Cardiology News /Recent Literature Review Third Quarter 2012

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TCT Meeting will take place in Miami, 22-26/10/12

HCS Meeting to be held in Athens, 1-3/11/12

AHA 2012 is scheduled for Los Angeles, 3-7/11/12

EuroEcho will take place in Athens, 5-8/12/2012

HCS Working Group Seminars: Thessaloniki, 14-16/2/2013

ACC Meeting: San Francisco, 9-11/3/13

HRS Meeting: Denver, 8-11/5/13

EuroPCR: Paris, 21-24/5/13

EuroPace: Athens, 23-26/6/13

ESC Congress: Amsterdam, 31/8-4/9/13

Dennmark Cohort Study: In Patients with AF, Interruption of Warfarin Confers Increased Short-Term Risk of Death or Thrombo-Embolic Events

In total, 48,989 atrial fibrillation (AF) patients receiving warfarin were included in this retrospective cohort study. Of these, 35,396 patients had at least one episode of warfarin treatment interruption. In all, 8255 deaths or thromboembolic events occurred during treatment interruption showing an initial clustering of events during 0–90 days. The first 90-day interval of treatment interruption was associated with a markedly higher risk of death or thrombo-embolism (incidence rate ratio-IRR 2.5) vs the interval of 271–360 days. The authors concluded that in this patient population with AF, almost 3 out of 4 patients on warfarin treatment had one or more periods of treatment interruption. Interruption of warfarin therapy was associated with a significantly increased short-term risk of thrombo-embolism or death during the first 90 days of interruption (Raunso J et al, ***Eur Heart J*** 2012; 33: 1886–1892).

Left Ventricular Dyssynchrony May Determine Outcome Following CRT in Patients with RBBB and Help in the Selection of CRT Candidates

Echocardiography was performed in 561 cardiac resynchronization therapy (CRT) recipients (89 with RBBB & 472 with LBBB) before and 6 months after CRT. RBBB patients had a higher prevalence of male gender, ischemic heart disease, atrial fibrillation, and lower exercise capacity when compared with LBBB patients, despite smaller left ventricular (LV) volumes. In addition, the extent of both interventricular and LV dyssynchrony was less in RBBB patients. At 6 months, RBBB patients also showed limited LV reverse remodelling. LV dyssynchrony and mitral regurgitation were identified as independent predictors of all-cause mortality or heart failure hospitalization among RBBB patients. The authors concluded that RBBB patients referred for CRT exhibit interventricular and LV dyssynchrony, albeit less than their LBBB counterparts; preimplantation LV dyssynchrony may be an important determinant of death or heart failure hospitalization among CRT recipients with RBBB (Leong DP et al, ***Eur Heart J*** 2012; 33: 1934–1941).

Danish Cohort Study: Psoriasis is Associated With Increased Risk of AF and Ischemic Stroke

In this cohort study of the entire Danish population followed from 1997 to 2006, 36,765 patients with mild psoriasis and 2,793 with severe psoriasis were compared with the reference population (4,478,926 individuals). In patients with mild psoriasis, the adjusted rate ratios (RRs) for atrial fibrillation (AF) were 1.50 and 1.16 in patients aged <50 & ≥50 years, respectively. Patients with severe psoriasis had a higher risk of AF with RRs 2.98 in patients aged <50 years & 1.29 in patients aged ≥50 years. Patients with psoriasis also demonstrated a disease severity-dependent increased risk of ischemic stroke. The authors concluded that psoriasis is a risk factor for AF and ischemic stroke with highest risk in young patients with severe psoriasis. The results add to accumulating evidence indicating that patients with psoriasis are at increased cardiovascular risk (Ahlenhoff O et al, ***Eur Heart J*** 2012; 33, 2054–2064).

CRUSADE Registry: In-hospital Major Bleeding Confers Increased Mortality in Older Patients Hospitalized for NSTEMI

Among 32,895 NSTEMI patients aged ≥65 years, 11.9% (n=3902) had an in-hospital major bleeding event. Cumulative mortality was higher in those who had a major bleed vs those without at 30 days, 1 year, and 3 years. Major bleeding was significantly associated with higher mortality over time in the overall population: (i) discharge to 30 days (hazard ratio-HR 1.33); (ii) 31 days-1 year (1.19); (iii) 1-3 years (1.09), & (iv) attenuating beyond 3 years (1.14). In-hospital bleeding continued to be significantly associated with higher mortality even beyond 3 years (1.25). The authors concluded that in-hospital major bleeding is associated with short-, intermediate-, and long-term mortality among older patients hospitalized for NSTEMI—this association is strongest within the first 30 days. Regarding the longer duration of risk, major bleeding rather identifies patients with an underlying risk for mortality (Lopes RD et al, ***Eur Heart J*** 2012; 33: 2044–2053).

LIPSIA-NSTEMI Trial: No Advantage of Immediate Invasive Over an Early or a Selective Invasive Approach in NSTEMI Patients

Patients with NSTEMI were randomized to either an immediate (<2 h; n=201), an early (10–48 h; n=200), or a selective invasive approach (n=201). The median time from randomization to angiography was 1.1 h in the immediate vs 18.6 h in the early & 67.2 h in the selective invasive group (P<0.001). There was no significant difference in the peak CK-MB activity among groups. The key secondary clinical endpoints were similar among groups at 6-month follow-up: death and infarction: 21 vs 16 vs 14.5%; P=NS; death, infarction, refractory ischemia: 20.9 vs. 21.5 vs. 22%; P=NS; death, infarction, refractory ischemia, rehospitalization: 26.0 vs. 26.5 vs. 24.5%; P=NS. The authors concluded that in NSTEMI patients, an immediate invasive approach does not offer an advantage over an early or a selective invasive approach with respect to large myocardial infarctions as defined by peak CK-MB levels, which is supported by similar clinical outcomes (Thiele H et al, ***Eur Heart J*** 2012;33:2035–2043).

LBBB Induced by TAVI Increases Risk of Death

Of 679 patients analyzed, 387 (57%) underwent TAVI with the Medtronic CoreValve system and 292 (43%) with the Edwards SAPIEN valve. A total of 233 patients (34.3%) developed new LBBB. Median follow-up was ~450 days. All-cause mortality was 37.8% (n=88) in patients with LBBB and 24% (n=107) in patients without LBBB (*P*=0.002). Independent predictors of all-cause mortality were TAVI-induced LBBB (hazard ratio -HR, 1.54), chronic obstructive lung disease (HR, 1.56), female gender (HR, 1.39), left ventricular ejection fraction ≤50% (HR, 1.38), and baseline creatinine (HR, 1.32). LBBB was more frequent after implantation of the Medtronic CoreValve System than after Edwards SAPIEN implantation (51% & 12%, respectively; *P*<0.001), but device type did not influence the mortality risk of TAVI-induced LBBB. The authors concluded that all-cause mortality after TAVI is higher in patients who develop LBBB than in patients who do not; TAVI-induced LBBB is an independent predictor of mortality (Houthuizen P et al, ***Circulation*** 2012; 126:720-728).

Subclinical Thyroid Dysfunction: Risk of Heart Failure Increases both with Lower and Higher TSH Levels, particularly with TSH Levels ≥10.0 mIU/L and <0.10 mIU/L

A pooled analysis of 25,390 participants in 6 prospective cohorts in US & Europe revealed subclinical hypothyroidism (TSH: 4.5-19.9 mIU/L) in 2068 (8.1%) and subclinical hyperthyroidism (<0.45 mIU/L) in 648 (2.6%) (all with normal free thyroxine levels). Risks of heart failure events were increased with both higher and lower TSH levels (*P* <0.01); the hazard ratio was 1.01 for TSH of 4.5 to 6.9 mIU/L, 1.65 for TSH of 7.0 to 9.9 mIU/L, 1.86 for TSH of 10.0 to 19.9 mIU/L (*P* for trend <0.01) and 1.31 for TSH of 0.10-0.44 mIU/L and 1.94 for TSH <0.10 mIU/L (*P* for trend=0.047). Risks remained similar after adjustment for cardiovascular risk factors. The authors concluded that risks of heart failure events are increased with both higher and lower TSH levels, particularly for TSH ≥10 and <0.10 mIU/L (Gencer B et al, ***Circulation*** 2012;126: 1040-1049).

Multiple (≥2) Arterial Grafts Improve Late Survival of Patients Undegoing CABG

Among 8622 Mayo Clinic patients who underwent coronary artery bypass graft (CABG) surgery for multivessel coronary disease (1993-2009) with LIMA plus saphenous veins (LIMA/SV) (n=7435) or multiple arterial grafts (MultiArt) (n=1187), operative mortality was 0.8% (n=10) in the MultArt and 2.1% (n=154) in the LIMA/SV (*P*=0.005) group; not statistically different in multivariate or matched analysis (propensity score analysis matched 1153 patients). Late survival was greater for MultArt vs LIMA/SV. MultArt subgroups with bilateral internal mammary artery/SV (n=589) and bilateral internal mammary artery only (n=271) had improved 15-year survival and patients with bilateral internal mammary artery/radial artery (n=147) and LIMA/radial artery (n=169) had greater 10-year survival vs LIMA/SV. In multivariate analysis, MultArt grafts remained a strong independent predictor of survival (hazard ratio, 0.79; *P*=0.007). The authors concluded that late outcome of surgical revascularization is improved when at least 2 arterial grafts are used (Locker C et al, ***Circulation*** 2012;126:1023-1030).

Danish Registries: High Risk of Bleeding is Immediately Evident with Triple Therapy after MI/PCI in Patients with Atrial Fibrillation

Among 11,480 patients (mean age 75.6 years, males 61%) with atrial fibrillation admitted with myocardial infarction (MI) or for percutaneous coronary intervention (PCI) between 2000 and 2009 and within 1 year, 728 bleeding events were recorded (6.3%); 79 were fatal (0.7%). Within 30 days, rates were 22.6, 20.3, and 14.3 bleeding events per 100 person-years for triple therapy (TT) (warfarin/aspirin/clopidogrel), dual therapy (warfarin/antiplatelet), and dual antiplatelet therapy (aspirin/clopidogrel), respectively. Both early (within 90 days) and delayed (90–360 days) bleeding risk with TT exposure in relation to dual therapy was increased; hazard

ratio-HR 1.47 and 1.36, respectively. No significant difference in thromboembolic risk was observed for TT vs dual therapy; HR, 1.15. The authors concluded that high risk of bleeding is immediately evident with TT after MI/PCI in patients with atrial fibrillation. A continually elevated risk associated with TT indicates no safe therapeutic window, and TT should only be prescribed after thorough bleeding risk assessment of patients (Lamberts M et al, ***Circulation*** 2012;126:1185-1193).

Association of Circulating MicroRNAs and Incident MI With MiR-223 and MiR-197 Showing Negative Associations and MiR-126 Showing a Positive Association With Subsequent MIs

A total of 19 candidate microRNAs were quantified by real-time polymerase chain reactions in 820 participants. In multivariable analysis, 3 microRNAs were consistently and significantly related to incident myocardial infarction (MI): miR-126 showed a positive association (hazard ratio-HR: 2.69, p = 0.002), whereas miR-223 and miR-197 were inversely associated with disease risk (HR: 0.47, p = 0.002, and 0.56, p = 0.036). To determine their cellular origin, healthy volunteers underwent limb ischemia-reperfusion generated by thigh cuff inflation, and plasma miRNA changes were analyzed; 6 distinct miRNA clusters were identified, of which one cluster included all miRNAs associated with the risk of future MI, predominantly expressed in platelets. The authors concluded that their study showed an association of circulating miRNAs, as novel biomarkers, and incident MI with miR-223 and miR-197 indicating negative associations and miR-126 showing a positive association with subsequent MIs (Zampetaki A et al, ***J Am Coll Cardiol*** 2012;60:290–299).

XAMI Trial: Second-Generation Everolimus Eluting Stents (EES) Display Fewer Cardiac Events than the First-Generation Sirolimus Eluting Stents (SES) in Acute Myocardial Infarction (AMI) Patients

A total of 625 patients with AMI were randomized (2:1) to receive EES (n=404) or SES (n=221). The major adverse cardiac event (MACE) rate was 4.0% for EES and 7.7% for SES; relative risk 0.52. One-year cardiac mortality was low at 1.5% for EES vs 2.7% for SES (p=NS), and 1-year incidence of definite and/or probable stent thrombosis was 1.2% for EES vs 2.7% for SES (p = NS). The authors concluded that second-generation EES were noninferior to SES, while superiority for MACE was suggested. Stent thrombosis rate in EES at 1-year was low, but long-term follow-up and larger studies are needed to show whether very late stent thrombosis rates will also be improved in newer DES (Hofma SH et al, ***J Am Coll Cardiol*** 2012;60:381–387).

Left Atrial Appendage (LAA) Morphology Correlates with Risk of Stroke in Atrial Fibrillation (AF): Patients with Chicken Wing LAA Morphology are Less Likely to Have an Embolic Event

Among 932 patients with AF (aged 59$\pm$10 years, 79% male, 14% with CHADS2 score $\geq$2) scheduled for catheter ablation, CT (n=499) and MRI (n= 433) scans were analyzed. The distribution of different LAA morphologies was Cactus (n=278; 30%), Chicken Wing (n=451; 48%), Windsock (n=179; 19%), and Cauliflower (n= 24; 3%). Of the 932 patients, 78 (8%) had a history of ischemic stroke or TIA. The prevalence of pre-procedure stroke/TIA in Cactus, Chicken Wing, Windsock, and Cauliflower morphologies was 12%, 4%, 10%, and 18%, respectively (p=0.003). In a multivariable analysis, Chicken Wing morphology was found to be 79% less likely to have a stroke/TIA history (odd ratio: 0.21, p = 0.036). Compared with Chicken Wing, Cactus was 4.08 times (p = 0.046), Windsock was 4.5 times (p = 0.038), and Cauliflower was 8.0 times (p = 0.056) more likely to have had a stroke/TIA. The authors concluded that patients with Chicken Wing LAA morphology are less likely to have an embolic event (Di Biase L et al, ***J Am Coll Cardiol*** 2012;60:531–538).

CONFIRM Trial: A Revolutionary Focal Approach to Atrial Fibrillation Ablation

A computational approach to map and ablate localized sources of atrial fibrillation (AF) (focal impulse and rotor modulation-FIRM) was developed and compared to conventional ablative technique in 92 patients during 107 consecutive ablation procedures for paroxysmal or persistent (72%) AF. Cases were prospectively treated, in a 2-arm 1:2 design, by ablation at sources (FIRM-guided) followed by conventional ablation (n=36), or conventional ablation alone (n=71). Localized rotors or focal impulses were detected in 98 (97%) of 101 cases with sustained AF, each exhibiting 2.1 $\pm$ 1.0 sources. The acute endpoint (AF termination or consistent slowing) was achieved in 86% of FIRM-guided cases vs 20% of FIRM-blinded cases (p < 0.001). FIRM ablation alone at the primary source terminated AF in a median 2.5 min. Total ablation time did not differ between groups. During a median 273 days after a single procedure, FIRM-guided cases had higher freedom from AF (82.4% vs. 44.9%; p < 0.001) after a single procedure than FIRM-blinded cases with rigorous, often implanted, electrocardiography monitoring. Adverse events did not differ between groups. The authors concluded that focal impulse and rotor modulation (FIRM) ablation to eliminate local sources was able to abruptly terminate or consistently slow persistent and paroxysmal AF in the vast majority of

cases, and substantially improve long-term AF elimination over conventional ablation alone (Narayan SM et al, ***J Am Coll Cardiol*** 2012;60: 628–36)

Coronary Bypass (CABG) Compared with Percutaneous Coronary Revascularization (PCI) is Associated with an Increased Risk of Stroke

A meta-analysis of 19 trials including 10,944 patients randomized to CABG vs PCI showed that the 30-day rate of stroke was 1.20% after CABG compared with 0.34% after PCI (odds ratio-OR: 2.94, $p < 0.0001$). Similar results were observed after a median follow-up of 12.1 months (1.83% vs. 0.99%, OR: 1.67, $p = 0.02$). The extent of coronary artery disease (single vessel vs multivessel vs left main) did not affect the relative increase in the risk of stroke observed with CABG compared with PCI at either 30 days or midterm follow-up. Similar results were observed when the outcomes in 33,980 patients from 27 observational studies were analyzed. The authors concluded that coronary revascularization by CABG compared with PCI is associated with an increased risk of stroke at 30 days and at the mid-term follow-up (Palmerini T et al, J Am Coll Cardiol 2012;60:798–805).

Renal Artery Denervation Reduces Blood Pressure in Patients with Drug-resistant Hypertension and Reduces AF Recurrences when Combined with Pulmonary Vein Isolation (PVI)

Patients (n= 27) with a history of symptomatic paroxysmal or persistent AF refractory to $\geq$2 antiarrhythmic drugs and drug-resistant hypertension (systolic blood pressure >160 mm Hg despite triple drug therapy) were randomized to PVI only (n=14) or PVI with renal artery denervation (n=13). At 1 year, significant reductions in systolic (from 181$\pm$7 to 156$\pm$5, $p < 0.001$) and diastolic blood pressure (from 97$\pm$6 to 87$\pm$4, $p<0.001$) were observed in patients treated with PVI with renal denervation without significant change in the PVI only group. Nine of the 13 patients (69%) treated with PVI with renal denervation were AF-free vs 4 (29%) of the 14 patients in the PVI-only group ($p = 0.033$). The authors concluded that renal artery denervation reduces systolic and diastolic blood pressure in patients with drug-resistant hypertension and reduces AF recurrences when combined with PVI (Pokushalov E et al, ***J Am Coll Cardiol*** 2012;60:1163–1170).

Rhythm Control Therapy in Atrial Fibrillation Seems to be Superior in the Long-term

Among 26,130 patients aged $\geq$66 years hospitalized with a diagnosis of atrial fibrillation (AF) receiving new drug prescription, and followed for a mean period of 3.1 years, there were 13,237 deaths (49.5%). After adjusting for covariates, we found that the effect of rhythm vs rate control drugs changed over time: after a small increase in mortality for patients treated with rhythm control in the 6 months following treatment initiation (hazard ratio-HR, 1.07), the mortality was similar between the 2 groups until year 4 but decreased steadily in the rhythm control group after year 5 (HR, 0.89; and HR, 0.77, after 5 and 8 years, respectively). The authors concluded that little difference was found in mortality within 4 years of treatment initiation between patients with AF initiating rhythm control therapy vs those initiating rate control therapy. However, rhythm control therapy seems to be superior in the long-term (Ionescu-Ittu R et al, ***Arch Intern Med*** 2012; 172:997-1004).

Important Review and Other Articles

ESC Guidelines for the diagnosis & treatment of acute & chronic heart failure 2012 (McMurray et al, *Eur Heart J* 2012; 33:1787-1847), Contrast-induced kidney injury (Seeliger *E* et al, ***Eur Heart J*** 2012; 33: 2007-2015), High-senstivity cardiac troponins in acute cardiac care (Thygesen K et al, ***Eur Heart*** J 2012; 33:2252-2257), AF ablation (Tung R et al, ***Circulation*** 2012; 126:223-229), Dietary sodium intake in heart failure (Gupta D et al, ***Circulation*** 2012; 126;479-485), Periprocedural bridging management of anticoagulation (Wysokinski & McBane II, ***Circulation*** 2012; 126: 486-490), Assessment of endothelial function (Flammer AJ et al, ***Circulation*** 2012; 126:753-767), 2012 ACCF/AHA Focused Update of the Guideline for the management of patients with unstable angina/NSTEMI (Jneid H et al, ***Circulation*** 2012; 126:875-910), Pulmonary hypertension due to left heart disease (Guazzi & Borlaug, ***Circulation*** 2012; 126: 975-990), Advances in resuscitation (Mottram & Page, ***Circulation*** 2012; 126: 991-1002), Acute aortic regurgitation (Hamirani YS et al, ***Circulation*** 2012; 126:1121-1126), Body fat distribution and cardiovascular risk (Despres J, ***Circulation*** 2012; 126:1301-1313), Sleep apnea and cardiovascular disease (Kasai T et al, ***Circulation*** 2012; 126: 1495-1510), Guided antithrombotic therapy (Fuster V et al, ***Circulation*** 2012;126: 1645-1662), Current status of TAVI (Webb & Wood, ***J Am Coll Cardiol*** 2012; 60:483-492), Genetics of hypertrophic cardiomyopathy (Maron BJ et al, ***J Am Coll Cardiol*** 2012; 60: 705-715), Silent brain injury after cardiac surgery (Sun X et al, ***J Am Coll Cardiol*** 2012; 60: 791-797), Controversies of statin therapy (Jukema JW et al, ***J Am Coll Cardiol*** 2012; 60:875-881), Cardiorenal syndrome type 1 (Ronco C et al, ***J Am Coll Cardiol*** 2012; 60: 1031-1042).