Cardiology News /Recent Literature Review / Third Quarter 2013

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HCS Meeting: Athens, 10-12/10/2013

TCT Meeting: San Francisco, 28/10-1/11/13

AHA 2013: Dallas, 16-20/11/13

ACC 2014: Washington, DC, 29-31/3/2014

Athens Cardiology Update 2014: Athens (Crown Plaza Hotel), 10-12/4/2014

HRS Meeting: San Francisco, 7-10/5/2014

EuroPCR: Paris, 20-23/5/2014

CardioStim 2014: Nice, 18-21/6/2014

Percutaneous Left Atrial Appendage Closure May be a Therapeutic Alternative in Patients with Atrial Fibrillation (AF) and Absolute Contraindications to Anticoagulation Therapy

Left atrial appendage closure (LAAC) with the AMPLATZER Cardiac Plug (ACP) was successfully performed in 51 of 52 (98%) patients (aged 74±8 years) with AF and absolute contraindications to anticoagulation therapy. Most patients received dual-antiplatelet therapy after the procedure for 1-3 months and single antiplatelet therapy thereafter. Main complications were device embolization (1.9%) and pericardial effusion (1.9%), with no cases of periprocedural stroke. At follow-up (20±5 months), death rate was 5.8%, stroke 1.9%, systemic embolism 0%, pericardial effusion 1.9%, and major bleeding 1.9%. The presence of mild peridevice leak was observed in 16.2% of patients at the 6-month follow-up as evaluated by transesophageal echo. There were no cases of device thrombosis. The authors concluded that in patients with nonvalvular AF at high risk of cardioembolic events and absolute contraindications to anticoagulation, LAAC using the ACP device followed by dual-/single-antiplatelet therapy was associated with a low rate of embolic and bleeding events and no device thrombosis at short and midterm follow-up (Urena M et al, ***J Am Coll Cardiol*** 2013;62:96–102).

Preliminary Favorable Experience With Percutaneous Left Atrial Appendage Suture Ligation Using the LARIAT Device in Patients With Atrial Fibrillation

Percutaneous ligation of the left atrial appendage (LAA) with the LARIAT device (a snare with a pre-tied suture guided epicardially over the LAA) was successfully performed in 85 of 89 (96%) patients with complete closure achieved in 81 patients, while 4 had a ≤2-3-mm residual LAA leak. There were 3 complications (during pericardial access, n=2; & transseptal catheterization, n=1). Adverse events included severe pericarditis post-operatively (n=2), late pericardial effusion (n=1), sudden death (n=2), & late strokes (n=2). At 1 (81 of 85) & 3 months (77 of 81) post-ligation, 95% of the patients had complete LAA closure by transesophageal echo (TEE). Of the 65 patients undergoing 1-year TEE, there was 98% complete LAA closure, including patients with previous leaks. The authors concluded that LAA closure with the LARIAT device can be performed effectively with acceptably low complication rate (Bartus et al, ***J Am Coll Cardiol*** 2013;62:108–118).

NEXT Trial: Low Rate of Restenosis and Stent Thrombosis With the Biodegradable Polymer Biolimus-Eluting Stent

A biodegradable polymer biolimus-eluting stent-BES (Nobori) (n=1617) was compared with a durable polymer cobalt-chromium everolimus-eluting stent-EES (Xience/ Promus) (n=1618). The primary efficacy endpoint (target lesion revascularization-TLR at 1 year) occurred in 67 patients (4.2%) in the BES group, and in 66 patients (4.2%) in the EES group, demonstrating noninferiority of BES over EES. Cumulative incidence of definite stent thrombosis was low and similar between the 2 groups (0.25% vs. 0.06%, p=NS). An angiographic substudy enrolling 528 patients (BES: n=263, and EES: n=265) demonstrated noninferiority of BES over EES regarding the primary angiographic endpoint of in-segment late loss (0.03±0.39 mm vs. 0.06±0.45 mm) at 266±43 days after stent implantation. The authors concluded that 1-year clinical and angiographic outcome after BES implantation was noninferior to and not different from that after EES implantation. Both BES and EES had a low rate of TLR and extremely low rate of stent thrombosis (Natsuaki et al, ***J Am Coll Cardiol*** 2013;62:181–190).

ATLAS-ACS 2 TIMI 51: Reduction of Stent Thrombosis in Patients With Acute Coronary Syndromes (ACS) Treated With Rivaroxaban

A total of 15,526 patients with recent ACS were randomized to receive either 2.5 mg or 5 mg bid of rivaroxaban or placebo for a mean of 13 months and up to 31 months. Among patients who had a stent placed before or at the time of the event (n=9,631 or 63%), rivaroxaban significantly reduced definite and probable stent thrombosis in the pooled (1.9% vs 1.5%; hazard ratio - HR: 0.65; p=0.017) and the 2.5 mg bid (1.9% vs 1.5%; HR: 0.61; p=0.023) treatment groups when compared with placebo, with a trend toward a reduction in the 5 mg bid group (1.9% vs. 1.5%; HR: 0.70; p = 0.089). Among patients who received dual antiplatelet therapy (DAPT)

with both aspirin and a thienopyridine, the benefit of rivaroxaban emerged during the period of active treatment with DAPT (HR: 0.68; combined rivaroxaban group vs. placebo). Among stented patients treated with DAPT, there was a mortality reduction among those treated with rivaroxaban 2.5 mg bid (HR: 0.56; p=0.014), but not with the 5 mg bid dose. The authors concluded that among stented patients with ACS treated with DAPT, administration of rivaroxaban 2.5 mg bid was associated with a reduction in stent thrombosis and mortality (Gibson et al, ***J Am Coll Cardiol*** 2013;62:286–290).

PLATO Trial: Ticagrelor Compared With Clopidogrel Reduces the Incidence of Stent Thrombosis in Acute Coronary Syndromes Patients

Of 18 624 patients hospitalized for acute coronary syndromes (ACS), 11289 (61%) had ≥1 intracoronary stent. Ticagrelor reduced stent thrombosis compared with clopidogrel across all definitions: definite, 1.37% (n=71) vs 1.93% (n=105; hazard ratio-HR, 0.67; *P*=0.009); definite or probable, 2.21% (n=118) vs 2.87% (n=157; HR, 0.75; *P*=0.017); and definite, probable, and possible, 2.94% (n=154) vs 3.77 (n=201; HR, 0.77). The reduction in definite stent thrombosis was consistent regardless of ACS type, presence of diabetes mellitus, stent type, CYP2C19 genetic status, loading dose of aspirin, dose of clopidogrel, and use of glycoprotein IIb/IIIa inhibitors. The reduction in stent thrombosis with ticagrelor was greater for late (>30 days; HR, 0.48) and subacute (4 hours–30 days; HR, 0.60) compared with acute (<24 hours; HR, 0.94) stent thrombosis or for patients compliant to therapy compared with less compliant patients. Randomization to ticagrelor was a strong independent inverse predictor of definite stent thrombosis (HR, 0.65). The authors concluded that ticagrelor compared with clopidogrel reduces stent thrombosis in patients with ACS, with consistent benefit across a broad range of patient, stent, and treatment characteristics (Steg et al, ***Circulation*** 2013;128:1055-1065).

GENERATIONS Trial: Prasugrel 5 mg in the Elderly Despite Lower Platelet Inhibition Maintains Non-inferiority to Prasugrel 10 mg in Nonelderly Patients

Prasugrel 5 mg in the elderly (≥75 years, n=73; aged 79±3 years) met the primary pharmacodynamic non-inferiority criterion vs prasugrel 10 mg in non-elderly (≥45 to <65 years; n=82; aged 56±5 years) stable coronary artery disease (CAD) patients receiving background aspirin. For prasugrel 5 mg, maximum platelet aggregation (MPA) was significantly lower (57 ± 14%) than clopidogrel (63 ± 14%; p < 0.001) in elderly but higher than prasugrel 10 mg in non-elederly (46± 12%; p <0.001). Pharmacodynamic response by 3 different assays during all treatments appeared similar between age cohorts. Prasugrel 5 mg resulted in fewer elderly poor responders than clopidogrel. Rates of mild bleeding were higher with prasugrel 10 mg but similar for prasugrel 5 mg vs clopidogrel 75 mg. The authors concluded that in aspirin-treated stable CAD patients, prasugrel 5 mg in the elderly had lower platelet inhibition but met the noninferiority criterion vs prasugrel 10 mg in no-elderly, with significantly better pharmacodynamic response and fewer poor responders compared to clopidogrel 75 mg in the elderly (Erlinge et al, ***J Am Coll Cardiol*** 2013;62:577–583).

Continuous Positive Airway Pressure (CPAP) Therapy of Obstructive Sleep Apnea Reduces Atrial Fibrillation (AF) Recurrences After Catheter Ablation

Among 62 patients with obstructive sleep apnea (OSA) out of 426 patients with AF undergoing pulmonary vein isolation (PVI), 32 were "CPAP users" and 30 "CPAP nonusers." CPAP therapy resulted in higher AF-free survival rate (72% vs. 37%; p = 0.01) and AF-free survival off antiarrhythmic drugs or repeat ablation following PVI (66% vs. 33%; p = 0.02). AF recurrence rate of CPAP-treated patients was similar to a group of patients without OSA (HR: 0.7, p = 0.46). AF recurrence following PVI in CPAP nonuser patients was significantly higher (HR: 2.4, p < 0.02) and similar to that of OSA patients managed medically without ablation (HR: 2.1, p=NS). The authors concluded that CPAP is an important therapy in OSA patients undergoing PVI that improves arrhythmia free survival, while PVI offers limited value to OSA patients not treated with CPAP (Fein et a, ***J Am Coll Cardiol*** 2013; 62:300–305).

Obstructive Sleep Apnea: a Novel Risk Factor for Sudden Cardiac Death?

During a 5-year follow-up of 10,701 consecutive adults undergoing polysomnography for obstructive sleep apnea (OSA), 142 patients had sudden cardiac death (SCD) (annual rate 0.27%). In multivariate analysis, independent risk factors for SCD were age, hypertension, coronary artery disease, cardiomyopathy or heart failure, ventricular ectopy or nonsustained ventricular tachy-cardia, and lowest nocturnal O2sat (per 10% decrease, hazard ratio-HR: 1.14; p=0.029). SCD was best predicted by age >60 years (HR: 5.53), apnea-hypopnea index >20 (HR: 1.60), mean nocturnal O2sat <93% (HR: 2.93), and lowest nocturnal O2sat <78% (HR: 2.60; all p < 0.0001). The authors conclude that among adults referred for polysomnography, OSA predicted incident SCD. Nocturnal hypoxemia strongly predicted SCD independently of well-established risk factors. These

findings implicate OSA as a novel risk factor for SCD (Gami et al, J ***Am Coll Cardiol*** 2013;62:610–616).

Air Pollution is an Acute Trigger of Atrial Fibrillation

Among 300 eligible patients out of 1143 screened, 200 with dual-chamber implantable cardioverter defibrillator (ICD) devices were enrolled and 176 were followed for at least 90 days. The association of AF onset with air quality including ambient particulate matter <2.5 mm aerodynamic diameter ($PM_{2.5}$), black carbon, sulfate, particle number, NO_2, SO_2, and O_3 in the 24 h prior to the arrhythmia was examined utilizing a case-crossover analysis. Of 176 patients followed for an average of 1.9 years, 49 patients had 328 episodes of AF lasting ≥30 s. Positive but nonsignificant associations were found for $PM_{2.5}$ in the prior 24 h, but stronger associations were found with shorter exposure windows. The odds of AF increased by 26% for each 6.0 mg/m^3 increase in $PM_{2.5}$ in the 2 h prior to the event (p=0.004). The authors concluded that particulate matter was associated with increased odds of AF onset within hours following exposure in patients with known cardiac disease, indicating that acute exposure to air pollution triggers AF (Link et al, ***J Am Coll Cardiol*** 2013;62:816–825).

Community Study: Patients With Heart Failure are at Increased Risk of Cancer

A case-control community study compared patients newly diagnosed with heart failure (HF) and age-, sex-, and date-matched controls without HF (961 pairs); also patients and individuals without cancer at the index date (596 pairs) were followed for development of cancer. Before the index date, 22% of HF cases and 23% of controls had a history of cancer (odds ratio - OR: 0.94). During 9,203 person-years of follow-up (7.7 ± 6.4 years), 244 new cancer cases were identified; HF patients had a 68% higher adjusted risk of developing cancer (hazard ratio - HR: 1.68). The HRs were similar for men and women, with a trend toward a stronger association among subjects ≤75 years of age (p = 0.22) and during the most recent time period (p = 0.075). Among HF cases, incident cancer increased the adjusted risk of death (HR: 1.56). The authors concluded that HF patients are at increased risk of cancer, which appears to have increased over time, while cancer further increases mortality in HF patients (Hasin et al, ***J Am Coll Cardiol*** 2013;62:881–886).

RE-LY: Integrating Ischemic and Bleeding Events as "Ischemic Stroke Equivalents" Indicates Similar Benefits of the 2 Doses of Dabigatran Over Warfarin

In patients with AF, although the higher dose (150 mg bid) of dabigatran reduces ischemic stroke and increases bleeding compared with the lower dose (110 mg bid), the 2 doses confer similar mortality. Ischemic and bleeding events were integrated as "ischemic stroke equivalents" in an analysis of the 18,113 AF patients in the RE-LY trial, in order to compare a weighted benefit of the 2 doses of dabigatran with each other, and with that of warfarin. The analysis indicated that, compared with warfarin, there was a significant decrease in ischemic stroke equivalents with both dabigatran doses: –0.92 per 100 patient years (p = 0.02) with dabigatran 110 mg bid and –1.08 (p = 0.01) with dabigatran 150 mg bid, while there was no difference between the 2 doses. The authors concluded that both doses of dabigatran as compared with warfarin have similar benefits when considering a weighted estimate of efficacy and safety, supporting the individualization of the dose based on patient characteristics and physician and patient preferences (Eikelboom et al, ***J Am Coll Cardiol*** 2013;62:900–908).

Triple Antithrombotic Therapy May be Replaced by Oral Anticoagulant + Clopidogrel Without Additional Thrombotic Risk and With a Lower Risk of Bleeding

Among 12,165 AF patients hospitalized with myocardial infarction (MI) and/or undergoing PCI, within 1 year, MI or coronary death occurred in 2,255 patients (18.5%), ischemic stroke in 680 (5.6%), and bleeding events in 769 (6.3%). Compared to triple therapy (oral anticoagulant-OAC +aspirin +clopidogrel), no increased risk of recurrent coronary events was seen for dual therapy (OAC +clopidogrel: hazard ratio-HR: 0.69; OAC + aspirin: HR: 0.96; or aspirin + clopidogrel: HR: 1.17), but aspirin plus clopidogrel was associated with a higher risk of ischemic stroke (HR: 1.50). Also, OAC + aspirin (HR: 1.52) and aspirin +clopidogrel (HR: 1.60) were associated with a significantly increased risk of all-cause death. When compared to triple therapy, bleeding risk was nonsignificantly lower for OAC + clopidogrel (HR: 0.78) and significantly lower for OAC + aspirin and aspirin + clopidogrel. The authors concluded that AF patients with indication for triple antithrombotic therapy after MI/PCI, OAC and clopidogrel may be equal or better on both benefit and safety issues compared to triple therapy (Lamberts et al, ***J Am Coll Cardiol*** 2013;62:981–989).

Left Atrial Pouch Thrombus Mimics Myxoma

A 70-year-old woman with chronic atrial fibrillation underwent echocardiography which showed a large ovoid mass attached to the interatrial septum in the left atrium; the mass was further characterized by transesophageal echocardiography and was diagnosed as a myxoma. She was placed on anticoagulant therapy with warfarin before elective cardiac surgery and had no thromboembolic event during a 2.5-month period. Preoperative transesophageal echo showed the disappearance of the

intracardiac mass and the presence of a left atrial septal pouch, suggesting that the mass was a thrombus originating from the left atrial septal pouch (Shimamoto K et al, ***J Clin Ultrasound*** 2013 Aug 27. doi: 10.1002/jcu.22087).

Malignant Bileaflet Mitral Valve Prolapse Syndrome

Among 24 victims of idiopathic out-of-hospital cardiac arrest (i.e., no ischemia, cardiomyopathy, or channelopathy) having an implantable cardioverter defibrillator (ICD) (16 women, median age 33.5 years), bileaflet mitral valve prolapse (MVP) was found in 10 (42%). Compared with patients with normal mitral valves, patients with bileaflet MVP were predominantly women (9 of 10 or 90% vs. 7 of 14 or 50%, p = 0.04); had a higher prevalence of biphasic or inverted T waves (7 of 9 or 78% vs. 4 of 14 or 29%, p =0.04); and on Holter monitoring had more frequent ventricular ectopy (ventricular bigeminy 100% vs 10%, p<0.0001; ventricular tachycardia 78% vs 10%, p=0.006, and premature ventricular contractions - PVCs originating from the outflow tract alternating with the papillary muscle or fascicular region 78% vs 20%, p=0.02). Over a median 1.8 years, 13 of 24 patients (54%) received appropriate ICD shocks. Only bileaflet MVP was associated with ventricular fibrillation recurrences requiring ICD therapy on follow-up (odds ratio: 7.2; p = 0.028). The authors concluded that a "malignant" subset of patients with MVP may experience life-threatening ventricular arrhythmias and is characterized by bileaflet MVP, female sex, and frequent complex ventricular ectopic activity, including PVCs of the outflow tract alternating with papillary muscle or fascicular origin (Sriram et al, ***J Am Coll Cardiol*** 2013;62:222–230).

"Low-Adenosine Syncope": a Distinct Entity With Recent Sudden Onset in Middle/Old Age (>40 Years) Without Prodromes, Normal Heart and Normal ECG

A group of 15 patients with sudden-onset syncope without prodromes with normal heart and normal ECG were compared with 31 patients with established vasovagal syncope (VVS). Patients in the study group were older than those with VVS (age 61±12 vs 46± 17 years) and had a history of fewer episodes of syncope (median of 2 vs 9 years) that were of more recent onset (median of 1 vs 10.5 years). The study group had lower median baseline adenosine plasma levels than the VVS group (0.25 vs 0.85 mmol/l). Adenosine plasma level of ≤0.36 best discriminated between groups, displaying 73% sensitivity and 93% specificity. Tilt table testing was more frequently positive in patients with VVS than in the study group (74% vs. 33%), with a similarly high positivity rate of adenosine/ATP testing in both groups (33-60% vs 37-43%). The authors concluded that clinical features and a low adenosine level define a distinct type of syncope, different from VVS, and suggest a causal role of the adenosine pathway (Deharo et al, ***J Am Coll Cardiol*** 2013;62:1075–1080).

EnligHTN I: A New Multi-Electrode Ablation Catheter is Effective for Renal Denervation

A novel multi-electrode system (EnligHTN™) was employed for catheter-based renal artery denervation in 46 patients (67% male, mean age 60 years, and mean baseline office blood pressure 176/96 mmHg) with drug-resistant hypertension. Office blood pressure was significantly reduced from baseline to 1, 3, and 6 months by 228/10, 227/10 and 226/10 mmHg, respectively (P < 0.0001). No acute renal artery injury or other serious vascular complications occurred, with small, non-relevant, changes in average estimated glomerular filtration rate. The authors concluded that renal sympathetic denervation, using the new catheter resulted in a rapid and significant office blood pressure reduction that was sustained through 6 months (Worthley et al, ***Eur Heart J*** 2013; 34: 2132–2140).

Pulmonary Artery Denervation (PADN): a First-in-Man Application to Treat Idiopathic Pulmonary Artery Hypertension (IPAH) / Feasible and Efficacious at Short-Term Follow-up

Of 21 patients with IPAH, 13 underwent the PADN procedure and were compared with the other 8 who refused (control group). PADN was performed at the bifurcation of the main pulmonary artery (PA), and at the ostial right & left PA. At 3 months, PADN patients showed significant reduction of mean PA pressure (from 55±5 mmHg to 36±5 mmHg, p<0.01), and improvement of the 6-min walk test (from 324± 21 m to 491±38 m, p < 0.006) and of the tricuspid excursion (Tei) index (from 0.7±0.04 to 0.50±0.04, p<0.001). The authors concluded that PADN had a beneficial effect on functional capacity and hemodynamics in patients with drug-refractory IPAH (Chen et al, ***J Am Coll Cardiol*** 2013;62:1092–100).

FinCV Study: High Thromboembolic Risk After Cardioversion of Acute Atrial Fibrillation (AF) in Patients with Conventional Risk Factors

There were 38 (0.7%) definite thromboembolic events (31 strokes) and 4 TIAs within 30 days (median 2 days) after 5,116 successful cardioversions (CV) in 2,481 patients with AF lasting <48 h who received neither oral anticoagulation nor peri-procedural heparin therapy. Age (odds ratio-OR: 1.05), female sex (OR: 2.1), heart failure (OR: 2.9), and diabetes (OR: 2.3) were the independent predictors of definite embolic events. The highest risk of thromboembolism (9.8%) was observed among patients

with heart failure and diabetes, whereas patients with no heart failure and age <60 years had the lowest risk of thromboembolism (0.2%). The authors concluded that the post-CV thromboembolic complications were increased in certain subgroups of patients when no anticoagulation is used after CV of acute AF (Airaksinen et al, ***J Am Coll Cardiol*** 2013;62:1187–1192).

Residual SYNTAX Score: a Powerful Predictor of 5-Year Mortality in the SYNTAX Trial

In the PCI group of the SYNTAX Trial (n=903), 5-year clinical outcomes were stratified by complete (CR) (residual SYNTAX Score 0) and incomplete revascularization (ICR) (residual SYNTAX Score >0). The mean baseline SYNTAX Score was 28.4±11.5 and residual SYNTAX Score was 4.5±6.9. A progressively higher residual SYNTAX Score (CR 0, n=386, 42.7%; ICR >0-4, n=184, 20.4%; ICR >4-8, n=167, 18.5%; ICR>8, n=153, 16.9%) was shown to be a marker of increasing clinical comorbidity and anatomic complexity. Subjects with CR or residual SYNTAX Scores ≤8 had comparable 5-year mortality (CR, 8.5%; residual SYNTAX Score >0–4, 8.7%; >4–8, 11.4%; *P*=0.60). A residual SYNTAX Score >8 was associated with 35% all-cause mortality at 5-years (*P*<0.001). Similar results were obtained from the analysis of the medically treated diabetic and left main subgroups. The authors concluded that residual SYNTAX Score was a powerful indicator of 5-year mortality by determining the completeness of revascularization (Farooq et al, ***Circulation*** 2013;128:141-151).

RELY-ABLE: a Higher Rate of Major Bleeding With the Higher Dabigatran Dose

A total of 5851 patients (48%) enrolled in the RE-LY trial continued to receive dabigatran for up to 28 months after RE-LY (median follow-up, 2.3 years). Rates of stroke or systemic embolism were 1.46% and 1.60%/y on dabigatran 150 and 110 mg bid, respectively (hazard ratio - HR, 0.91). Rates of major hemorrhage were 3.74% and 2.99%/y on dabigatran 150 & 110 mg (HR, 1.26). Rates of death were 3% & 3.1%/y (HR, 0.97). Rates of hemorrhagic stroke were 0.13% & 0.14%/y. The authors concluded that during 2.3 years of continued treatment with dabigatran after RE-LY, there was a higher rate of major bleeding with dabigatran 150 mg bid in comparison with 110 mg, and similar rates of stroke and death (Connolly et al, ***Circulation*** 2013;128:237–243).

ARISTOTLE Secondary Analysis: Stroke, Mortality, & Major Bleeding Risks are Lower With Apixaban than Warfarin Regardless of AF Type and Duration

A secondary analysis of the ARISTOTLE trial which included 18201 patients with atrial fibrillation (AF) (2786 or 15.3% paroxysmal and 15412 or 84.7% persistent or permanent) comparing apixaban with warfarin indicated a consistent reduction in stroke or systemic embolism (P for interaction = 0.71), all-cause mortality (P for interaction = 0.75), and major bleeding (P for interaction = 0.50) with apixaban compared with warfarin for both AF types. Rate of stroke or systemic embolism was significantly higher in patients with persistent or permanent AF than patients with paroxysmal AF (1.52 vs. 0.98%; P = 0.003, adjusted P = 0.015) with a trend towards higher mortality in patients with persistent or permanent AF (3.90 vs. 2.81%; P = 0.0002, adjusted P = 0.066). The authors concluded that the risks of stroke, mortality, and major bleeding were lower with apixaban than warfarin regardless of AF type and duration (Al-Khatib et al, ***Eur Heart J*** 2013; 34: 2464–2471).

Atrial Fibrillation (AF) Epidemic: Prevalence of 8.8 Million Adults >55 Years in 2010 in the European Union Estimated to Double by 2060 to 17.9 Million

According to estimates from the Rotterdam Study and projections from the European Union's statistics office, prevalence of AF for the group 55–59 years was 1.3% in men and 1.7% in women and increased to 24.2% in men, and 16.1% in women, for ages >85 years. Furthermore, it is estimated that in the European Union, 8.8 million adults over 55 years had AF in 2010 and projected that this number will double by 2060 to 17.9 million. The authors conclude that from 2010 to 2060, the number of adults >55 years with AF in the European Union will more than double with major public health implications (Krijthe et al, ***Eur Heart J*** 2013; 34: 2746–2751).

Totally Subcutaneous ICD: a Viable Alternative to Conventional ICD?

A subcutaneous implantable cardioverter defibrillator (ICD) was successfully implanted in 314 of 321 patients in whom it was attempted (74% male, mean age 52±16 years and mean left ventricular ejection fraction of 36±16%; 13% had a previous transvenous ICD). The 180-day system complication-free rate was 99%, and sensitivity analysis of the acute ventricular fibrillation conversion rate was >90% in the entire group. Over a mean of 11 months, there were 38 discrete spontaneous episodes of ventricular tachycardia/ ventricular fibrillation recorded in 21 patients (6.7%), all of which successfully converted. A total of 41 patients (13.1%) received an inappropriate shock. The authors concluded that these findings support the efficacy and safety of the subcutaneous ICD System for the treatment of life-threatening ventricular arrhythmias (Weiss et al, ***Circulation*** 2013;128:944-953).

Brugada Syndrome Behind Complete RBBB

A group of 11 patients with no structural heart disease who had Brugada syndrome (BS) and complete right bundle branch block (CRBBB) were studied. In 7 patients, BS was diagnosed before the development of CRBBB. BS was diagnosed upon spontaneous resolution of CRBBB (n=1) or by right ventricular pacing (n=3). On repeated ECGs, new additional upward-convex ST-segment elevation was found in V2 or V3 in 3 patients. In 2 patients, new ST-segment elevation was induced by class IC drugs. The QRS duration was more prolonged in patients with BS and CRBBB compared with age- and sex-matched controls: 170±13 vs 145±15 ms in V1 and 144±19 vs 128±7 ms in V5 (both $P<0.0001$). The amplitude of R in V1 was larger in BS patients than in the controls ($P=0.03$), but that of R′ was similar ($P=0.056$). The authors concluded that BS can coexist behind CRBBB, and CRBBB can completely mask BS. BS might be demonstrated by resolution of CRBBB or by spontaneous or drug-induced ST-segment elevation (Aizawa et al, ***Circulation*** 2013;128:1048-1054).

Greatest Benefit from Cardiac Resynchronization Therapy (CRT): Patients with LBBB & QRS > 150 ms

Among 24169 patients receiving CRT-D, 1-year and 3-year mortality rates were 9.2% and 25.9%, respectively. Risk of 3-year mortality was lowest among patients with LBBB and QRS duration of ≥150 ms (21%), compared with LBBB and QRS duration of 120-149 ms (26.5%; hazard ratio - HR, 1.30), no LBBB and QRS ≥150 ms (~31%; HR, 1.34), and no LBBB and QRS of 120-149 ms (32%; HR, 1.52). Risk of 1-year all-cause readmission was also lowest among patients with LBBB and QRS ≥150 ms (~39%), compared with LBBB and QRS of 120-149 ms (45%; HR, 1.18), no LBBB and QRS ≥150 ms (~46%; HR, 1.16), and no LBBB and QRS of 120-149 ms (49.6%; HR, 1.31). There were no observed associations with complications. The authors concluded that LBBB and QRS ≥150 ms, compared with LBBB and QRS <150 ms or no LBBB regardless of QRS duration, was associated with lower risk of all-cause mortality and of all-cause, cardiovascular, and heart failure readmissions (Peterson et al, ***JAMA*** 2013;310:617-626).

REVERSE Study: Beneficial Effects of Cardiac Resynchronization Therapy (CRT) in Patients with Mild Heart Failure (HF) are Sustained Over 5 Years

According to the 5-year results of the REVERSE study on CRT in 419 NYHA Class I-II HF patients with QRS ≥120 ms and left ventricular (LV) ejection fraction (LVEF) ≤40%, maximal improvement in function and LV remodeling were achieved at 2 years, with an increase of the 6-min walk test by mean of 18 m and quality of life by 8 units. There was a mean decrease in LV end-systolic volume index by ~23 mL/m^2 and in end-diastolic volume index by 25 mL/m^2; the mean increase in LVEF was 6% ($P < 0.0001$) with sustained improvement thereafter. The annual and 5-year mortality was 2.9 and 13.5% and the annual and 5-year rate of death or first HF hospitalization 6.4, and 28%. The 5-year LV lead-related complication rate was 12.5%. The authors concluded that in patients with mild HF, CRT produced reverse LV remodelling and very low mortality and need for heart failure hospitalization. These effects were sustained over 5 years (Linde et al, ***Eur Heart J*** 2013; 34: 2592–2599).

CHANCE: Clopidogrel plus Aspirin is Superior to Aspirin Alone for Secondary Prevention in Minor Stroke or TIA Without Further Hemorrhagic Risk

A total of 5170 patients within 24 hours after the onset of minor ischemic stroke or high-risk transient ischemic attack (TIA) were assigned to combination therapy with clopidogrel and aspirin (clopidogrel initially 300 mg, followed by 75 mg qd for 90 days, plus aspirin at a dose of 75 mg qd for the first 21 days) or to placebo plus aspirin (75 mg qd for 90 days). Stroke recurred in 8.2% of patients in the clopidogrel–aspirin group, as compared with 11.7% of those in the aspirin group (hazard ratio, 0.68; P<0.001). Hemorrhage developed in 7 patients (0.3%) in the clopidogrel–aspirin group and in 8 (0.3%) in the aspirin group (P=NS); the rate of hemorrhagic stroke was 0.3% in each group. The authors concluded that in patients with TIA or minor stroke treated within 24 hours, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage (Wang et al, ***N Engl J Med*** 2013;369:11-19).

ACCOAST: Pretreatment With Prasugrel has no Effect on Ischemic Events But Increases Major Bleeding

A total of 4033 patients with non-ST elevation acute coronary syndromes (ACS) received prasugrel (30-mg loading dose) before coronary angiography (pretreatment group) or placebo (control group), with an additional 30 mg of prasugrel given in the pretreatment group and 60 mg in the control group at time of PCI. The rate of the primary efficacy end point (death, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy) through day 7, did not differ significantly between the two groups. The rate of the key safety end point of all major bleeding episodes, whether related or not related to coronary-artery bypass grafting (CABG), through day 7 was increased with pretreatment (hazard ratio, 1.90; P=0.006). The authors concluded that among patients with ACS who were scheduled to undergo

catheterization, pretreatment with prasugrel did not reduce the rate of major ischemic events up to 30 days but increased the rate of major bleeding complications (Montalescot et al, ***N Engl J Med*** 2013; 369:999-1010).

PRAMI: Dilating NonCulprit Lesions in Acute Myocardial Infarction Confers Significant Benefit (Preventive Angioplasty)

A total of 465 patients with ST elevation myocardial infarction (STEMI), undergoing primary angioplasty (PCI) of the infarct-related artery (2008-2013), were randomly assigned to either preventive PCI (234 patients) or no preventive PCI (231 patients). Over a mean of 23 months, the primary outcome (cardiac death, nonfatal myocardial infarction, or refractory angina) occurred in 21 patients in the preventive PCI group and in 53 patients in the control group (infarct-artery-only PCI) (overall hazard ratio-HR, 0.35; P<0.001 / HR 0.34 for cardiac death, 0.32 for nonfatal myocardial infarction, and 0.35 for refractory angina). The authors concluded that in patients with STEMI and multivessel coronary artery disease undergoing infarct-artery PCI, preventive PCI in noninfarct vessel stenoses significantly reduced the risk of adverse cardiovascular events, compared with PCI limited to the culprit lesion (Wald et al, ***N Engl J Med*** 2013; 369:1115-1123).

Combined Therapy With Vasopressin-Epinephrine + Methylprednisolone During CPR and Stress-Dose Hydrocortisone in Postresuscitation Shock Confers Improved Survival in Cardiac Arrest Victims

Cardiac arrest victims (n=268) received either vasopressin plus epinephrine (VSE group, n = 130) or saline placebo plus epinephrine (control group, n = 138) for the first 5 CPR cycles after randomization, followed by additional epinephrine if needed. During the first CPR cycle after randomization, patients in the VSE group additionally received methylprednisolone (40 mg). Shock after resuscitation was treated with stress-dose hydrocortisone (300 mg daily for 7 days maximum and gradual taper) (VSE group, n = 76) or saline placebo (control group, n = 73). Patients in the VSE group vs patients in the control group had higher probability for return of spontaneous circulation (ROSC) of 20 min or longer (84% vs 66%; odds ratio-OR, 2.98; *P* =0 .005) and survival to hospital discharge (14% vs 5%; OR, 3.28; *P* =0 .02). Patients in the VSE group with post-resuscitation shock vs respective patients in the control group had higher probability for survival to hospital discharge with adequate neurological function (21%] vs ~8%; OR, 3.74; *P* =0 .02. Adverse events were similar in the 2 groups. The authors concluded that combined vasopressin-epinephrine and methylprednisolone during CPR and stress-dose hydrocortisone in postresuscitation shock resulted in improved survival to hospital discharge with favorable neurological status (Mentzelopoulos et al, ***JAMA*** 2013;310:270-279).

MIDA Registry: Early Surgical Intervention is Superior to Watchful Waiting for Mitral Regurgitation Due to Flail Mitral Valve Leaflets

Among 1021 patients with flail mitral valve regurgitation, 575 patients were initially medically managed and 446 underwent mitral valve surgery within 3 months. There was no significant difference in early mortality (1.1% for early surgery vs 0.5% for medical management, *P*=NS) and new-onset heart failure rates (0.9% for early surgery vs 0.9% for medical management, *P*=NS) between treatment strategies at 3 months. In contrast, long-term survival rates were higher for patients with early surgery (86% vs 69% at 10 years, *P* <0 .001); 5-year mortality was reduced by 52.6% (*P* <0 .001). Long-term heart failure risk was also lower with early surgery (7% vs 23% at 10 years, *P* <0 .001). Reduction in late-onset atrial fibrillation was not observed. The authors concluded that patients with mitral valve regurgitation due to flail mitral leaflets, performance of early mitral surgery compared with initial medical management was associated with greater long-term survival and a lower risk of heart failure, with no difference in new-onset atrial fibrillation (Suri et al, ***JAMA*** 2013;310:609-616).

Important Review and Other Articles

Genetics in channelopathies (Schwartz et al, ***J Am Coll Cardiol*** 2013;62:169-180), TAVI in Europe (Mylotte et al, ***J Am Coll Cardiol*** 2013;62:210-219), Renal denervation (Davis et al, ***J Am Coll Cardiol*** 2013;62:231-241), Heart failure with preserved ejection fraction (Paulus et al, ***J Am Coll Cardiol*** 2013;62:263-271), ACCF/AHA/SCAI 2013 Update of the Clinical Competence Statement on Coronary Artery Interventional Procedures (Harold et al, ***J Am Coll Cardiol*** 2013;62:357–396), Obstructive sleep apnea (Drager et al, ***J Am Coll Cardiol*** 2013;62:569–576), Early repolarization (Adler et al, ***J Am Coll Cardiol*** 2013;62:863-868), ICD use (Hohnloser & Israel ***Circulation*** 2013; 128:172-183), Cognitive function after CABG (Hogan et al, ***Circulation*** 2013; 128:162-171), Cardiovascular function and treatment in β-thalassemia major (Pennell et al, ***Circulation*** 2013; 128:281-308), Device infections (Mulpuru et al, ***Circulation*** 2013;128:1031-1038), Acute aortic syndrome (Sheikh et al, ***Circulation*** 2013; 128:1122-1127), ARVC (Saguner et al, ***Circulation*** 2013;128:1381-1386), Telemedicine & cardiac implants (Varma & Ricci, ***Eur Heart J*** 2013;34:1885-1893), Practical guide on use of new oral anticoagulants (Heidbuchel et al, ***Eur Heart J*** 2013;34:2094-2106), Catheter based renal denervation (Mahfoud et al, ***Eur Heart J*** 2013;34:2149-2157), 2013 ESH/ESC Guidelines for the management of arterial hypertension (Mancia et al, ***Eur Heart J*** 2013;34:2159-2219),

2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy (Brignole et al, ***Eur Heart J*** 2013;34:2281-2329), Diabetes & vascular disease (Paneni et al, ***Eur Heart J*** 2013;34:2436-2443 / Beckman et al, ***Eur Heart J*** 2013;34:2444-2452), Myocarditis (Caforio et al, ***Eur Heart J*** 2013;34:2636-2648), Coronary collaterals (Seiler et al, ***Eur Heart J*** 2013;34:2674-2682), STEMI: adjunctive reperfusion strategy (Curzen et al, ***Lancet*** 2013; 382:633-643)

2013 European Society of Cardiology Congress News

In a Hot Line session the results from the phase II **RE-ALIGN** study were presented, indicating that the oral anticoagulant dabigatran failed to protect patients with mechanical valves from thromboembolic events. Rather, a higher number of thromboembolic and bleeding complications occurred in these patients compared to standard treatment with warfarin. This was the reason that prompted the early termination of this study after enrolment of 252 patients. The composite of stroke, TIA, systemic embolism, MI or death occurred in 15 patients (9%) in the dabigatran group and in 4 patients (5%) in the warfarin group. Major bleeding occurred in 7 patients (4%) on dabigatran and 2 (2%) on warfarin.

The factor Xa inhibitor edoxaban was found to be non-inferior to standard therapy with warfarin for the prevention of venous thromboembolism (VTE) in the **Hokusai-VTE** trial. The study included 4921 patients with deep vein thrombosis and 3319 patients with pulmonary embolism, who were randomized to 60 mg edoxaban daily (or 30 mg for those considered at higher risk of bleeding) or warfarin for 3-12 months. The primary end-point (recurrent symptomatic VTE) occurred in 3.2% of patients on edoxaban and 3.5% of patients on warfarin. In the subgroup with pulmonary embolism, recurrent events were reported in 3.3% on edoxaban and 6.2% on warfarin. Bleeding occurred in 8.5% for edoxaban and 10.3% for warfarin.

The investigational anticoagulant otamixaban had increased rates of bleeding with no reduction noted in mortality or MI events in patients with non-ST elevation ACS, according with the results of the phase III **TAO** study. Another negative study was presented, the **TASTE** trial, whereby aspiration of thrombus prior to angioplasty and stenting in STEMI patients did not improve survival compared with primary PCI and stenting alone.

Patients with STEMI who have additional preventive angioplasty have significantly better outcomes than thos who only undergo to primary PCI of the infarct-artery, according to the **PRAMI** trial. STEMI patients after completion of infarct-artery PCI were randomized to either preventive (additional) PCI of other significant coronary stenosis (n=234) or no further PCI (n=231). At 23 months, the primary outcome (cardiac death, non-fatal MI, or refractory angina) occurred in 21 patients assigned to preventive PCI and in 53 patients assigned to no preventive PCI, an absolute risk reduction of 14% and a relative risk reduction of 65% (hazard ratio 0.35).

According with the results of the **ACCOAST** trial, pretreatment with prasugrel in patients with non-ST elevation ACS was associated with an increased (almost double) risk of major bleeding (2.6% vs 1.4% at 7 days and 2.9% vs 1.5% at 30 days).

Two trials of oral anti-hyperglycemic agents, dipeptidyl peptidase 4 (DPP-4) inhibitors saxagliptin and alogliptin, were reported to meet the non-inferiority criterion for ischemic target. According to the results of the phase IV **SAVOR-TIMI 450** (saxagliptin) and the **EXAMINE** (alogliptin) studies, diabetic patients receiving these drugs did not have any increase or decrease of major adverse cardiac events. In another negative trial, the **ASSURE** study, the apoA-1 inducer RVX-208 did not raise HDL levels and failed to promote atheromatous plaque regression. A rather neutral study (**AQUARIUS)** was also reported, which showed that the renin inhibitor, aliskiren, neither improves nor slows the progression of coronary atherosclerosis. Another phase II trial (**ATOMIC-AHF**) testing the cardiac myosin activator omecamtiv mecarbil in heart failure reported that the drug did not achieve its primary efficacy endpoint in reducing dyspnea in patients with acute heart failure.

An important study for cardiac resynchronization therapy (CRT), the **Echo-CRT study**, included 809 patients with narrow QRS, NYHA class III-IV heart failure, left ventricular ejection fraction $\leq$35%, who were randomized 1:1 to CRT (n=404) or control (n=405) with the device turned off in the control group. At a mean follow-up of 19.4 months, the primary endpoint (death or first hospitalization for worsening heart failure) occurred in 28.7% of patients in the CRT group and 25.2% in the control group. In addition, 11.1% of CRT patients died vs 6.4% in the control group, with cardiovascular mortality in 9.2% of CRT patients vs 4.2% in the control group. Thus, the conclusion was that CRT in patients with narrow QRS has no benefit and may even harm patients with heart failure, results which are quite similar with the recently reported findings of the LESSER EARTH study.

New **ESC guidelines** (2013) were reported: Guidelines for *Cardiac Pacing & CRT*, Guidelines on *Diabetes & Cardiovascular Disease* (in collaboration with the European Association for the Study of Diabetes-EASD), Guidelines on *Hypertension* (developed with the European Society of Hypertension), & Guidelines on *Stable Coronary Artery Disease* (http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/GuidelinesList.aspx).