Cardiology News /Recent Literature Review / Last Quarter 2011

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The **ACC** Meeting is slated for 24-27/3/2012 in Chicago

The **Athens Cardiology Update 2012** is slated for April 5-7, 2012

The **HRS** 33rd Meeting will be held in Boston, 9-12/5/12

The **ESC** Congress will be held in Munich, 25-29/8/2012

ALLHAT Trial: Once Heart Failure Develops in High-Risk Hypertensive Patients, Mortality is High

At a mean follow-up of 8.9 years, of 1761 participants in the ALLHAT trial with incident heart failure (HF) in-trial, 1348 (77%) died. Mortality rates were similar across treatment comparisons, with adjusted 10-year all-cause mortality rates per 100 persons of 83 for chlorthalidone, 86 for amlodipine, and 87 for lisinopril. Mortality was similar for those with preserved (81%) and low ejection fraction (84%). Thus, once HF develops, risk of death is high and consistent across randomized treatment groups. Measures to prevent the development of HF, especially blood pressure control, must be a priority if mortality associated with the development of HF is to be addressed (Piller LB et al, ***Circulation*** 2011;124:1811-1818).

Isolated Low HDL-Cholesterol is Associated with Increased Coronary Risk

Data from 220 060 participants (87% Asian) in 37 studies from the Asia-Pacific region indicated low HDL-C (HDL <40 mg/dl in men and <50 mg/dl in women) among 33.1% of Asians vs 27.0% of non-Asians (P<0.001). The prevalence of low HDL-C in the absence of other lipid abnormalities (isolated low HDL-C) was higher in Asians compared with non-Asians: 22.4% vs 14.5%, respectively (P<0.001). After 6.8 years, there were 574 coronary heart disease and 739 stroke events. There was an inverse relationship between low HDL-C with coronary heart disease in all individuals (hazard ratio, 1.57). In Asians, isolated low levels of HDL-C were as strongly associated with coronary heart disease risk as low levels of HDL-C combined with other lipid abnormalities (hazard ratio, 1.67 vs 1.63, respectively). There was no association between low HDL-C and stroke risk (Huxley RR et al, ***Circulation***2011;124:2056-2064).

Occluded Artery Trial (OAT) Extended Follow-up: No Reduction of Long-term Rates of Clinical Events After Routine PCI in Stable Patients

OAT randomized 2201 stable patients with infarct-related artery total occlusion >24 hours (days 3–28) after myocardial infarction (MI), excluding patients with severe inducible ischemia, rest angina, class III-IV heart failure, and 3-vessel/left main disease. At extended follow-up (6-year median survivor follow-up; longest, 9 years), rates of fatal and nonfatal MI, death, and class IV heart failure were similar for the PCI and medical therapy alone groups. The vast majority of patients at each follow-up visit did not report angina. There was less angina in the PCI group through early in follow-up; there was a trend toward less angina in the PCI group at 3 and 5 years. The 7-year rate of PCI of the infarct-related artery during follow-up was 11.1% for the PCI group compared with 14.7% for the medical therapy alone group (hazard ratio, 0.79; P=0.06). The authors concluded that extended follow-up of the OAT cohort showed no reduction of long-term rates of clinical events after routine PCI in stable patients with a totally occluded infarct-related artery and without severe inducible ischemia in the subacute phase after MI (Hochman JS et al, ***Circulation*** 2011;124:2320-2328).

No Mortality Advantage for Transfer for Primary PCI over Onsite Thrombolysis when Transfer Door-to-needle Time Exceeds ~2 Hours

Among ST-segment–elevation myocardial infarction (STEMI) patients enrolled in a registry within 12 hours of pain onset, 81% of transfer for PCI patients were matched (n=9506) to onsite thrombolysis patients (n=9506). In the matched cohort, PCI was performed with delays >90 minutes in 68%. Multivariable analysis found no mortality advantage for transfer for PCI over onsite thrombolysis when transfer door-to-needle time exceeded ~120 minutes. The authors concluded that PCI-related delays are extensive among patients transferred for PCI and are associated with poorer outcomes. No differential excess in mortality was seen with transfer for PCI compared with onsite thrombolysis even with long PCI-related delays, but as transfer door-to-needle time times increase, the mortality advantage for PCI over onsite thrombolysis declines (Pinto DS et al, ***Circulation*** 2011;124:2512-2521).

ALPHEE Study: Celivarone was not Effective for the Prevention of ICD Interventions or Sudden Death

Celivarone, a noniodinated benzofuran derivative is a multichannel blocker and like amiodarone and dronedarone, it has class I, II, III, and IV antiarrhythmic effects, but may have an improved side-effect profile, faster time to effect and elimination times, and a reduced potential for drug-drug interactions. Celivarone (50, 100, or 300 mg/d) was compared with placebo and amiodarone (200 mg/d after loading dose of 600 mg/d for 10 days) in 486 patients with a left ventricular ejection fraction $\leq$40%

and at least 1 ICD intervention for ventricular tachycardia (VT) or ventricular fibrillation (VF) in the previous month or ICD implantation in the previous month for documented VT/VF. At a median treatment duration of 9 months, the proportion of patients experiencing an appropriate ICD intervention or sudden death was 61.5% in the placebo group; 67.0%, 58.8%, and 54.9% in the celivarone 50-, 100-, and 300-mg groups, respectively; and 45.3% in the amiodarone group. None of the comparisons vs placebo were statistically significant. Thus, celivarone was ineffective, although it had an acceptable safety profile (Kowey PR et al, ***Circulation*** 2011;124:2649-2660).

ROCKET-AF: Patients with AF and Moderate Renal Insufficiency Receiving Rivaroxaban Have Higher Rates of Stroke and Bleeding

In the ROCKET-AF study, 14 264 patients with AF were randomized to rivaroxaban 20 mg/day [15 mg/day if creatinine clearance (CrCl) 30–49 mL/min] or dose-adjusted warfarin (target INR 2.0–3.0). Compared with patients with CrCl >50 mL/min (mean age 73 years), the 2950 (21%) patients with CrCl 30–49 mL/min were older (79 years) and had higher event rates irrespective of study treatment. Among those with CrCl 30–49 mL/min, stroke or systemic embolism occurred in 2.32 per 100 patient-years with rivaroxaban 15 mg/day vs. 2.77 per 100 patient-years with warfarin [hazard ratio (HR) 0.84] in the per-protocol population. Intention-to-treat analysis yielded similar results (HR 0.86) to the per-protocol results. Rates of major and clinically relevant non-major bleeding (17.82 vs. 18.28 per 100 patient-years; P= NS) and intracranial bleeding (0.71 vs. 0.88 per 100 patient-years; P =NS) were similar with rivaroxaban or warfarin. Fatal bleeding (0.28 vs. 0.74% per 100 patient-years; P = 0.047) occurred less often with rivaroxaban (Fox KAA et al, ***Eur Heart J*** 2011; 32: 2387–2394).

GREATER-EARTH STUDY: Left ventricular (LV) Pacing is not Superior to Biventricular (BiV) Pacing, but Nonresponders to BiV Pacing May Respond Favorably to LV Pacing

The effects of LV and biventricular (BiV) pacing on exercise tolerance and LV remodeling were compared in 121 patients with an LV ejection fraction $\leq$35%, QRS $\geq$120 ms, and symptoms of heart failure. Exercise duration at 75% of peak VO2 (primary outcome) increased from 9.3$\pm$6.4 to 14.0$\pm$11.9 and 14.3$\pm$12.5 min with LV and BiV pacing, respectively, with no difference between groups (*P*=NS). LV ejection fraction improved from 24$\pm$6% to 32$\pm$11% and 31$\pm$10% with LV and BiV pacing, respectively, with no difference between groups (*P*=NS). Reductions in LV end-systolic volume were also similar (*P*=NS). The percentage of clinical responders ($\geq$20% increase in exercise duration) to LV and BiV pacing was 48.0% and 55.1% (*P*=NS). Positive remodeling responses ($\geq$15% reduction in LV end-systolic volume) were noted in 46.7% and 55.4% (*P*=0.0881). Overall, ~31% of LV nonresponders improved with BiV and 17% of BiV nonresponders improved with LV pacing (Thibault B et al, ***Circulation*** 2011; 124:2874-2881).

TREAT Study: Darbepoetin Alfa Increases Strokes in Patients With Type 2 Diabetes Mellitus, Chronic Kidney Disease, and Anemia

In 4038 patients with diabetes mellitus, chronic kidney disease, and anemia, randomized to receive darbepoetin alfa or placebo, the risk of stroke was doubled with darbepoetin alfa: 154 patients had a stroke, 101/2012 (5.0%) in the darbepoetin alfa arm and 53/2026 (2.6%) in the placebo arm (hazard ratio 1.9). Independent predictors of stroke included assignment to darbepoetin alfa (odds ratio 2.1), history of stroke (odds ratio 2.0), more proteinuria, and known cardiovascular disease. In patients assigned to darbepoetin alfa, postrandomization systolic and diastolic blood pressure, hemoglobin level, platelet count, and darbepoetin alfa dose did not differ between those with and without stroke. Thus, the authors concluded that the 2-fold increase in stroke with darbepoetin alfa in TREAT could not be attributed to any baseline characteristic or to postrandomization blood pressure, hemoglobin, platelet count, or dose of treatment. These readily identifiable factors could not be used to mitigate the risk of darbepoetin alfa–related stroke (Skali H et al, ***Circulation*** 2011;124:2903-2908).

2-Year Results of the PACE Trial: Biventricular (Biv) Pacing is Superior to Right Ventricular Apical (RVA) Pacing in Bradycardia Patients with Preserved Systolic Function

Patients (n = 177) with bradycardia and preserved left ventricular (LV) ejection fraction (EF $\geq$45%) were randomized to receive RVA or BiV pacing. In the RVA pacing group (81 patients completing 2-year follow-up), LVEF further decreased from the first to the second year, but it remained unchanged in the BiV pacing group (n=82), leading to a significant difference of 9.9 % points between groups at 2-year follow-up (P < 0.001). Similarly, LV end-systolic volume (ESV) continued to enlarge from the first to the second year in the RVA pacing group (a difference of 13.0 mL; P < 0.001). Eighteen patients in the BiV pacing group (20.2%) and 55 in the RVA pacing group (62.5%) had a significant reduction of LVEF (of $\geq$5%, P < 0.001). Thus, the authors concluded that LV adverse remodelling and deterioration

of systolic function continues at the second year after RVA pacing. This deterioration is prevented by BiV pacing (Chan JY et al, ***Eur Heart J*** 2011; 32:2533-2540).

Everolimus Eluting Stents (EES) are Associated with Significant Reductions in Stent Thrombosis, Target Vessel Revascularization (TVR) and Myocardial Infarction (MI) compared to non–Everolimus-Eluting Drug Eluting Stents (DES)

A total of 13 randomized trials (n = 17,101) were identified with a 22-month mean follow-up. Compared with non–everolimus eluting DES, the EES significantly reduced stent thrombosis (relative risk [RR]: 0.55; p = 0.001), TVR (RR: 0.77; p = 0.004), and MI (RR: 0.78; p = 0.02). There was no difference in cardiac mortality between the groups (RR: 0.92; p = 0.38). The treatment effect was consistent by different follow-up times and duration of clopidogrel use. The treatment effects increased with higher baseline risks of the respective control groups with the strongest correlation observed for stent thrombosis (R^2 = 0.89, p < 0.001) (Baber U et al, ***J Am Coll Cardiol*** 2011;58:1569–1577).

HORIZONS-AMI Trial: Patients with In-hospital Major Bleeding (IHMB) after Primary PCI Have Increased 3-Year Rates of Morbidity and Mortality

Primary PCI was performed in 3,345 (92.9%) of 3,602 patients in the HORIZONS-AMI trial; in-hospital major bleeding (IHMB) developed in 231 (6.9%). At 3-year follow-up, patients with IHMB had higher mortality (24.6% vs. 5.4%, p < 0.0001) and major adverse cardiovascular events (40.3% vs. 20.5%, p < 0.0001). The harmful effect of major bleeding was observed within 1 month, between 1 month and 1 year, and between 1 and 3 years. IHMB was an independent predictor of mortality (hazard ratio: 2.80, p < 0.0001) at 3-year follow up. Thus, the authors concluded that patients with IHMB after primary PCI have significantly increased 3-year rates of morbidity and mortality. Further investigation is warranted to understand the mechanisms underlying this relationship and to further improve outcomes in patients with ST-segment myocardial infarction (Suh J et al, ***J Am Coll Cardiol*** 2011;58: 1750–1756).

EPHESUS Substudy: Mineralocorticoid Receptor Antagonism Provides Cardiovascular Protection Beyond its Diuretic and Potassium-sparing Properties

In the EPHESUS study, in which 6,080 patients with acute MI and heart failure with left ventricular dysfunction received eplerenone, a diuretic effect was indirectly estimated by changes at 1 month that was superior to the median changes in the placebo group in body weight (-0.05 kg) and in the estimated plasma volume reduction (+1.4%). In the eplerenone group, body weight (p < 0.0001) and plasma volume (p = 0.047) decreased, whereas blood protein and serum potassium increased (both, p < 0.0001), as compared with the placebo group, suggesting an eplerenone-induced diuretic effect, associated with a potassium-sparing effect. A diuretic effect, as an estimated plasma volume reduction, was independently associated with 11% to 19% better outcomes (lower all-cause death, cardiovascular death or cardiovascular hospitalization, all-cause death or hospitalization, hospitalization for heart failure). Potassium sparing was also independently associated with 12% to 34% better outcomes. There was no significant interaction between the observed beneficial effects of eplerenone (9% to 17%) on cardiovascular outcomes and potassium-sparing or diuretic effects. Thus, the authors concluded that eplerenone's beneficial effects on long-term survival and cardiovascular outcomes were independent from early potassium-sparing or diuretic effects, suggesting that mineralocorticoid receptor antagonism provides cardiovascular protection beyond its diuretic and potassium-sparing properties (Rossignol P et al, ***J Am Coll Cardiol*** 2011;58:1958–66).

U.K. TAVI Registry: Midterm to Long-term Survival after Transcatheter Aortic Valve Implantation (TAVI) is Encouraging, Although a Substantial Proportion of Patients Die Within the First Year

Data were collected prospectively on 870 patients undergoing 877 TAVI procedures up until December 31, 2009. Survival at 30 days was 92.9%, at 1 year 78.6% and at 2 years 73.7%. There was a marked attrition in survival between 30 days and 1 year. In a univariate model, survival was significantly adversely affected by renal dysfunction, the presence of coronary artery disease, and a nontransfemoral approach; whereas left ventricular function (ejection fraction <30%), the presence of moderate/severe aortic regurgitation, and chronic obstructive pulmonary disease remained the only independent predictors of mortality in the multivariate model. Thus, the authors concluded that midterm to long-term survival after TAVI was encouraging, although a substantial proportion of patients died within the first year (Moat NE et al, ***J Am Coll Cardiol*** 2011;58:2130–8).

"Real World" Adhoc PCI With Use of Sirolimus Eluting Stents (SES) and a Uniform Single-Operator Approach with 0.5 mm Stent Oversizing and High-Pressure (>12-18 bar) Deployment Routinely Combined with Long-term Dual Antiplatelet Therapy Results in Excellent 1 & 2 Year Oucomes

Among 260 patients receiving SES and/or other stents, 3 groups were compared: 104 (40%) patients receiving

SES alone (Group A), 122 patients receiving SES plus other drug-eluting stents (DES) (Group B), and 34 patients receiving SES plus bare metal stents (BMS) (Group C).The majority (93.8%) of PCI procedures were performed adhoc. Procedural success (99-100%) and residual stenosis (<0-10%) were similar among the 3 groups. Multivessel PCI and stenting was performed in 120 (46.3%) patients and multilesion PCI in the majority (89.2%) in this cohort. A median of 2 stents (mean of 2.6±1.3 stents) were implanted. There was one occurrence of subacute stent thrombosis in group C (0.4%). All patients received combined therapy with aspirin and clopidogrel for >24 months. Over 16.3±14.7 months of follow-up, survival free of events (death, MI, stroke, repeat revascularization and restenosis) was excellent at 98%, 96%, and 97% at 12 months and 95%, 90% and 97% at 24 months for groups A, B and C respectively; p = 0.27. Clinical restenosis rates were low in all 3 groups (0% vs 1.6% vs 5.9%) (p=NS). Possible very late stent thrombosis could be suspected in 1 patient (group B). Thus, the authors concluded that in 260 patients receiving SES and/or other stents, a uniform single-operator approach with 0.5 mm stent oversizing and high-pressure (>12-18 bar) deployment routinely combined with long-term dual antiplatelet therapy resulted in high procedural success (>99%), very low rate of subacute (0.4%) and late stent thrombosis (0.4%), very low clinical restenosis rates (0-5.9%) and overall excellent survival free of cardiovascular events at 1 and 2 years (Manolis et al, ***Hosp Chronicles*** 2011; 6: 182-194).

Correction of Mitral Regurgitation in Nonresponders to Cardiac Resynchronization Therapy by MitraClip Has a Beneficial Effect

A total of 51 patients with severe symptoms not responding to cardiac resynchronization therapy (CRT) who also had significant functional mitral regurgitation (MR) (grade ≥2) underwent perutaneous MR correction with insertion of the MitraClip (MC). MC treatment was feasible in all patients (49% 1 clip, 46% 2 clips). There were 2 periprocedural deaths. Median follow-up was 14 months. New York Heart Association functional class improved acutely upon discharge (73%) and continued to improve progressively during follow-up. The proportion of patients with significant residual MR (grade ≥2) progressively decreased during follow-up. Reverse LV remodeling and improved LVEF were detected at 6 months, with further improvement at 12 months. Overall 30-day mortality was 4.2%. Mortality during follow-up was 19.9 per 100 person-years. Nonsurvivors had more compromised clinical baseline conditions, longer QRS duration, and a more dilated heart. Thus, the authors concluded that functional MR treatment with the MitraClip in CRT nonresponders was feasible, safe, and demonstrated improved functional class, increased LVEF, and reduced LV volumes in about 70% of patients. (Auricchio A et al, ***J Am Coll Cardiol*** 2011;58:2183–2189).

PRELUDE Registry: VT/VF Inducibility is Unable to Identify High-risk Brugada Syndrome Patients

The registry included 308 patients with a spontaneous or drug-induced Brugada type I ECG and without history of cardiac arrest. Programmed electrical stimulation was performed at enrollment and ventricular tachyarrhythmias were induced in 40% of patients.. During a median follow-up of 34 months, 14 arrhythmic events (4.5%) occurred: 13 appropriate shocks of the implantable defibrillator (ICD), and 1 cardiac arrest. Arrhythmia inducibility was not a predictor of events at follow-up (9 of 14 events occurred in noninducible patients). History of syncope and spontaneous type I ECG (hazard ratio - HR: 4.20), ventricular refractory period <200 ms (HR: 3.91), and QRS fragmentation (HR: 4.94) were significant predictors of arrhythmias. Thus, the authors concluded that VT/VF inducibility was unable to identify high-risk patients, while the presence of a spontaneous type I ECG, history of syncope, ventricular effective refractory period <200 ms, and QRS fragmentation seemed useful to identify candidates for prophylactic ICD (Priori SG et al, ***J Am Coll Cardiol*** 2012;59:37–45).

Important Review and Other Articles

Mechanisms of coronary artery spasm (Lanza et al, ***Circulation*** *2011;124:1774-1782),* Calcific aortic valve disease (Rajamannan et al, ***Circulation*** *2011;124:1783-1791),* Assessing adiposity (Cornier M-A et al, ***Circulation*** 2011; 124: 1996-2019), 2011 ACCF/AHA Focused Update of the Guideline for the management of patients with peripheral artery disease (Rooke TW et al, ***Circulation*** 2011; 2020-2045), Atrial fibrillation pathophysiology (Iwasaki Y et al, ***Circulation*** 2011; 124: 2264-2274), 2011 ACCF/AHA/SCAI Guideline for PCI (Levine GN et al, ***Circulation*** 2011;124:e574-e651), 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery (Hillis LD et al, ***Circulation*** 2011; 124: e652-e735), 2011 ACCF/AHA Guideline for the diagnosis & treatment of hypertrophic cardiomyopathy (Gersh BJ et al, ***Circulation*** 2011;124: e783-e831), ESC Guidelines for management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (***Eur Heart J*** 2011; 32: 2999-3054), ESC Guidelines on the management of cardiovascular diseases during pregnancy (Regitz-Zagrosek V et al, ***Eur Heart J*** 2011;32: 3147-3197).