrate positive outcomes and warrant initiation of larger Phase 2, double-blind, placebo controlled clinical trials to demonstrate the efficacy of myoblast transplantation in heart failure patients.

**Efficacy and Safety of Intracoronary Injection of Mononuclear Bone Marrow Cells After Thrombolytic Therapy of Acute Myocardial Infarction**

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**Introduction:** Controversial results have been reported of the effects of bone-marrow derived stem-cells (BMC) in patients treated with primary coronary intervention (PCI) of an acute STEMI. This study was designed to assess the efficacy and safety of BMC therapy after thrombolytic therapy of an acute STEMI. **Methods:** In a two-center study (FINCELL trial), 80 consecutive patients with an acute STEMI, treated with thrombolysis followed by PCI 1–5 days after STEMI, were randomly assigned to receive intracoronary BMCs or placebo medium into the infarct artery. Efficacy was assessed by measurement of global ejection fraction by left ventricular angiography and 2-D echocardiography. Safety was assessed by measuring various arrhythmia risk variables, such as heart rate variability, late potentials on signal-averaged ECG and exercise-induced T-wave alternans, and by assessing the restenosis of the stented culprit lesion by intravascular ultrasound. These procedures were performed 0–3 days after BMC delivery and repeated 6 months after the STEMI. By June 2007, 66 patients have underwent the six months’ procedures. **Results:** At six months, the patients randomized to BMC therapy (n=33) showed a significant increase of the global EF measured by angiography (from 59±8% to 67±9, p<0.0001) and 2-D echocardiography (p<0.01). The EF remained unchanged in the placebo group (n=33) evaluated both by angiography and 2-D echocardiography (NS for both), the mean EF being 62±12% at baseline and 64±14% at six months in angiography (p<0.02 for the change in EF between the BMC and placebo group). No differences were observed between the groups in the measures of heart rate variability, signal-averaged ECG, prevalence of positive T-wave alternans tests, or the minimal lumen diameter and area of the stented culprit lesion. **Conclusion:** We conclude that intracoronary BMC-therapy is associated with an improvement of global left ventricular function and neutral effects on arrhythmia risk profile and restenosis of the stented coronary lesions in patients treated with thrombolytic therapy of an acute STEMI.

**Intramuscular or Intracoronary Administration of Autologous Bone Marrow Cells Fails to Improve Contractility of Scarred Myocardium**

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To study whether bone marrow cells (BMCs) improve the contractility of scarred akinetic myocardium and to elucidate the best route of delivery, a double blinded randomized study involving 63 elective bypass grafting patients, with established infarct scars ondobutamine stress echocardiogram (DSE) and confirmed at surgery, was conducted. Patients were allocated into one of the following groups: control (no injection), intramuscular (IM) or intracoronary (IC). BMCs were obtained from the iliac crest during surgery, separated and diluted in autologous serum. At the end of surgery, 10 ml of diluted BMCs were injected (500 µl/injection 1 cm apart) into the mid-depth of the scar area in the IM group or via the graft conduit supplying the scar area in the IC group. A mean(±SD) of 81±56 x10⁶ and 124±73 x10⁶ BMCs and 135±163 x10⁶ and 285±261 x10⁶ CD34+/CD117+ cells were injected in the IM and IC groups, respectively. Regional function was assessed by DSE before and 6 months after treatment using the American Society of Echocardiography 16 segment model. Cardiac MRI was also performed for the last 33 patients. There were no complications or deaths related to BMCs injections. The change in segmental wall motion score index at rest, at low and high dose DSE were similar in all three groups (p≠AS). Fractional thickening did not improve significantly with BMCs at rest (control -5.7±6.8 to -1.7±11.1%; IM -3.4±8.5 to -2.9±7.9%; IC -5.7±6.6 to -4.5±8.1%; p≠AS) and at low dose stress (control -5.5±6.8 to -2.5±15.0%; IM -3.7±6.6 to -2.5±15.0%; IC -7.8±6.5 to -4.1±11.3%; p≠AS). The % infarct volume and gadolinium delayed enhancement and ejection fraction were not improved by BMCs. Similarly, the end-systolic and diastolic LV volumes were not significantly affected by treatment. In conclusion, IM or IC administration of autologous BMCs into scarred myocardium does not improve contractility of the injected areas.