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CARDIOLOGY CORNER

Cardiology News / Recent Literature Review / Third Quarter 2016

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HCS Panhellenic Congress: Athens, 20-22/10/2016
TCT Conference: Washington, DC, 29/10-2/11/2016
AHA Scientific Sessions: New Orleans, 12-16/11/2016
AF Symposium: Orlando, 12-14/1/2017
ACC.17: Washington, DC, 17-19/3/2017
HRS Scientific sessions: Chicago, 10-13/5/2017
EHRA Europace-Cardiostim: Vienna, 18-21/6/2017
ESC Congress: Barcelona, 26-30/8/2017

POST 2 Study: Patients with Vasovagal Syncope Improved Modestly with Fludrocortisone 0.2 mg daily with Insignificant 31% Reduction in the Hazard of Fainting in the Intent-to-Treat Analysis

Among 210 patients (71% female, median age 30 years) with recurrent vasovagal syncope randomized to fludrocortisone or placebo at highest tolerated doses from 0.05 mg to 0.2 mg daily, there was a marginally nonsignificant reduction in syncope in the fludrocortisone group (hazard ratio - HR: 0.69; p=0.069). In a multivariable model, fludrocortisone significantly reduced the likelihood of syncope (HR: 0.63; p=0.024). When the analysis was restricted to outcomes after 2 weeks of dose stabilization, there was a significant benefit due to fludrocortisone (HR: 0.51; p=0.019) (Sheldon R et al, *J Am Coll Cardiol* 2016;68:1-9).

Patients With Variant Angina Presenting With Aborted Sudden Arrhythmic Death (SCD) Face a Worse Prognosis Than Those Without SCD, While Therapy With Vasodilator Drugs is not Sufficiently Protective / Additional ICD Implantation Might be Necessary as a Secondary Prevention Treatment

Among 188 patients with variant angina with atherosclerosis (ASCD) and 1,844 patients with variant angina without ASCD (predictors of ASCD: age, hypertension, hyperlipidemia, family history of sudden cardiac death, multivessel spasm, and left anterior descending artery spasm), over a median of 7.5 years, the incidence of cardiac death was higher in ASCD patients (24.1 vs 2.7 per 1,000 patient-years; hazard ratio - HR: 7.26; p <0.001). Death from any cause also occurred more frequently in ASCD patients (27.5 vs 9.6 per 1,000 patient-years; HR: 3; p <0.001). The incidence rate of recurrent ventricular tachyarrhythmia in ASCD patients was 32.4 per 1,000 patient-years, and the composite of cardiac death and ventricular tachyarrhythmia was 44.9 per 1,000 patient-years. A total of 24 ASCD patients received ICDs (Ahn JM et al, *J Am Coll Cardiol* 2016;68:137-145).

High-Output Heart Failure (HF): The Most Frequent Causes Have Changed Over Time, and Today Include Obesity, Liver Disease, and Arteriovenous Fistulas, Although Pulmonary and Myeloproliferative Diseases are Additional, Underappreciated Causes / Outcomes Differ Little From Those in Patients With Low-Output HF Due to Systolic Dysfunction

The most common etiologies of high-output HF (n=120) were obesity (31%), liver disease (23%), arteriovenous shunts (23%), lung disease (16%), and myeloproliferative disorders (8%). Compared with controls (n=24), subjects with high-output HF displayed eccentric left ventricular remodeling, greater natriuretic peptide activation, higher filling pressures, pulmonary hypertension, and increased cardiac output, despite similar ejection fraction. Mortality was increased in high-output HF as compared with controls (hazard ratio: 3.4). Hemodynamics and outcomes were poorest amongst patients with the lowest systemic vascular resistance (Anand IS et al, *N Engl J Med* 2016;68:483-486).

Early Strokes in Patients with TAVI: Predictors Comprise Female Sex, Chronic Kidney Disease, New-Onset AF, and Early Phase of Implementation at a Clinical Site / Valve Type (Balloon-Expandable Vs. Self-Expandable) and Vascular Access Route (Transfemoral vs Nontransfemoral) Are Not

Analysis of 64 studies comprising 72,318 patients (2,385

patients with a stroke within 30 days post-TAVI) showed an incidence of strokes of 1-11% (median 4%). The RRs indicated lower risk for men (RR: 0.82; p=0.02) and higher risk for patients with chronic kidney disease (RR: 1.29; p=0.03) and with new-onset AF post-TAVI (RR: 1.85; p=0.005), and for procedures performed within the first half of center experience (RR: 1.55; p=0.003). The use of balloon post-dilation tended to be associated with a higher risk (RR: 1.43; p=0.07). Valve type (balloon-expandable vs. self-expandable, p=0.26) and approach (transfemoral vs. nontransfemoral, p=0.81) were not predictors (Auffret VM et al, *J Am Coll Cardiol* 2016;68:673-684).

RE-LY Trial: Presence of any Valvular Heart Disease (VHD) did not Influence the Comparison of Dabigatran with Warfarin

In a post hoc analysis of the RE-LY trial, there were 3950 patients with any VHD: 3101 with mitral regurgitation, 1179 tricuspid regurgitation, 817 aortic regurgitation, 471 aortic stenosis, and 193 with mild mitral stenosis. At baseline, patients with any VHD had more heart failure, coronary disease, renal impairment, and persistent AF. Patients with any VHD had higher rates of major bleeds (hazard ratio - HR, 1.32) but similar stroke or systemic embolism event rates (HR, 1.09). For patients receiving dabigatran 110 mg, major bleed rates were lower than for patients taking warfarin (HR, 0.73 with VHD; HR, 0.84 without VHD), and major bleed rates for dabigatran 150 mg were similar to those for warfarin in patients with VHD (HR, 0.82) or without VHD (HR, 0.98). For dabigatran 150 mg, stroke/systemic embolic event rates were lower compared with warfarin in those with VHD (HR, 0.59) and those without VHD (HR, 0.67), and stroke/ systemic embolic event rates were similar for warfarin and dabigatran 110 mg regardless of the presence of VHD. Intracranial bleeds and death rates for dabigatran 150 and 110 mg were lower compared with warfarin independently of the presence of VHD (Ezekowitz MD et al, *Circulation* 2016;134:589-598).

A History of AF in Patients Undergoing PCI is Associated With an Increased Risk of In-Hospital Adverse Outcomes, Including Bleeding, Post-Procedural Heart Failure, Cardiogenic Shock, and Mortality

Among 113,283 PCI cases, history of AF was present in 13,912 patients (12%), who were older and more likely to have comorbid congestive heart failure, cardiomyo-pathy, cerebrovascular disease, and chronic lung disease. Patients with a history of AF were more likely to have in-hospital complications, including in-hospital mortality (3% vs 1%). In propensity-matched analysis, patients with a history of AF were more likely to be treated with a bare-metal stent (27% vs 18%). In the propensity-matched model, AF remained independently associated with an increased risk of developing post-procedural bleeding (odds ratio - OR: 1.32), heart failure (OR: 1.33), cardiogenic shock (OR: 1.26), and in-hospital mortality (OR: 1.41) (Sutton NRD et al, *J Am Coll Cardiol* 2016;68:895-904).

OMEGA-REMODEL Trial: A Beneficial Effect for High-Dose Omega-3 Fatty Acid Treatment on Adverse LV Remodeling After Acute MI with Attenuation of Fibrosis Within Noninfarcted Myocardium and Lower Levels of Systemic Biomarkers of Myocardial Inflammation and Cardiac Fibrosis

Among patients presenting with an acute MI, randomly assigned to 6 months of high-dose omega-3 fatty acids (n=180) or placebo (n=178), active treatment patients experienced a significant reduction of LV systolic volume index (-5.8%, *P*=0.017), and noninfarct myocardial fibrosis (-5.6%, *P*=0.026). Per-protocol analysis revealed that those patients who achieved the highest quartile increase in red blood cell omega-3 index experienced a 13% reduction in LV systolic volume index in comparison with the lowest quartile. In addition, patients in the omega-3 fatty acid arm underwent significant reductions in serum biomarkers of systemic and vascular inflammation and myocardial fibrosis with no adverse events (Heydari B et al, *Circulation* 2016;134:378-391).

Associations Between Food Fortification With Folic Acid and Reductions in the Birth Prevalence of Specific Congenital Heart Disease (CHD) Subtypes

Among 5,901,701 live births and stillbirths, the overall birth prevalence rate of CHDs was 12.3 per 1000 total births. Rates of most CHD subtypes decreased between 1990 and 2011 except for atrial septal defects, which increased significantly. Folic acid food fortification was associated with lower rates of conotruncal defects (rate ratio - RR, 0.73), coarctation of the aorta (RR, 0.77), ventricular septal defects (RR, 0.85), and atrial septal defects (RR, 0.82) but not severe nonconotruncal heart defects (RR, 0.81) and other heart or circulatory system abnormalities (RR, 0.98) (Liu S et al, *Circulation* 2016;134:647-655).

Higher Free T4 (FT4) Levels are Associated with an Increased Risk of SCD, even in Euthyroid Participants

Among 10,318 participants from the Rotterdam Study ≥45 years with thyroid-stimulating hormone or free thyroxine (FT4) measurements there were 261 incident sudden cardiac deaths (SCDs) (median follow-up, 9.1 years). Higher levels of FT4 were associated with an increased SCD risk, even in the normal range of thyroid function (hazard ratio, 2.28 per 1 ng/dL FT4). Stratification by age or gender and sensitivity analyses did not change the risk estimates substantially. The absolute 10-year risk of SCD increased in euthyroid participants from 1% to 4% with increasing FT4 levels (Chaker L et al, *Circulation* 2016;134:713-722).

CHAMPION PHOENIX trial: Cangrelor Compared with Clopidogrel Significantly Reduces MI

A total of 462 (4.2%) among 11,145 patients having percutaneous coronary intervention (PCI) had an MI. Treatment with cangrelor reduced the incidence of MI at 48 hours (3.8% vs 4.7%; odds ratio - OR, 0.80; *P*=0.02). Similar effects were seen in the evaluation of the effects of cangrelor on MIs of different definitions. MIs defined by any of definitions were associated with increased risk of death at 30 days. Treatment with cangrelor reduced the composite end point of death, MI, ischemia-driven revascularization, or definite stent thrombosis (1.4% vs 2.1%; OR, 0.69) (Cavender MA et al, *Circulation* 2016;134:723-733).

Long QT 3: β-Blocker Therapy Reduces the Risk of Life-threatening Cardiac Events in Females / Efficacy in Males could not be Determined Conclusively Because of the Low Number of Events

Among 391 LQT3 patients known to be event free during the first year of life, 118 (41 males, 77 females) (30%) experienced at least 1 cardiac event (CE) (syncope, aborted cardiac arrest, or long-QT syndrome–related sudden death), and 24 (20%) suffered from LQT3-related aborted cardiac arrest/sudden death. The risk of a first CE was directly related to the degree of QTc prolongation. Time-dependent β-blocker therapy was associated with an 83% reduction in CEs in females (*P*=0.015) but not in males (who had many fewer events), with a significant sex × β-blocker interaction (*P*=0.04). Each 10-ms increase in QTc duration up to 500 ms was associated with a 19% increase in CEs. Prior syncope doubled the risk for life-threatening events (*P* <0.02) (Wilde AAM et al, *Circulation* 2016;134:872-882).

VANISH: In Patients with Ischemic Cardiomyopathy and an ICD and Ventricular Tachycardia (VT) Despite Drug Therapy, Ablation Decreased Death, VT Storm, or Appropriate ICD Shocks

Of 259 patients, 132 were assigned to ablation and 127 to escalated drug-therapy. During a mean of 27.9±17.1 months, the primary outcome (death, VT storm or appropriate ICD shocks) occurred in 59.1% of patients in the ablation group and 68.5% of the escalated-therapy group (hazard ratio in the ablation group, 0.72; P=0.04). There was no significant between-group difference in mortality. There were two cardiac perforations and three cases of major bleeding in the ablation group and two deaths from pulmonary toxic effects and one from hepatic dysfunction in the escalated-therapy group (Sapp JL et al, *N Engl J Med* 2016; 375:111-121).

LEADER Trial: Lower Rate of Cardiovascular Death, MI, or Stroke in Diabetic Patients With Liraglutide Than With Placebo

Among 9340 diabetic patients randomized to liraglutide or placebo, at a median follow-up of 3.8 years, the primary outcome (cardiovascular death, MI or stroke) occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients or 13%) than in the placebo group (694 of 4672 or 14.9%) (hazard ratio-HR, 0.87; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients or 4.7%) than in the placebo group (278 or 6%) (HR, 0.78; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients or 8.2%) than in the placebo group (447 or 9.6%) (HR, 0.85; P=0.02). The rates of MI, stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group (Marso SP et al, *N Engl J Med* 2016; 375:311-322).

DANISH Trial: Prophylactic ICD Implantation in Patients With Nonischemic Cardiomyopathy Was Not Associated With a Significantly Lower Long-Term Mortality

After a median of 67.6 months, among 556 non-ischemic cardiomyopathy patients with symptomatic systolic heart failure (ejection fraction, ≤35%) assigned to receive an ICD, and 560 patients assigned to receive usual clinical care (control group) (58% receiving CRT in both groups), total mortality occurred in 120 patients (21.6%) in the ICD group and in 131 patients (23.4%) in the control group (hazard ratio-HR, 0.87; P=0.28). Sudden death occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (HR, 0.50; P=0.005). Device infection occurred in 27 patients (4.9%) in the ICD group & in 20 patients (3.6%) in the control group (P=NS) (Køber L et al, *N Engl J Med* 2016;375:1221-1230).

NORSTENT Trial: In Patients Undergoing PCI, There Were no Significant Differences in Death and MI Between those Receiving Drug-Eluting Stents (DES) or Bare-Metal Stents (BMS) / Rates of Repeat Revascularization Were Lower in the DES Group

At 6 years, among 9013 patients with stable or unstable coronary artery disease randomly assigned to undergo PCI with the implantation of either contemporary DES (everolimus- or zotarolimus-eluting stents) or BMS, the rates of the primary outcome (death and MI) were 16.6% in the group receiving DES and 17.1% in the BMS group (hazard ratio-HR, 0.98; P=0.66). The 6-year rates of any repeat revascularization were 16.5% in the group receiving DES and 19.8% in the BMS group (HR, 0.76; P <0.001); the rates of definite stent thrombosis were 0.8% and 1.2%, respectively (P=0.0498). Quality-of-life measures did not differ significantly between the two groups (Bønaa KH et al, *N Engl J Med* 2016; 375:1242-1252).

ANNEXA-4: Initial Bolus Followed by 2-Hour Infusion of Andexanet Substantially Reduced Anti–Factor Xa Activity in Patients With Acute Major Bleeding Associated With Factor Xa Inhibitors, With Effective Hemostasis Occurring in 79%

All 67 patients (mean age 77 years) with acute major

(gastrointestinal or intracranial) bleeding who received a bolus of andexanet, a factor Xa inhibitor, at a mean of 4.8±1.8 h, followed by a 2-h infusion of the drug, were evaluated within 18 h after the administration of a factor Xa inhibitor. After the bolus administration, the median anti–factor Xa activity decreased by 89% among patients receiving rivaroxaban and by 93% among patients receiving apixaban. These levels remained similar during the 2-h infusion. At 4 h after the end of the infusion, there was a relative decrease from baseline of 39% in the measure of anti–factor Xa activity among patients receiving rivaroxaban and of 30% among those receiving apixaban. At 12 h after the andexanet infusion, clinical hemostasis was adjudicated as excellent or good in 37 of 47 patients in the efficacy analysis (79%). Thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up (Connolly SJ et al, *N Engl J Med* 2016; 375:1131-1141).

SAVE Trial: CPAP did not Prevent Cardiovascular Events in Obstructive Sleep Apnea (OSA)

After a mean follow-up of 3.7 years, among 2717 patients (45-75 years of age) with OSA randomly assigned to CPAP treatment plus usual care (CPAP group) or usual care alone (usual-care group), the primary composite end point (death from cardiovascular causes, MI, stroke, or hospitalization for unstable angina, heart failure, or TIA) occurred in 229 participants in the CPAP group (17%) and in 207 participants in the usual-care group (15.4%) (hazard ratio, 1.10; P=0.34). CPAP significantly reduced snoring and daytime sleepiness and improved health-related quality of life and mood (McEvoy RD et al; *N Engl J Med* 2016; 375:919-931).

RELY: Marked Unexplained Inter-Regional Variations in Stroke and Mortality Occurrence Suggest that Factors Other Than Clinical Variables Might be Important / Prevention of Death from Heart Failure Should be a Major Priority in Treating Atrial Fibrillation (AF)

According to a prospective registry of 15,400 patients in 47 countries presenting to the emergency department with AF or atrial flutter in 8 geographical regions, 1758 (11%) patients died within 1 year. Fewer deaths occurred among patients presenting with a primary diagnosis of AF compared with patients who had AF as a secondary diagnosis (377 or 6% of 6825 patients *vs* 1381 or 16% of 8536, p <0.0001). Twice as many patients had died by 1 year in South America (192 or 17% of 1132) and Africa (225 or 20% of 1137) compared with North America, western Europe, and Australia (366 or 10% of 3800, p <0.0001). Heart failure was the most common cause of death (519 or 30% of 1758); stroke caused 148 (8%) deaths. 604 (4%) of 15361 patients had had a stroke by 1 year; 170 (3%) of 6825 for whom AF was a primary diagnosis and 434 (5%) of 8536 for whom it was a secondary diagnosis (p <0.0001). The highest number of strokes occurred in Africa (89 or 8% of 1137), China (143 or 7% of 2023), and southeast Asia (88 or 7% of 1331) and the lowest occurred in India (20 or <1% of 2536). 94 (3%) of 3800 patients in North America, western Europe, and Australia had a stroke (Healey JS et al, *Lancet* 2016;388:1161–1169).

PRIMA Trial: In Patients With Refractory Migraine With Aura and PFO, PFO Closure did not Reduce Overall Monthly Migraine Days

Among 83 patients completing 1-year follow-up of 107 migraine patients randomly allocated to treatment with an Amplatzer PFO Occluder (*N*=53) or control with medical management with aspirin and clopidogrel (*N*=54), mean migraine days were not significantly reduced (Mattle HP et al, *Eur Heart J* 2016;37:2029-2036).

Important Review and Other Articles

- **New 2016 ESC Guidelines for Atrial Fibrillation** (Kirchhof P et al, *Eur Heart J* 2016;37:2893-2962), Non-statin therapies (ACC Expert Consensus) for LDL-cholesterol lowering (Lloyd-Jones DM et al, *JACC* 2016;68:92-125), Spontaneous coronary artery dissection (Saw J et al, *J Am Coll Cardiol* 2016;68:297-312.), High-risk cardiac disease in pregnancy (Elkayam U et al, JACC 2016; ;68:396-410 & 502-516), Cardiac sarcoidosis (Birnie DH et al, *J Am Coll Cardiol* 2016;68:411-421), Left ventricular non-compaction (Arbustini E et al, *J Am Coll Cardiol* 2016;68:949-966), Duration of dual antiplatelet therapy in patients with CAD (Levine et al, *J Am Coll Cardiol* 2016;68:1082-1115 & Bittl JA et al, *J Am Coll Cardiol* 2016;68:1116-1139), Contrast-induced acute kidney injury (McCullough PA et al, *J Am Coll Cardiol* 2016;68:1465-1473), Pharmacological therapy for heart failure (Yancy CW et al, *J Am Coll Cardiol* 2016;68:1476-1488), Bioresorbable vascular scaffolds (Kereiakes DJ et al, *Circulation* 2016; 134:168-182), Management of bleeding with NOACs (Ruff CT et al, *Circulation* 2016;134:248-261), AF ablation (Link MS et al, *Circulation* 2016;134:339-352), Drugs causing or exacerbating heart failure (Page RL et al, *Circulation* 2016;134:e32-e69), Chest compression only CPR (Ewy GA, *Circulation* 2016;134:695-697), Atrial fibrillation (stroke prevention / rate & rhythm control) (*Lancet* 2016; 388: 806-840).

Addendum (Just in!): On October 28, 2016, based on the accumulated evidence, the U.S. Food and Drug Administration approved the Amplatzer PFO Occluder device for prevention of recurrent strokes in patients with a cryptogenic stroke and a PFO (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm527096.htm).