

## Cardiology News / Recent Literature Review / Third Quarter 2017

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*Rhythmios 2017;12(4):71-78.*

HCS 2017, 28<sup>th</sup> Panhellenic Cardiology Congress: Athens, 19-21/10/2017

TCT Congress: Denver, Colorado, 29/10-2/11/2017

AHA Meeting: Anaheim, Ca, 11-15/11/2017

ACC.18 Congress: Orlando, FL, 10-12/3/2018

HRS Meeting: Boston, 9-12/5/2018

ESC Meeting: Munich, 25-29/8/2018

### **Long QT syndrome (LQTS): Although Outcomes Have Improved, 1 in 4 Patients with Prior Symptoms Experience at Least 1 Subsequent, Albeit Nonlethal, Cardiac Event Demanding Further Optimization of Treatment Strategies**

Among 606 patients with LQTS (LQT1 in 47%, LQT2 in 34%, and LQT3 in 9%), a potentially lethal cardiac channelopathy with a 1-5% annual risk of LQTS-triggered syncope, aborted cardiac arrest, or sudden cardiac death, there were 166 (27%) patients who were symptomatic prior to their first Mayo Clinic evaluation at a median age of 12 years at first symptom. Treatment strategies included no active therapy in 47 (8%) patients, beta-blockers alone in 350 (58%) patients, ICDs alone in 25 (4%) patients, left cardiac sympathetic denervation alone in 18 (3%) patients, and combination therapy in 166 (27%) patients. Over a median follow-up of 6.7 years, 556 (92%) patients did not experience a cardiac event. Only 8 of 440 (2%) previously asymptomatic patients experienced a single event. In contrast, 42 of 166 (25%) previously symptomatic patients experienced  $\geq 1$  events. Among the 30 patients with  $\geq 2$  events, 2 patients died and 3 LQT3 patients underwent cardiac transplantation (Rohatgi RK et al, *J Am Coll Cardiol* 2017;70:453–62).

### **TRAC-AF Study: Temperature-Controlled Irrigated Ablation Produces Rapid, Efficient, and Durable PV Isolation**

A novel irrigated RF catheter (DiamondTemp -DT) designed with a diamond-embedded tip (for rapid cooling) and thermocouples to monitor tissue temperature, was first used in 6 pigs for atrial ablation in a temperature control mode (60°C/50 W) until there was ~80% EGM amplitude reduction; lesion histology revealed transmural in 51 of

55 lesions (92.7%). In a clinical feasibility study, the study group of 35 patients having PV isolation with the DT catheter, compared with a control group of 35 patients undergoing PV isolation with a standard force-sensing catheter, had shorter mean RF application duration ( $26.3 \pm 5.2$  min vs.  $89.2 \pm 27.2$  min;  $p < 0.001$ ), shorter mean fluoroscopic time ( $11.2 \pm 8.5$  min vs.  $19.5 \pm 6.8$  min;  $p < 0.001$ ), and lower acute dormant PV reconnection (0 of 35 vs. 5 of 35;  $p = 0.024$ ). At 3 months, among 23 patients undergoing remapping, 39 of 46 PV pairs (84.8%) remained durably isolated in 17 of these patients (73.9%) (Iwasawa J et al, *J Am Coll Cardiol* 2017;70:542-553).

### **Elevated Cardiac Troponin Concentration, Well Within the Normal Range, is Associated With an Increased Risk of Incident Cardiovascular Disease (CVD) Outcomes in the General Population**

In the PROSPER trial, hs-cTnT was detectable in 3,853 (87.5%) of 4,402 participants and positive associations were observed between hs-cTnT and CVD outcomes. In a meta-analysis of 28 studies involving 154,052 participants, cardiac troponin was detectable in 80% (hs-cTnI: 82.6%; hs-cTnT: 69.7%), and the relative risks comparing the top vs the bottom troponin third were 1.43 for CVD (11,763 events), 1.67 for fatal CVD (7,775 events), 1.59 for CHD (7,061 events), and 1.35 for stroke (2,526 events) (Willeit P et al, *J Am Coll Cardiol* 2017;70: :558–568).

### **Patients With a New Diagnosis of Cancer Face an Increased Risk of Arterial Thromboembolism, Especially During the First 6 Months After Diagnosis**

Among 279,719 pairs of patients with cancer and matched control patients, the 6-month cumulative incidence of arterial thromboembolism was 4.7% in patients with cancer compared with 2.2% in control patients (hazard ratio - HR: 2.2). The 6-month cumulative incidence of myocardial infarction was 2% in patients with cancer compared with 0.7% in control patients (HR: 2.9). The 6-month cumulative incidence of ischemic stroke was 3% in patients with cancer compared with 1.6% in control patients (HR: 1.9). Excess risk varied by cancer type (greatest for lung), correlated with cancer stage, and generally had resolved by 1 year (Navi BB et al, *J Am Coll Cardiol* 2017;70:926-938).

### **In Patients with Non-Ischemic Cardiomyopathy (NICM), CRT-D was Superior to CRT-P, Particularly in Patients with LV Midwall Fibrosis (MWF), which Emerged as an Independent Predictor of Mortality and Morbidity in Patients with NICM Undergoing CRT**

Among NICM patients with (+) ( $n=68$ ) or without (–) left ventricular midwall fibrosis (MWF) ( $n=184$ ), detected by cardiac magnetic resonance, +MWF emerged as an

independent predictor of total mortality (adjusted hazard ratio-HR: 2.31), total mortality or heart failure hospitalization (HR: 2.02), total mortality or hospitalization for major adverse cardiac events (HR: 2.02), death from pump failure (HR: 1.95), and sudden cardiac death (HR: 3.75) over a maximum follow-up period of 14 years (median 3.8 years for +MWF and 4.6 years for -MWF). In separate analyses of +MWF and -MWF, total mortality (HR: 0.23), total mortality or heart failure hospitalization (HR: 0.32), and total mortality or hospitalization for major adverse cardiac events (HR: 0.30) were lower after CRT-D than after CRT-P in +MWF but not in -MWF (Leyva F et al, *J Am Coll Cardiol* 2017;70:1216-1227).

**In Patients With Atrial Fibrillation (AF), More Severe Left Atrial (LA) Late Gadolinium Enhancement (LGE) was Associated With Increased Risk of Major Adverse Cardiovascular/Cerebrovascular Events (MACCE)**

Among 1,228 AF patients who underwent LGE-cardiac MRI to quantify LA fibrosis, there occurred 62 strokes or TIAs, 42 MIs, 156 HF events, and 38 CV deaths. In disease risk score (DRS) stratified analysis, the hazard ratio comparing patients with advanced stage vs early stage LA LGE was 1.67 for the MACCE outcome. The only individual component of the MACCE outcome to remain significantly associated with advanced LGE following DRS stratification was stroke or TIA (hazard ratio: 3.94 (King JB et al, *J Am Coll Cardiol* 2017;70: 1311-1321).

**The Danish Diet, Cancer, and Health Study: Moderate Chocolate Intake May be Inversely Associated With Atrial Fibrillation (AF) Risk (11–20% Lower Rate)**

Among 55,502 participants (26,400 men / 29,102 women) aged 50–64 years, during a median of 13.5 years there were 3346 AF cases. Compared with chocolate intake <once per month, the rate of AF was lower for people consuming 1–3 servings/month (hazard ratio -HR 0.90), 1 serving/week (HR 0.83), 2–6 servings/week (HR 0.80) and  $\geq 1$  servings/day (HR 0.84; p-linear trend <0.0001), with similar results for men and women (Mostofsky E et al, *Heart* 2017; 103:1163-1167).

**ADHERENCE Trial: In Patients With High-Dose Statin Intolerance, Combined Low-Dose Statin (LDS) and Nutraceuticals (Armolidip Plus) Were Efficacious**

Low-dose statin (LDS) therapy vs combined therapy of LDS plus a nutraceutical containing red yeast rice, policosanol, berberine, folic acid, coenzyme Q10 and astaxanthin (Armolidip Plus) was tested in 100 participants having undergone PCI who were high-dose statin intolerant. After 3 months, patients in the LDS + Armolidip Plus (n = 50) group had a greater reduction of LDL-C and total cholesterol (p < 0.0001), and 70%

achieved the therapeutic target (LDL-C <70 mg/dl). Six patients (3 from each group) dropped out due to myalgia (Marazzi G et al, *Am J Cardiol* 2017; 120:893-7).

**SWEDHEART Registry: In Type 1 Diabetes (T1D) Patients With Multivessel Coronary Artery Disease, CABG was Associated With a Lower Risk of Coronary Mortality, MI, and Repeat Revascularization Compared With PCI**

Among 683 patients who underwent CABG and 1,863 patients who underwent PCI, over a mean of 10.6 years, 53% of patients in the CABG group and 45% in the PCI group died. PCI, compared with CABG, was associated with a similar risk of all-cause mortality (HR: 1.14), but higher risks of death from coronary disease (HR: 1.45), MI (HR: 1.47), and repeat revascularization (HR: 5.64). No differences in risks of stroke or heart failure were found (Nystrom T et al, *J Am Coll Cardiol* 2017;70:1441-1451).

**Diabetes does not Adversely Influence the Long-term Patency of Coronary Artery Bypass Grafts / Internal Mammary Artery Grafts have Excellent Patency in Patients with and without Diabetes Even 20 Years Post-operatively**

Long-term graft patency was evaluated in 57,961 patients with and without diabetes, who underwent primary isolated coronary artery bypass grafting (CABG). Internal mammary artery (IMA) graft patency was stable over time and similar in patients with and without diabetes at 1, 5, 10, and 20 years, 97%, 97%, 96%, and 96% in patients with diabetes, and 96%, 96%, 95%, and 93% in patients without diabetes, respectively (early p = 0.20; late p = 0.30). In contrast, saphenous vein graft (SVG) patency declined over time and similarly in patients with and without diabetes: at 1, 5, 10, and 20 years, 78%, 70%, 57%, and 42% in patients with diabetes, and 82%, 72%, 58%, and 41% in patients without diabetes, respectively (early p < 0.002; late p = 0.60). The authors concluded that diabetes did not influence long-term patency of bypass grafts with excellent patency of IMA documented in patients with and without diabetes even after 20 years (Raza S et al, *J Am Coll Cardiol* 2017; 70:515-24).

**FRAILITY-AVR Study: Assessment of Frailty Using a Brief 4-Item Scale Encompassing Lower-Extremity Weakness, Cognitive Impairment, Anemia, and Hypoalbuminemia Adds Incremental Prognostic Value**

The incremental predictive value of 7 different frailty scales to predict poor outcomes following TAVI or surgical AVR was tested in 1,020 patients with a median age of 82 years. Depending on the scale used, the prevalence of frailty ranged from 26% to 68%. Frailty as measured by the Essential Frailty Toolset (EFT) was the

strongest predictor of death at 1 year (adjusted odds ratio - OR: 3.72) with a C-statistic improvement of 0.071 ( $p < 0.001$ ) and integrated discrimination improvement of 0.067 ( $p < 0.001$ ). Moreover, the EFT was the strongest predictor of worsening disability at 1 year (OR: 2.13) and death at 30 days (OR: 3.29). The authors concluded that frailty is a risk factor for death and disability following TAVI and surgical AVR. A brief 4-item scale including lower-extremity weakness, cognitive impairment, anemia, and hypoalbuminemia outperformed other frailty scales and is recommended for use in this setting (Afilalo J et al, *J Am Coll Cardiol* 2017; 70:689-700).

### **EFFORTLESS Registry: the Subcutaneous ICD (S-ICD) Remains Safe and Effective, With Low Incidence of Device Upgrade for Bradycardia, CRT, or ATP, and Low Rate of Implant Complications**

All 985 patients with S-ICD (mean age 48 years, 28% women, ejection fraction  $43 \pm 18\%$ ; 65% with a primary prevention indication) were followed for  $3.1 \pm 1.5$  years; 82 completed 5-year follow-up. The complication rate was 4.1% at 1 month and 8.4% at 1 year. The 1-year complication rate trended toward improvement from the first to last quartile of enrollment (11.3% to 7.4%;  $p = 0.06$ ). Few device extractions occurred due to need for antitachycardia ( $n = 5$ ), or biventricular ( $n = 4$ ) or bradycardia pacing ( $n = 1$ ). Inappropriate shocks occurred in 8.1% at 1 year and 11.7% after 3.1 years. At implant, 99.5% of patients had a successful conversion of induced ventricular tachycardia/fibrillation. The 1- and 5-year rates of appropriate shock were 5.8% and 13.5%, respectively. Conversion success for discrete spontaneous episodes was 97.4% overall (Boersma L et al, *J Am Coll Cardiol* 2017; 70:830-841).

### **CoreValve Evolut R FORWARD study: The Next-Generation, Self-expanding Evolut R Valve is Clinically Safe and Effective for Treatment of Older Patients with Severe Aortic Stenosis (AS)**

TAVI with the next-generation self-expanding valve was attempted in 1,038 patients with symptomatic, severe AS (mean age  $81.8 \pm 6.2$  years, 64.9% women, mean STS score  $5.5 \pm 4.5\%$ , 33.9% frail). Repositioning of the valve was applied in 25.8% of patients. A single valve was implanted in 98.9% of patients. The mean aortic valve gradient was  $8.5 \pm 5.6$  mmHg, and moderate or severe aortic regurgitation was 1.9% at discharge. All-cause mortality was 1.9%, and disabling stroke occurred in 1.8% at 30 days. The expected-to-observed early surgical mortality ratio was 0.35. A pacemaker was implanted in 17.5% of patients (Grube E et al, *J Am Coll Cardiol* 2017; 70:845-853).

### **Gasping During Cardiopulmonary Resuscitation (CPR) is Independently Associated With a Higher Likelihood of 1-Year Survival With Favorable Neurological Status After Out-Of-Hospital Cardiac Arrest (OHCA)**

The rates of 1-year survival with a Cerebral Performance Category (CPC) score of  $\leq 2$  were 5.4% (98 of 1,827) overall, and 20% (36 of 177) and 3.7% (61 of 1,643) for individuals with and without spontaneous gasping or agonal respiration during CPR, respectively. In multivariable analysis, 1-year survival with  $CPC \leq 2$  was independently associated with younger age (odds ratio - OR for 1 SD increment 0.57), gasping during CPR (OR: 3.94), shockable initial recorded rhythm (OR: 16.50), shorter CPR duration (OR: 0.31), lower epinephrine dosage (OR: 0.47), and pulmonary edema (OR: 3.41). Gasping combined with a shockable initial recorded rhythm had a 57-fold higher OR of 1-year survival with  $CPC \leq 2$  vs no gasping and no shockable rhythm (Debaty G et al, *J Am Coll Cardiol* 2017; 135:1467-1476).

### **N-Acetylcysteine (NAC) is an Effective and Safe Alternative to Currently Available Antithrombotic Agents to Restore Vessel Patency After Arterial Occlusion**

IV administration of NAC promotes lysis of arterial thrombi that are resistant to conventional approaches such as recombinant tissue-type plasminogen activator (rTPA), direct thrombin inhibitors, and antiplatelet treatments. Through in vitro and in vivo experiments, evidence was provided that the molecular target underlying the thrombolytic effects of NAC is principally the von Willebrand factor (VWF) that cross-link platelets in arterial thrombi. Coadministration of NAC and a nonpeptidic GpIIb/IIIa inhibitor further improved its thrombolytic efficacy, by accelerating thrombus dissolution and preventing rethrombosis. Thus, in a new large-vessel thromboembolic stroke model in mice, this cotreatment significantly improved ischemic lesion size and neurological outcome. Importantly, NAC did not worsen hemorrhagic stroke outcome, suggesting that it exerts thrombolytic effects without significantly impairing normal hemostasis (de Lizarrondo SM et al, *Circulation* 2017; 136:646-660).

### **NACIAM Trial: High-Dose IV N-Acetylcysteine (NAC) Administered With Low-Dose IV Nitroglycerin is Associated With Reduced Infarct Size in Patients With STEMI Undergoing PCI**

The effects of IV high-dose NAC (29 g over 2 days) with background low-dose nitroglycerin (7.2 mg over 2 days) on early cardiac MRI (CMR)-assessed infarct size were evaluated in 112 randomized patients with STEMI,

of whom 75 (37 in NAC group, 38 in placebo group) underwent early CMR. Median duration of ischemia pretreatment was 2.4 hours. Those randomized to NAC exhibited an absolute 5.5% reduction in CMR-assessed infarct size relative to placebo (median, 11%; vs 16.5%;  $P=0.02$ ). Myocardial salvage was approximately doubled in the NAC group (60%) compared with placebo (27%;  $P<0.01$ ) and median creatine kinase areas under the curve were 22 000 and 38 000 IU·h in the NAC and placebo groups, respectively ( $P=0.08$ ) (Pasupathy S et al, *Circulation* 2017;136:894-903).

### **Rising Pandemic of Obesity: Nearly 70% of the Deaths That were Related to High BMI were Due to Cardiovascular (CV) Disease, and >60% of Those Deaths Occurred Among Obese Persons**

In 2015, a total of 107.7 million children and 603.7 million adults were obese. Since 1980, the prevalence of obesity has doubled in more than 70 countries and has continuously increased in most other countries. Although the prevalence of obesity among children has been lower than that among adults, the rate of increase in childhood obesity in many countries has been greater than the rate of increase in adult obesity. High BMI accounted for 4 million deaths globally, nearly 40% of which occurred in persons who were not obese. More than two thirds of deaths related to high BMI were due to CV disease. The disease burden related to high BMI has increased since 1990; however, the rate of this increase has been attenuated owing to decreases in underlying rates of death from CV disease (The GBD 2015 Obesity Collaborators, *N Engl J Med* 2017; 377:13-27).

### **Declining Risk of Sudden Death (SD) in Heart Failure**

Analysis of data from 40,195 patients who had heart failure with reduced ejection fraction, enrolled in any of 12 clinical trials (1995-2014), with 3583 sudden deaths reported, indicated that these patients were older, more often male, with an ischemic cause of heart failure and worse cardiac function, than those without SD. There was a 44% decline in the rate of SD across the trials ( $P=0.03$ ). The cumulative incidence of SD at 90 days after randomization was 2.4% in the earliest trial and 1% in the most recent trial. The rate of SD was not higher among patients with a recent diagnosis of heart failure than among those with a longer-standing diagnosis (Shen L et al, *N Engl J Med* 2017; 377:41-51).

### **Idarucizumab for Rapid, Durable & Safe Dabigatran Reversal**

Among 301 patients with uncontrolled bleeding (group A) and 202 who were to undergo an urgent procedure (group B) who received 5 g of i.v. idarucizumab, the

median maximum percentage reversal of dabigatran was 100%, on the basis of either the diluted thrombin time or the ecarin clotting time. In group A, 137 patients (45.5%) presented with gastrointestinal bleeding and 98 (32.6%) presented with intracranial hemorrhage; among the patients who could be assessed, the median time to the cessation of bleeding was 2.5 h. In group B, the median time to the initiation of the intended procedure was 1.6 h; periprocedural hemostasis was assessed as normal in 93.4% of the patients, mildly abnormal in 5.1%, and moderately abnormal in 1.5%. At 90 days, thrombotic events had occurred in 6.3% of the patients in group A and in 7.4% in group B, and the mortality rate was 18.8% and 18.9%, respectively. There were no serious adverse events (Pollack CV et al, *N Engl J Med* 2017; 377:431-441).

### **ROOBY-FS Trial: Off-Pump CABG Led to Lower Rates of 5-Year Survival and Event-Free Survival Than On-Pump CABG**

Among 2203 patients randomly assigned to undergo either on-pump or off-pump CABG, the rate of death at 5 years was 15.2% in the off-pump group vs 11.9% in the on-pump group (relative risk, 1.28;  $P=0.02$ ). The rate of major adverse cardiovascular events at 5 years was 31% in the off-pump group vs 27.1% in the on-pump group (relative risk, 1.14;  $P=0.046$ ). For the 5-year secondary outcomes, no significant differences were observed: for nonfatal MI, the rate was 12.1% in the off-pump group and 9.6% in the on-pump group ( $P=0.05$ ); for death from cardiac causes, the rate was 6.3% and 5.3%, respectively ( $P=0.29$ ); for repeat revascularization, the rate was 13.1% and 11.9%, respectively ( $P=0.39$ ); and for repeat CABG, the rate was 1.4% and 0.5%, respectively ( $P=0.02$ ). (Shroyer AL et al, *N Engl J Med* 2017; 377:623-632).

### **CANVAS Trials: Canagliflozin Had a Lower Risk of Cardiovascular (CV) Events Than Those Who Received Placebo But a Greater Risk of Amputation (Level of the Toe or Metatarsal)**

Among 10,142 participants with type 2 diabetes and high CV risk (mean age 63.3 years, 35.8% women, mean duration of diabetes 13.5 years, 65.6% with history of CV disease), randomly assigned to canagliflozin or placebo, the rate of the primary outcome (CV death, MI or stroke) was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio - HR, 0.86;  $P<0.001$  for noninferiority;  $P=0.02$  for superiority). A possible benefit of canagliflozin was shown with respect to the progression of albuminuria (HR, 0.73) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (HR, 0.60). Adverse reactions were consistent with the

previously reported risks associated with canagliflozin except for an increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; HR, 1.97), primarily at the level of the toe or metatarsal (Neal B et al; *N Engl J Med* 2017; 377:644-657).

**CLOSE Trial: Among Patients With a Recent Cryptogenic Stroke Attributed to PFO With an Associated Atrial Septal Aneurysm or Large Interatrial Shunt, the Rate of Stroke Recurrence was Lower Among those Assigned to PFO Closure**

Among 663 PFO patients (16-60 years old), followed for a mean of 5.3±2.0 years, no stroke occurred among the 238 patients in the PFO closure group, whereas stroke occurred in 14 of the 235 patients in the antiplatelet-only group (hazard ratio, 0.03;  $P<0.001$ ). Procedural complications from PFO closure occurred in 14 patients (5.9%). The rate of atrial fibrillation was higher in the PFO closure group than in the antiplatelet-only group (4.6% vs. 0.9%,  $P=0.02$ ). The number of serious adverse events did not differ significantly between the treatment groups ( $P=0.56$ ). Stroke occurred in 3 of 187 patients assigned to oral anticoagulants and in 7 of 174 patients assigned to antiplatelet therapy alone (Mas J-L et al, *N Engl J Med* 2017; 377:1011-1021).

**RESPECT Trial: Among Adults With a Cryptogenic Ischemic Stroke, Closure of a PFO was Associated with a Lower Rate of Recurrent Ischemic Strokes Than Medical Therapy Alone During Extended Follow-Up**

Among 980 patients (mean age, 45.9 years), followed for a median of 5.9 years, recurrent stroke occurred in 18 patients in the PFO closure group and in 28 patients in the medical-therapy group, resulting in rates of 0.58 and 1.07 events per 100 patient-years, respectively (hazard ratio with PFO closure vs medical therapy, 0.55;  $P=0.046$  by the log-rank test). Recurrent ischemic stroke of undetermined cause occurred in 10 patients in the PFO closure group and in 23 patients in the medical-therapy group (hazard ratio, 0.38;  $P=0.007$ ). Venous thromboembolism (which comprised events of pulmonary embolism and deep-vein thrombosis) was more common in the PFO closure group than in the medical-therapy group (Saver JL et al, *N Engl J Med* 2017; 377:1022-1032).

**REDUCE Study: In PFO Patients With a Cryptogenic Stroke, the Risk of Ischemic Stroke was Lower Among Those Assigned to PFO Closure/ However, PFO Closure was Associated With Higher Rates of Device Complications and Atrial Fibrillation**

Among 664 PFO patients (mean age, 45.2 years, 81% with moderate or large interatrial shunts), over 3.2 years, clinical ischemic stroke occurred in 6 of 441 patients

(1.4%) in the PFO closure group and in 12 of 223 patients (5.4%) in the antiplatelet-only group (hazard ratio, 0.23;  $P=0.002$ ). The incidence of new brain infarctions was significantly lower in the PFO closure group than in the antiplatelet-only group (22 patients - 5.7% vs 20 patients - 11.3%; relative risk, 0.51;  $P=0.04$ ), but the incidence of silent brain infarction did not differ significantly between the study groups ( $P=0.97$ ). Serious adverse events occurred in 23.1% in the PFO closure group and in 27.8% in the antiplatelet-only group ( $P=0.22$ ). Serious device-related adverse events occurred in 6 patients (1.4%) in the PFO closure group, and AF occurred in 29 patients (6.6%) after PFO closure (Søndergaard L et al, *N Engl J Med* 2017; 377:1033-1042).

**CANTOS Trial: Antiinflammatory Therapy Targeting Interleukin-1 $\beta$  With Canakinumab at a s.c. Dose of 150 mg Every 3 Months Led to a Significantly Lower Rate of Recurrent Cardiovascular Events Than Placebo, Independent of Lipid-Level Lowering**

Among 10,061 patients with previous MI and a hsCRP  $\geq 2$  mg/l, randomized to 3 doses of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1 $\beta$ , or placebo, at 48 months the median reduction from baseline in the hs-CRP was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group. Canakinumab did not reduce lipid levels from baseline. At a median of 3.7 years, the incidence rate for the primary end point (nonfatal MI, nonfatal stroke, or CV death) was 4.50 events per 100 person-years in the placebo group, 4.11 in the 50-mg group (hazard ratio-HR 0.93;  $p=NS$ ), 3.86 in the 150-mg group (HR 0.85;  $p=0.021$ ), and 3.90 in the 300-mg group (HR 0.86;  $p=0.031$ ). The 150-mg dose, but not the other doses, met the threshold for statistical significance for the primary and secondary end points (HR 0.83;  $P=0.005$ ). Canakinumab was associated with a higher incidence of fatal infection than was placebo. There was no significant difference in all-cause mortality. Interestingly, lung cancer mortality was lower with canakinumab than with placebo (Ridker PM et al, *N Engl J Med* 2017; 377:1119-1131).

**DETO2X-SWEDEHEART Trial: Routine Oxygen Use in Patients With Suspected Myocardial Infarction Without Hypoxemia did not Reduce 1-Year Mortality**

Among 6629 patients with suspected MI and an oxygen saturation of  $\geq 90\%$ , randomized to oxygen or ambient air, the primary end point of death from any cause within 1 year after randomization occurred in 5% of patients (166 of 3311) assigned to oxygen and in 5.1% of patients (168 of 3318) assigned to ambient air (hazard ratio, 0.97;

P=0.80). Rehospitalization with MI within 1 year occurred in 126 patients (3.8%) assigned to oxygen and in 111 patients (3.3%) assigned to ambient air (HR, 1.13; P=0.33) (Hofmann R et al, *N Engl J Med* 2017; 377:1240-1249).

### **Meta-Analysis of Trials Comparing an Early vs a Delayed Invasive Strategy in Patients Presenting With Non-ST Elevation Acute Coronary Syndromes (NSTEMI-ACS): An Early Invasive Strategy Might Reduce Mortality in High-Risk, but not in all Other, Patients**

Analysis of 8 trials (n=5324 NSTEMI-ACS patients) with a median follow-up of 6 months, indicated that overall, there was no significant mortality reduction in the early invasive group compared with the delayed invasive group (HR 0.81; p=0.0879). In pre-specified analyses of high-risk patients, there was lower mortality with an early invasive strategy in patients with elevated cardiac biomarkers at baseline (HR 0.761), diabetes (0.67), a GRACE risk score more than 140 (0.70), and aged 75 years older (0.65), although tests for interaction were inconclusive. (Jobs A et al, *Lancet* 2017; 390 (10096):737-746).

### **Meta-Analysis of Fibrinolysis Trials: Differences Exist Among Various Fibrinolytics in STEMI / Alteplase (Accelerated Infusion), Tenecteplase, and Reteplase Should be Considered Over Streptokinase and Non-Accelerated Infusion of Alteplase / The Addition of Glycoprotein IIb/IIIa Inhibitors to Fibrinolytic Therapy Should be Discouraged**

According to 40 studies involving 128 071 patients treated with 12 different fibrinolytic regimens, compared with accelerated infusion of alteplase with parenteral anticoagulants as background therapy, streptokinase and non-accelerated infusion of alteplase were significantly associated with an increased risk of all-cause mortality (risk ratio -RR 1.14 for streptokinase plus parenteral anticoagulants; RR 1.26 for non-accelerated alteplase plus parenteral anticoagulants). No significant difference in mortality risk was recorded between accelerated infusion of alteplase, tenecteplase, and reteplase with parenteral anticoagulants as background therapy. For major bleeding, a tenecteplase-based regimen tended to be associated with lower risk of bleeding compared with other regimens (RR 0.79). The addition of glycoprotein IIb/IIIa inhibitors to fibrinolytic therapy increased the risk of major bleeding by 1.27–8.82-times compared with accelerated infusion alteplase plus parenteral anticoagulants (RR 1.47 for tenecteplase plus parenteral anticoagulants plus glycoprotein inhibitors; RR 1.88 for reteplase plus parenteral anticoagulants plus glycoprotein inhibitors) (Jinathongthai P et al, *Lancet* 2017;390:747-759).

### **Bioresorbable Vascular Scaffolds (BVS) are Associated With Increased Rates of Composite Device-Oriented Adverse Events and Device Thrombosis at 2 Years and Between 1 and 2 Years of Follow-Up Compared With Metallic Everolimus-Eluting Stents (EES)**

Analysis of 7 trials with 5583 patients randomly assigned to Absorb BVS (n=3261) or metallic EES (n=2322) and followed up for 2 years, indicated that BVS had higher 2-year relative risks of the device-oriented composite endpoint than did EES (9.4% vs 7.4%; relative risk -RR 1.29), driven by increased rates of target vessel-related MI (5.8% vs 3.2%; RR 1.68, p=0.0003) and ischemia-driven target lesion revascularization (5.3% vs 3.9%; RR 1.40, p=0.0090) with BVS, with non-significant differences in cardiac mortality. Cumulative 2-year incidence of device thrombosis was higher with BVS than with EES (2.3% vs 0.7%; RR 3.35, p<0.0001). Analysis between 1 and 2 years also showed higher rates of the device-oriented composite endpoint (3.3% vs 1.9%; RR 1.64, p=0.0376) and device thrombosis (0.5% vs none, p<0.0001) in BVS-treated patients than in EES-treated patients (Ali ZA et al, *Lancet* 2017;390: 760-772).

### **In Patients with Ischemic (ICM) or Non-Ischemic Cardiomyopathy (NICM), Primary Prevention With ICD Therapy Versus Conventional Care Reduced the Incidence of Sudden and All-Cause Death**

Meta-analysis of 11 trials involving 8716 patients (4 comprising 1781 patients with NICM, 6 comprising 4414 patients with ICM, and 1 comprising 2521 patients with both types of cardiomyopathy), indicated that over a mean of 3.2 years, there was an overall reduction in all-cause mortality, from 28.26% with conventional care to 21.37% with ICD therapy (hazard ratio -HR, 0.81; P= 0.043). The magnitude of reduction was similar in the cohorts with non-ischemic (HR, 0.81) and ischemic (HR, 0.82) disease, although the latter estimate did not reach statistical significance. The rate of sudden death fell from 12.15% with conventional care to 4.39% with ICD therapy (HR, 0.41), with a similar magnitude of reduction in patients with ischemic (HR, 0.39) and those with non-ischemic disease (HR, 0.44). Noncardiac and any cardiac deaths did not differ significantly by treatment (Kołodziejczak M et al, *Ann Intern Med* 2017;167:103-111)

### **EPIC Study in 10 European Countries: Coffee Drinking was Associated With Reduced Risk for Death from Various Causes**

Among 521,330 persons enrolled in EPIC, over a mean of 16.4 years, 41,693 deaths occurred. Compared with non-consumers, participants in the highest quartile of coffee consumption had lower all-cause mortality (men: HR,

0.88;  $P$  for trend < 0.001; women: HR, 0.93;  $P$  = 0.009). Inverse associations were also observed for digestive disease mortality for men (HR, 0.41;  $P$  < 0.001) and women (HR, 0.60;  $P$  < 0.001). Among women, there was a significant inverse association of coffee drinking with circulatory (HR, 0.78;  $P$  < 0.001) and cerebrovascular disease mortality (HR, 0.70;  $P$  = 0.002) and a positive association with ovarian cancer mortality (HR, 1.31;  $P$  = 0.015). Also, higher coffee consumption was associated with lower serum alkaline phosphatase; alanine aminotransferase; aspartate aminotransferase;  $\gamma$ -glutamyltransferase; and, in women, C-reactive protein, lipoprotein(a), and glycated hemoglobin levels (Gunter MJ et al, *Ann Intern Med* 2017; 167:236-247).

### **SPRINT: Intensive Systolic Blood Pressure (SBP) Lowering Increased Risk for Incident Chronic Kidney Disease (CKD) Events, but this was Outweighed by Cardiovascular and All-Cause Mortality Benefits**

The difference in adjusted mean eGFR between the intensive and standard groups was  $-3.32$  mL/min/ $1.73$  m<sup>2</sup> at 6 months, was  $-4.50$  mL/min/ $1.73$  m<sup>2</sup> at 18 months, and remained relatively stable thereafter. An incident CKD event occurred in 3.7% of participants in the intensive group and 1% in the standard group at 3-year follow-up, with a hazard ratio of 3.54. The corresponding percentages for the composite of death or cardiovascular event were 4.9% and 7.1% at 3-year follow-up, with a hazard ratio of 0.71 (Beddhu S et al, *Ann Intern Med* 2017;167:375-383).

### **Cardiac Resynchronization Therapy (CRT) in the US: From 2003 to 2013, the Severity of Comorbid Conditions Increased and a Rising Trend was Observed in the Rate of Periprocedural Complications Among Patients Undergoing CRT**

From 2003 to 2013, 439,010 CRT implantations were performed in the U.S. (median age 72; 71% male). Overall, 6.1% had at least one complication. During the study period, comorbidity index and overall complication rate increased ( $P$  = 0.002 and  $P$  = 0.01, respectively). Mortality and length of stay showed no significant trend. Predictors of complications included: age  $\geq 65$ , female sex (OR: 1.19), Deyo-Charlson Comorbidity Index, and elective admission (OR: 0.61). (Hosseini S-M et al, *Eur Heart J* 2017;38: 2122-2128).

### **Optogenetics for Biological Management of Arrhythmias: Brief Local Epicardial Illumination of the Optogenetically Modified Adult Rat Heart Allowed Contact- and Shock-Free Termination of Ventricular Arrhythmias**

Optogenetics is a novel, biological technique allowing electrical modulation in a specific, reversible and trauma-

free manner using light-gated ion channels. Systemic delivery of cardiotropic adeno-associated virus vectors, encoding the light-gated depolarizing ion channel red-activatable channelrhodopsin (ReaChR), resulted in global cardiomyocyte-restricted transgene expression in adult Wistar rat hearts allowing ReaChR-mediated depolarization and pacing. Ventricular tachyarrhythmias (VTs) were induced in the optogenetically modified hearts by burst pacing in a Langendorff setup, followed by programmed, local epicardial illumination. A single 470-nm light pulse terminated 97% of monomorphic and 57% of polymorphic VTs vs 0% without illumination, as assessed by ECG recordings. Optical mapping showed significant prolongation of voltage signals just before arrhythmia termination. Pharmacological action potential duration (APD) shortening almost fully inhibited light-induced arrhythmia termination indicating an important role for APD in this process (Nyns ECA et al, *Eur Heart J* 2017;38:2132-2136).

### **EVITA: Vitamin D did not Reduce Mortality in Patients With Advanced Heart Failure (HF), While there was a Greater Need for Mechanical Support (MS)**

As 25-hydroxyvitamin D (25OHD) levels <75 nmol/L are associated with an increase in mortality risk, 400 HF patients with vitamin D deficiency were randomized to 4000 IU vitamin D daily or placebo for 3 years. Mortality was not different in patients receiving vitamin D (19.6%;  $n$  = 39) or placebo (17.9%;  $n$  = 36). The need for MS was however greater in patients assigned to vitamin D (15.4%,  $n$  = 28) vs. placebo (9%,  $n$  = 15; HR: 1.96;  $P$  = 0.031) (Zittermann A et al, *Eur Heart J* 2017;38:2279-86).

### **Extreme High High-Density Lipoprotein (HDL) Cholesterol is Paradoxically Associated With High Mortality in Men and Women / a New U-Shaped Curve /It All Comes down to HDL Functionality, not Quantity**

Among 52 268 men and 64 240 women during 745,452 person-years of follow-up, number of deaths from any cause were 5619 (mortality rate, 17.1/1000 person-years) in men and 5059 (mortality rate, 12.1/1000 person-years) in women. The association between HDL cholesterol concentrations and all-cause mortality was U-shaped for both men and women, with both extreme high and low concentrations being associated with high all-cause mortality risk. The concentration of HDL cholesterol associated with the lowest all-cause mortality was 73 mg/dL in men and 93 mg/dL in women. When compared with the groups with the lowest risk, the multi-factorially adjusted hazard ratios – HRs for all-cause mortality were 1.36 for men with HDL cholesterol of 97–115 mg/dL and 2.06 for men with HDL cholesterol



$\geq 116$  mg/dL. For women, corresponding HRs were 1.10 for HDL cholesterol of 116–134 mg/dL and 1.68 for HDL cholesterol  $\geq 135$  mg/dL (Madsen CM et al, *Eur Heart J* 2017;38:2478-86).

### **Individuals Who Work Long Hours ( $\geq 55$ per Week) are More Likely to Develop Atrial Fibrillation (AF) Than Those Working Standard Hours (35–40 h/Week)**

Among 85 494 working men and women (mean age 43.4 years) with no recorded AF, over 10 years, 1061 new cases of AF were identified (10-year cumulative incidence 12.4 per 1000). Individuals working long hours had a 1.4-fold increased risk of AF compared with those working standard hours (HR = 1.42,  $P = 0.003$ ). There was no significant heterogeneity between the cohort-specific effect estimates and the finding remained after excluding participants with coronary heart disease or stroke at baseline or during the follow-up ( $N = 2006$ , HR = 1.36,  $P = 0.0180$ ). Adjustment for potential confounding factors, such as obesity, risky alcohol use and high blood pressure, had little impact on this association (Kivimaki M et al, *Eur Heart J* 2017;38: 2621-28).

### **Bromocriptine Enhances LV Recovery and Reduces Morbidity/Mortality in Peripartum Cardiomyopathy (PPCM) Patients**

Among 63 PPCM patients with LVEF  $\leq 35\%$  assigned to short-term (1W: bromocriptine, 2.5 mg, 7 days) or long-term bromocriptine (8W: 5 mg for 2 weeks followed by 2.5 mg for 6 weeks) in addition to standard heart failure therapy, LVEF increased from  $28 \pm 10\%$  to  $49 \pm 12\%$  in the 1W-group, and from  $27 \pm 10\%$  to  $51 \pm 10\%$  in the 8W-group. Full-recovery (LVEF  $\geq 50\%$ ) was present in 52% of the 1W- and in 68% of the 8W-group with no differences in secondary end points between both groups. The risk within the 8W-group to fail full-recovery after 6 months tended to be lower. No patient in the study needed heart transplantation, LV assist device or died (Hilfiker-Kleiner D et al, *Eur Heart J* 2017;38: 2671-79).

### **SOURCE-3: A Low Complication Rate and Mortality at 1 Year with the Latest Generation Transcatheter Balloon-Expandable Valve**

The SAPIEN 3 was implanted in 1946 patients (mean age  $81.6 \pm 6.7$  years, 52% male). At 1 year, all-cause mortality was 12.6%, CV mortality 8%, stroke 3.1%, disabling stroke 1.4%, and rate of new pacemakers 13.2%. Causes of death were 62% CV and 38.0% non-CV, with heart failure (13.4%) and pulmonary complications (12.7%) being the main reasons for fatal outcomes. Multivariable analysis identified NYHA Class IV and renal insufficiency as predictors of mortality, while higher BMI's improved survival. Severe (zero) and moderate

paravalvular leakage (2.6%) was rare at 1 year (Wendler O et al, *Eur Heart J* 2017;38: 2717-26).

### **ADVANCE Study: Continued Valve Durability of the Self-Expanding Bioprosthesis at 5 Years With Low Rates of Reinterventions and Valve Dysfunction**

Among 1015 patients (mean age 81 years, mean logistic EuroSCORE  $19.3 \pm 12.3\%$ ), at 5 years, the rate of all-cause mortality was 50.7%, and major stroke 5.4%. Hemodynamic measures remained consistent with a mean gradient of  $8.8 \pm 4.4$  mmHg ( $n = 198$ ) and an effective orifice area of  $1.7 \pm 0.4$  cm<sup>2</sup> ( $n = 123$ ). Aortic regurgitation (AR) decreased over time and among paired patients dropped from 12.8% to 8% moderate AR at 5 years ( $n = 125$ ). Of the 860 patients with echocardiographic data or a reintervention after 30 days, there were 22 (2.6%) patients with valve dysfunction & 10 (1.2%) with a reintervention  $> 30$  days (Gerckens U et al, *Eur Heart J* 2017; 38;2729-38).

### **Important Review and Other Articles**

Vitamin D and CV disease (Al Mheid I et al, *J Am Coll Cardiol* 2017;70:89-100), Cardiovascular effects of cocaine (Havakuk O et al, *J Am Coll Cardiol* 2017;70:101-113), 2017 AHA/ACC Focused Update of the Guideline for the Management of Patients With Valvular Heart Disease (Nishimura RA et al, *J Am Coll Cardiol* 2017;70:252-289), Alcohol septal ablation for obstructive hypertrophic cardiomyopathy (*J Am Coll Cardiol* 2017;70:481-488 & 489-494), High-sensitivity cardiac troponin (Twerenbold R et al, *J Am Coll Cardiol* 2017;70:996-1012), Defibrillation of VF (Nichol G et al, *J Am Coll Cardiol* 2017;70:1496-1509), 2017 ACC/AHA/HFSA Guideline Update for the Management of Heart Failure (Yancy CW et al, *J Am Coll Cardiol* 2017; 70:776-803). Atrial cardiomyopathy (Guichard J-B & Nattel S, *J Am Coll Cardiol* 2017; 70:756-765), Modifiable risk factors for AF (Lau DH et al, *Circulation* 2017; 136: 583-596), Conduction disturbances after TAVI (Auffret V et al, *Circulation* 2017; 136: 1049-1069), Acute coronary syndromes (Crea F & Libby P, *Circulation* 2017;136: 1155-1166), Esophageal injury caused by ablation of AF (Kapur F et al, *Circulation* 2017;136: 1247-1255), Mechanical vs bioprosthetic aortic valves (Head SJ et al, *Eur Heart J* 2017;28:2183-91), ESC guidance for use of PCSK-9 inhibitors (Landmesser U et al, *Eur Heart J* 2017; 29:2245-55), Cardiac manifestations of sarcoidosis (Birnie DH et al, *Eur Heart J* 2017; 38:2663-70), 2017 ESC Guidelines for the management of valvular heart disease (Baumgartner H et al, *Eur Heart J* 2017;38:2739-91).