Cardiology News /Recent Literature Review / Third Quarter 2014

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HCS Annual Meeting: Athens, 23-25/10/2014

AHA: Chicago, 15-19/11/14

20th Annual Boston AF Symposium: Orlando, 8-10/1/15

HCS Working Groups Seminar: Ioannina, 2/2015

ACC: San Diego, 14-16/3/15

HRS: Boston, 13-16/5/15

EuroPCR: Paris, 19-22/5/15

Europace: Milan, 21-24/6/15

ESC: London, 29/8-2/9/15

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC): ICDs Save Lives & Antitachycardia Pacing (ATP) is Highly Successful Regardless of Heart Rate

Of 137 patients enrolled in a prospective North American ARVC registry, 108 received implantable cardioverter defibrillators (ICDs); 48 had 502 sustained episodes of ventricular arrhythmias (VAs) (489 monomorphic and 13 polymorphic). In the ICD patients, independent predictors of VAs in follow-up included spontaneous sustained VAs before ICD implantation and T-wave inversions inferiorly. The only independent predictor for life-threatening VAs, defined as sustained ventricular tachycardia (VT) ≥240 beats/min or ventricular fibrillation, was a younger age at enrollment. Anti-tachycardia pacing (ATP), independent of VT cycle length, was successful in terminating 92% of VT episodes. The authors concluded that in ARVC most VAs at follow-up are monomorphic. Risk factors for VAs were spontaneous VAs before enrollment and a younger age at ICD implantation. ATP is highly successful in terminating VT, and all ICDs should be programmed for ATP, even for rapid VT (Link M et al, ***J Am Coll Cardiol*** 2014;64:119-125).

PREVAIL: Left Atrial Appendage (LAA) Occlusion a Reasonable Alternative to Warfarin for Stroke Prevention in Non-Valvular Atrial Fibrillation?

In the PROTECT AF trial in patients with nonvalvular atrial fibrillation (NVAF), LAA occlusion with the Watchman device was noninferior to warfarin for stroke prevention, but procedural safety was questionable. The PREVAIL study further assessed efficacy and safety of this device in patients with NVAF who had a CHADS2 score ≥1-2. At 1½ years, the rate of first primary efficacy endpoint (composite of stroke, systemic embolism [SE], and cardiovascular/ unexplained death) was 0.064 in the device group (n=269) vs 0.063 in the control group (n=138) and did not achieve noninferiority criteria. The rate for the second primary efficacy endpoint (stroke or SE >7 days' post-randomization) was 0.0253 vs 0.0200 (risk difference 0.0053), achieving noninferiority. Early safety events occurred in 2.2% of the device arm (lower than in PROTECT AF). All adverse effects were lower in PREVAIL trial than in PROTECT AF (4.2% vs 8.7%; p = 0.004). Pericardial effusions requiring surgery decreased from 1.6% to 0.4% (p= 0.027), and those requiring peri-cardiocentesis decreased from 2.9% to 1.5% (p=NS). The authors concluded that LAA occlusion was noninferior to warfarin for ischemic stroke prevention or SE >7 days' post-procedure. Noninferiority was not achieved for overall efficacy but procedural safety improved (Holmes DR et al, ***J Am Coll Cardiol*** 2014;64:1-12).

SCAAR: New-Generation Drug Eluting Stents (DES) in STEMI Patients Undergoing PCI is Safe in Short- and Long-Term Follow-up, with a Lower Risk of Early/ Late Stent Thrombosis and a Low Risk of Very Late Stent Thrombosis, Similar to Bare Metal Stents (BMS)

In patients with acute ST-elevation myocardial infarction (STEMI), there is still some concern about the long-term safety of drug-eluting stents (DES). In the SCAAR registry, over 6 years (2007-2013), 34,147 patients with STEMI were treated by primary percutaneous coronary intervention (PCI) with new generation DES (n-DES) (n= 4,811), old-generation DES (o-DES) (n= 4,271), or bare metal stents (BMS) (n= 25,065). There was a significantly lower risk of early/late stent thrombosis (ST) in patients treated with n-DES (hazard ratio -HR: 0.65; p= 0.04) and o-DES (HR: 0.60; p= 0.01) compared with the BMS group. The risk of very late ST was similar between the n-DES and BMS groups (HR: 1.52; p=NS), whereas a higher risk of very late ST was observed with o-DES compared with BMS (HR: 2.88; p< 0.01). The authors concluded that patients treated with n-DES have a lower risk of early/late ST than patients treated with BMS. The risk of very late ST is low with n-DES and BMS up to 3 years, but o-DES are associated with an increased risk of very late ST (Sarno G et al, ***J Am Coll Cardiol*** 2014;64:16–24).

Alcohol Consumption, Even at Moderate Intakes, is a Risk Factor for Atrial Fibrillation (AF)

The association between alcohol consumption and AF risk was investigated by following 79,019 men and women who, at baseline, were free from AF. At follow-up (1998 to 2009), 7,245 incident AF cases were identified. The association between alcohol consumption and AF did not differ by gender. Compared with drinkers of <1 drink/ week (12 g alcohol/ drink), the multivariable relative risks

(RRs) of AF were 1.01 for 1-6 drinks/week, 1.07 for 7-14 drinks/week, 1.14 for 15-21 drinks/week, and 1.39 for >21 drinks/week. Results did not change after excluding binge drinkers. In meta-analysis of 7 prospective studies, among 12,554 AF cases, RRs were 1.08 for 1 drink/day, 1.17 for 2 drinks/day, 1.26 for 3 drinks/day, 1.36 for 4 drinks/day, and 1.47 for 5 drinks/ day, compared with nondrinkers. Thus, alcohol, even at moderate intakes, is a risk factor for AF (Larsson et al, ***J Am Coll Cardiol*** 2014;64:281-289).

TREAT-AF: In Patients With Recently Identified AF, Digoxin is Associated With Increased Risk of Death

According to data of the TREAT-AF study, among 122,465 male patients (aged 72±10 years) with newly diagnosed, nonvalvular atrial fibrillation (AF), 28,679 (23.4%) received digoxin. Mortality rates were higher for those who received digoxin vs those who did not (95 vs 67 per 1,000 person-years; p< 0.001). Digoxin use was independently associated with mortality (hazard ratio -HR: 1.26, p< 0.001). The risk of death was not modified by age, gender, heart failure, kidney function, or concomitant beta-blocker, amiodarone, or warfarin use. The authors concluded that digoxin was associated with increased risk of death in patients with newly diagnosed AF, independent of drug adherence, kidney function, cardiovascular comorbidities, and concomitant therapies. These findings challenge current recommendations on use of digoxin in AF (Turakhia MP et al, ***J Am Coll Cardiol*** 2014;64:660-668).

Blood Transfusions Conferring Higher In-Hospital Mortality in Acute Myocardial Infarction (AMI) Patients May Merely Reflect a Higher Risk Profile

Among 34,937 AMI hospitalizations, a total of 1,778 patients (5.1%) had at least 1 blood transfusion. In unadjusted analyses, transfusion conferred higher in-hospital mortality (odds ratio: 2.05). The majority of patients (91.1%) with and without transfusion had non-overlapping propensity scores, reflecting incomparable clinical profiles. After propensity matching those with overlapping scores, blood transfusion was associated with a reduced risk of in-hospital death (odds ratio: 0.73). The authors concluded that the majority of AMI patients receiving blood transfusion cannot be matched with non-transfused patients due to their different clinical profiles. Among comparable patients, blood transfusion was associated with a lower risk of in-hospital mortality (Salisbury AC et al, ***J Am Coll Cardiol*** 2014;64:811-819).

European Experience: Percutaneous Transcatheter Mitral Valve repair (TMVR) Efficacious in Reducing Severity of Primary Mitral Regurgitation (MR) With a Relatively Low Complication Rate

A total of 628 patients (aged 74 ± 10 years, 63% men) with mainly (72%) functional mitral regurgitation (FMR) (NYHA class ≥III; logistic EuroScore 20±17) underwent TMVR between 1/2011 and 12/2012 in 25 centers in 8 European countries. Acute success was high (95.4%) with one clip implanted in 61.4% of patients. In-hospital mortality was low (2.9%). The estimated 1-year mortality was 15.3%, which was similar for FMR and degenerative MR. The estimated 1-year rate of rehospitalization because of heart failure was 22.8%, significantly higher in the FMR group (25.8% vs 12.0%, p= 0.009). Paired echocardiographic data (n=368) showed a persistent reduction in the degree of MR at 1 year (6% of patients with severe MR). The authors concluded that TMVR is associated with high immediate success, low complication rates, and sustained 1-year reduction of the severity of MR and improvement of clinical symptoms (Nickenig G et al, ***J Am Coll Cardiol*** 2014;64:875-884).

MADIT-CRT: A Percentage as Low as ≥0.1% of Ectopic Beats Leads to <97% Biventricular Paced Beats and Higher Risk of Non-Response to CRT

From the MADIT-CRT, 801 patients with an implanted CRT-defibrillator device had data available on biventricular pacing percentage and pre-implantation 24-h Holter recordings. Ectopic beats accounted for a mean 3.2 ± 5.5% of all beats. The probability of subsequent low biventricular pacing percentage (<97%) was increased 3-fold (odds ratio: 3.37; p < 0.001) in patients with 0.1% - 1.5% ectopic beats and 13-fold (odds ratio: 13.42; p < 0.001) in patients with >1.5% ectopic beats compared with those with <0.1% ectopic beats. Patients with ≥0.1% ectopic beats had significantly less reverse remodeling (p < 0.001). The risk of heart failure/death and ventricular tachyarrhythmias was increased significantly in those with 0.1% - 1.5% ectopic beats (hazard ratio: 3.13 and 1.84, respectively) and for >1.5% ectopic beats (hazard ratio: 2.38 and 2.74, respectively). The authors concluded that a small percentage of ectopic beats (≥0.1%) dramatically increases the probability of low biventricular pacing (<97%), with reduced CRT efficacy (Ruwald MH et al, ***J Am Coll Cardiol*** 2014;64:971-981).

Nadolol Appears to be the Preferred β-Blocker in the General Management of Patients With Long QT Syndrome (LQTS)

Among 1,530 LQTS patients receiving β-blockers, relative to being off β-blockers, the hazard ratio for first cardiac events was 0.71 for atenolol, 0.70 for metoprolol, 0.65 for propranolol, and 0.51 for nadolol. In LQT1, the risk reduction for first cardiac events was similar among the 4 β-blockers, but in LQT2, nadolol provided the only significant risk reduction (hazard ratio: 0.40). Among patients who had a prior cardiac event while taking β-blockers, efficacy for recurrent events differed by drug (p

= 0.004), and propranolol was the least effective. The authors concluded that although the 4 β-blockers are equally effective in reducing the risk of a first cardiac event in LQTS, their efficacy differed by genotype; nadolol was the only β-blocker associated with a significant risk reduction in patients with LQT2. Patients experiencing cardiac events while on β-blocker therapy are at high risk for subsequent cardiac events, and propranolol is the least effective drug in this high-risk group (Abu-Zeitone A et al, ***J Am Coll Cardiol*** 2014;64:1352-1358).

ADVANCE III Trial: Programming a Long Detection Window Setting in ICDs Leads to a Reduction of Electrical Therapies and Shocks Even in the Subgroup of Secondary Prevention Patients

Of the 1902 patients enrolled in the ADVANCE III trial, 477 received a defibrillator (ICD) for secondary prevention; 248 patients were randomly assigned to a long detection setting (30/40 intervals) and 229 to the nominal setting (18/24 intervals) for ventricular arrhythmias with cycle length ≤320 ms (188 bpm). Over a median period of 12 months, the long detection period conferred a 25% reduction in the number of overall therapies and a 34% reduction in the number of ICD shocks. Appropriate therapies and appropriate shocks were also reduced. The authors concluded that a long detection window setting in ICDs leads to a reduction of electrical therapies in both primary and secondary prevention populations (Kloppe A et al, ***Circulation*** 2014;130:308-314).

Bilateral Internal Mammary Artery Grafts Improve Long-Term Survival

In a meta-analytic approach (9 observational studies, 15,583 patients), long-term (10-year) survival was compared between bilateral (BIMA, n=7313) and single internal mammary artery (SIMA, n=8270) grafting. Use of BIMA conferred a significant reduction in mortality (hazard ratio, 0.79). The authors concluded that BIMA grafting appears to have better survival with up to 10 years follow-up in comparison with SIMA grafting (Yi G et al, ***Circulation*** 2014;130:539-545).

Registry Study of 2169 Patients Indicates that Catheter Ablation Improves Long-term Outcome in Wolff-Parkinson-White (WPW) Syndrome

Among 2169 patients with WPW syndrome, 1168 (206 asymptomatic) underwent ablation (RFA group) and 1001 (550 asymptomatic) did not (no-RFA group). Over 8 years, in the no-RFA group, VF occurred in 1.5% of patients, mostly (13 of 15) in children (median age, 11 years), and was associated with a short accessory pathway antegrade refractory period (P<0.001) and atrioventricular reentrant tachycardia degenerating into atrial fibrillation (P<0.001) but not with symptoms. In the RFA group, ablation was successful in 98.5%, and after RFA, no patients developed malignant arrhythmias or VF. An anterograde effective refractory period of the accessory pathway of <240 ms predicted VF. The authors concluded that the prognosis of the WPW syndrome depends on electrophysiological properties of AP rather than on symptoms, and RFA improves the long-term outcomes (Pappone C et al, ***Circulation*** 2014;130:811-819).

Hybrid Coronary Revascularization is Performed in 1/3 of US Hospitals and May be a Safe Alternative for CABG

Hybrid (combined surgical and percutaneous) coronary revascularization (HCR) represented 0.48% (n=950; staged=809, concurrent=141) of the total CABG volume (n=198 622) during the period from July 2011 to March 2013, and was performed in 1/3 of hospitals (n=361) in the US. Patients who underwent HCR had higher cardiovascular risk profiles. In comparison with CABG, median sternotomy direct vision harvesting and cardiopulmonary bypass were less frequently used for staged and concurrent HCR, whereas robotic assistance was more common. No differences were observed for in-hospital mortality and major morbidity. There was no significant association between operative mortality and either treatment group. HCR, either as a staged or concurrent procedure, is performed in 1/3 of US hospitals, and may be an equally safe alternative for CABG (Harskamp RE et al, ***Circulation*** 2014;130:872-879).

Rate and Predictors if ICD Infection in a Large Cohort of Medicare Patients: Avoid Re-Intervention Except for Battery Replacement

Between 2006 and 2009 of 200,909 ICD implants, 3390 patients (1.7%) developed a device infection. Infection rate was 1.4%, 1.5%, and 2.0% for single, dual, and biventricular ICDs, respectively (P<0.001). Pulse generator replacement had a higher rate compared with initial implant (1.9% vs 1.6%, P<0.001). The factors associated with infection were adverse re-intervention (odds ratio -OR, 2.7), prior valve surgery (OR, 1.5), re-implantation for device upgrade, malfunction, or manufacturer advisory (OR, 1.35), renal failure on dialysis (OR, 1.34), chronic lung disease (OR, 1.21), cerebrovascular disease (OR, 1.17), and warfarin (OR, 1.15). The authors concluded that patients who developed an ICD infection were more likely to have had peri-ICD implant complications requiring early re-intervention, previous valve surgery, device replacement for reasons other than battery depletion, and increased comorbidity burden. Their advice is to avoid reentering the pocket at any time other than battery change (Prutkin JM et al, ***Circulation*** 2014;130:1037-1043).

STREAM 1-Year Follow-Up: A Dose-Adjusted Pharmaco-invasive Strategy is as Good as Primary PCI When Timely Primary PCI is Unattainable in STEMI

In the STREAM trial, a pharmaco-invasive (PI) strategy was compared with primary percutaneous coronary intervention (pPCI) in STEMI patients presenting within 3 hours after symptom onset but unable to undergo pPCI within 1 hour. The PI approach included tenecteplase coupled with antiplatelet and anticoagulant therapy followed by coronary angiography within 6 - 24 hours. From 2009 onward the dose of tenecteplase was reduced by 50% in patients aged ≥75 years to reduce intracranial bleed. For failed thrombolysis, rescue PCI was performed. At 30 days, the PI approach was associated with nonstatistically lower incidence of the composite primary end point of death, shock, congestive heart failure, and reinfarction when compared with pPCI. At 1 year, all-cause mortality (6.7% vs 5.9%) and cardiac mortality rates (4.0% vs 4.1%) were similar for PI and pPCI-treated patients. Overall, only 34 patients died between day 30 and 1 year, 20 in the PI arm and 14 in the pPCI arm, of whom 20 died of noncardiac reasons (13 in the PI and 7 in the pPCI arm). The authors concluded that at 1 year, mortality rates in the PI and pPCI arms were similar in STEMI patients presenting within 3 hours after symptom onset and unable to undergo pPCI within 1 hour (Sinnaeve PR et al, ***Circulation*** 2014;130:1139-1145.)

EFFORTLESS S-ICD Registry: Appropriate Performance for the Subcutaneous ICD With Event Rates and Inappropriate Shock Rates Comparable With Those of Conventional ICDs

The totally subcutaneous implantable-defibrillator (S-ICD) is a new alternative to the conventional transvenous ICD system to minimize intravascular lead complications. The EFFORTLESS S-ICD Registry included 472 patients (72% male, aged 49±18 years; mean left ventricular ejection fraction 42%). Complication-free rates were 97% at 1 month and 94% at 1 year. There were recorded 317 spontaneous episodes in 85 patients during the 1.5-year mean follow-up period; of these, 169 (53%) received therapy, 93 being for ventricular tachycardia/fibrillation (VT/VF). One patient died of recurrent VF and severe bradycardia. First shock conversion efficacy was 88% with 100% successful clinical conversion after a maximum of 5 shocks. The 1-year inappropriate shock rate was 7% with the majority occurring for oversensing (62/73 episodes), primarily (94%) of cardiac signals. The authors concluded that the S-ICD has appropriate performance with clinical event rates and inappropriate shock rates comparable with those reported for conventional ICDs (Lambiase PD et al, ***Eur Heart J*** 2014; 35:1657–1665).

Dresden NOAC Registry: Peri-Interventional Short-Term Interruption of Novel Anticoagulants (NOACs) is Safe / Bleeding Complications are Related to Major Procedures or to Peri-Procedural Heparin Bridging

Of 2179 patients receiving NOACs, 595 (27.3%) underwent 863 interventional procedures (15.6% minimal, 74.3% minor, and 10.1% major procedures). Until 1 month post-procedure, major cardiovascular events occurred in 1% and major bleeding complications in 1.2%. Cardiovascular (4.6%) and major bleeding complications (8%) were highest after major procedures. Heparin bridging did not reduce cardiovascular events, but led to higher rates of major bleeding (2.7% vs 0.5% with no bridging). Diabetes (odds ratio -OR 13.2) and major procedures (OR 7.3) were independent risk factors for cardiovascular events. Major procedures (OR 16.8) were an independent risk factor for major bleeding. The authors concluded that continuation or short-term interruption of NOAC is safe for most invasive procedures. Patients undergoing major procedures may benefit from heparin bridging, but at the expense of bleeding risk (Beyer-Westendorf J et al, ***Eur Heart J*** 2014; 35:1888–1896).

CENTURY II Trial: The New Sirolimus-Eluting Co-Cr Stent With Bioresorbable Polymer (Ultimaster BP-SES) is Safe and Effective as Everolimus-Eluting Co-Cr Stent With Permanent Polymer (Xience PP-EES)

The new sirolimus-eluting stent with bioresorbable polymer, Ultimaster (BP-SES), was compared with everolimus-eluting, permanent polymer, Xience stent (PP-EES) in 1123 patients undergoing percutaneous coronary intervention (PCI). The primary endpoint, freedom from target lesion failure (TLF) at 9 months (cardiac death, target-vessel-related myocardial infarction and target lesion revascularization) was 95.6% with BP-SES and 95.1% with PP-EES. Composite of cardiac death and MI rate was 2.9 and 3.8% (*P* = NS) and target vessel revascularization was 4.5% with BP-SES and 4.2% with PP-EES (*P* = NS). The stent thrombosis rate was 0.9% in both arms. The authors concluded that the new bioresorbable polymer sirolimus-eluting stent had similar safety and efficacy to durable polymer everolimus-eluting stent over 9 months (Saiot S et al, ***Eur Heart J*** 2014; 35:2021–2031).

Favorable Long-Term Survival After Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy

A total of 178 highly symptomatic (87% with dyspnea ≥3 class NYHA) patients with hypertrophic obstructive cardiomyopathy (HOCM) (58 ± 12 years, 53% women) were treated by alcohol septal ablation (ASA) (1998-2013). At the most recent examination, 87 patients (49%)

had dyspnea NYHA class I and 23 patients (13%) reported dyspnea of NYHA class ≥3. The left ventricular outflow gradient was significantly reduced (68 ± 42 vs. 20 ± 25 mmHg; $P < 0.01$). A total of 19 deaths (11%) occurred over 4.8 years (2.1% per year). Survival free of all-cause mortality at 1, 5, and 10 years was 97%, 92%, and 82%, respectively, which was comparable to the expected survival for age- and sex-comparable general population. The only independent predictor of all-cause mortality was age at ASA (hazard ratio 1.09; $P < 0.01$). The authors concluded that in symptomatic patients with HOCM undergoing ASA, long-term survival did not differ from that of the general population (Veselka J et al, ***Eur Heart J*** 2014;35: 2040-2045).

PROFICIO: Large and Rapid Reductions Achievable in Apo B and Its Related Lipoproteins, LDL-C, VLDL-C, and Non-HDL-C With Evolocumab

A pooled analysis of 1359 patients from 4 phase-2 studies of evolocumab, a monoclonal antibody to PCSK9, showed mean percentage reductions in LDL-C vs placebo ranging from 40.2% to 59.3% among the evolocumab groups (all P < 0.001). Significant reductions in apo-lipoprotein B (Apo B), non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides and lipoprotein (a) - Lp(a), and increases in HDL-C were also observed. Adverse events (AEs) and serious AEs with evolocumab were reported in 56.8 and 2.0% of patients, compared with 49.2% and 1.2% with placebo. Cardiac and cerebrovascular events were reported in 0.3 and 0% in the placebo and 0.9 and 0.3% in the evolocumab arms, respectively. The authors concluded that in addition to LDL-C reduction, evolocumab, dosed either every 2 weeks or every 4 weeks, demonstrated significant and favourable changes in other atherogenic and anti-atherogenic lipoproteins, and was well tolerated over the 12-week treatment period (Stein EA et al, ***Eur Heart J*** 2014; 35: 2249–2259).

REMINDER Study: Compared With Placebo, Addition of Eplerenone to Standard Therapy Within 24 h of Symptom Onset is Safe and Reduces BNP Levels of Patients Presenting With STEMI Without Known HF or LVEF<40%

A total of 1012 patients with STEMI and without a history of heart failure (HF) were assigned to receive either eplerenone (25–50 mg qd) or placebo in addition to standard therapy. The primary endpoint was the composite of CV mortality, re-hospitalization, or, extended initial hospital stay, due to diagnosis of HF, sustained ventricular tachycardia or fibrillation, ejection fraction ≤40%, or elevated BNP (>200 pg/mL)/ NT-proBNP (>450 pg/mL, age <50; >900 pg/mL, age 50-75; >1800 pg/mL age >75 years) at 1 month or more after randomization. Over a mean of 10.5 months, the primary endpoint occurred in 92 patients (18.2%) in the eplerenone group and in 149 patients (29.4%) in the placebo group (hazard ratio - HR, 0.58; P < 0.0001]. Adverse event rates were similar in both groups. Serum potassium levels exceeded 5.5 mmol/L in 5.6 vs 3.2% (P = 0.09) and were below 3.5 mmol/L in 1.4 vs 5.6% of patients (P = 0.0002), in the eplerenone and placebo groups, respectively. The authors concluded that adding eplerenone during the acute phase of STEMI is safe and well tolerated. It reduced the primary endpoint over a mean 13 months follow-up mostly because of significantly lower BNP/NT-proBNP levels (Montalescot G et al, ***Eur Heart J*** 2014; 35: 2295–2302).

PURE Studies: A Questionable Method of Estimated Sodium Excretion (from a Morning Urine Sample), Used as a Surrogate for Sodium Intake, Showed a Nonlinear Association of Sodium With Blood Pressure, Most Pronounced Among Persons Consuming High-Sodium Diets, Hypertensive and Older Persons / The Lowest Risk of Death and Cardiovascular Events was Seen at Sodium Excretion of 3-6 g/d. Both Higher and Lower Levels of Sodium Excretion Were Associated With Increased Risk (a J-Shaped Association Curve)

A total of 102,216 adults from 18 countries were studied. Estimates of 24-hour sodium and potassium excretion were made from a single fasting morning urine specimen and were used as surrogates for intake. Analysis showed increments of 2.11 mm Hg in systolic blood pressure and 0.78 mm Hg in diastolic blood pressure for each 1-g increment in estimated sodium excretion. The slope of this association was steeper with higher sodium intake and for hypertensive or older persons. Potassium excretion was inversely associated with systolic blood pressure. The authors concluded that the association of estimated intake of sodium and potassium with blood pressure was nonlinear and was most pronounced in persons consuming high-sodium diets, and hypertensive and older persons (Mente A et al, ***N Engl J Med*** 2014; 371:601-611).

In the second part of the study, over a mean follow-up of 3.7 years, the composite outcome of deaths and major cardiovascular events occurred in 3317 participants (3.3%). As compared with an estimated sodium excretion of 4-6 g/d, a higher estimated sodium excretion (≥7 g/d) was associated with an increased risk of the composite outcome (odds ratio, 1.15), with strongest association among hypertensive participants with an increased risk at an estimated sodium excretion of ≥6 g/d. An estimated sodium excretion <3 g/d was also associated with an increased risk of the composite outcome (odds ratio, 1.27).

Higher potassium excretion was associated with a reduced risk of the composite outcome. The authors concluded that sodium intake estimated on the basis of measured urinary excretion, between 3-6 g/d was associated with a lower risk of death and cardiovascular events than was either a higher or lower level of intake. Higher potassium excretion was associated with a lower risk of death and cardiovascular events (O'Donnell M et al, ***N Engl J Med*** 2014; 371:612-623). (The main critique to both these studies relates to the estimated sodium intake based on a morning fasting midstream urine sample rather than on 24-hour urine collection).

NUTRICODE Study: in 2010, a Total of 1.65 Million Cardiovascular Deaths Were Attributable to Sodium Consumption of >2 g/d (or Salt > 5 g/d)

Data from surveys on sodium intake, as determined by urinary excretion and diet in persons from 66 countries, were used to quantify the global consumption of sodium according to age, gender, and country. The effects of sodium on blood pressure were calculated from data in a meta-analysis of 107 randomized interventions, and the effects of blood pressure on cardiovascular mortality, according to age, were calculated from a meta-analysis of cohorts. In 2010, the estimated mean level of global sodium consumption was 3.95 g/d. Globally, 1.65 million annual deaths from cardiovascular causes were attributed to sodium intake above the reference level of >2 g/d (62% in men and 38% in women). These deaths accounted for nearly 1 of every 10 deaths from cardiovascular causes (9.5%). Four of every 5 deaths (84.3%) occurred in low- and middle-income countries, and 2 of every 5 deaths (40.4%) were premature (< age of 70 years), with highest death rate in the country of Georgia and lowest in Kenya. The authors concluded that 1.65 million deaths from cardiovascular causes that occurred in 2010 were attributed to sodium consumption above a reference level of 2.0 g/d (> 5 g of salt per day) (Mozaffarian D et al, ***N Engl J Med*** 2014; 371:624-634).

PARADIGM-HF: Angiotensin Receptor–Neprilysin Inhibition With Valsartan/Sucabitril (LCZ696) is Superior to ACE Inhibition Alone in Reducing Risks of Death and Hospitalization for Heart Failure / Strong Evidence that Combined Inhibition of the Angiotensin Receptor and Neprilysin is Superior to Inhibition of the Renin–Angiotensin System Alone in Patients With Chronic Heart Failure

A total of 8442 patients with class II-IV heart failure and an ejection fraction of ≤40% were randomly assigned to receive either valsartan/sucabitril (LCZ696) (200 mg bid) or enalapril (10 mg bid), in addition to recommended therapy. The trial was stopped early at a median follow-up of 27 months. The primary outcome (composite of death from cardiovascular causes or hospitalization for heart failure) had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio-HR 0.80; P<0.001); mortality was 17% vs 19.8% (HR, 0.84; P<0.001), and cardiovascular mortality 13.3% vs 16.5% (HR, 0.80; P<0.001), respectively. The new drug decreased the risk of hospitalization for heart failure by 21% (P<0.001). The new drug caused higher rates of hypotension and nonserious angioedema but lower rates of renal impairment, hyperkalemia, and cough than enalapril. The authors concluded that LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure (McMurray JJV et al, ***N Engl J Med*** 2014; 371:993-1004).

ATLANTIC study: Prehospital Ticagrelor in STEMI is not Necessary

A total of 1862 patients with STEMI of <6 hours' duration received ticagrelor as prehospital (in the ambulance) or in-hospital (in the catheterization laboratory) treatment (median time from randomization to angiography: 48 min; median time difference between the two treatment strategies: 31 min). The two coprimary end points (proportion of patients who did not have a ≥70% resolution of ST elevation before PCI and those who did not have TIMI flow grade 3 in the infarct-related artery at initial angiography) did not differ between the 2 groups. The absence of ST-elevation resolution of ≥70% after PCI (secondary end point) was reported for 42.5% and 47.5% of patients, respectively. Rates of major adverse cardiovascular events did not differ between the 2 groups. Rates of definite stent thrombosis were lower in the prehospital group (0% vs 0.8% in the first 24 hours; 0.2% vs 1.2% at 30 days). Rates of major bleeding were low and similar in the 2 groups. The authors concluded that prehospital administration of ticagrelor in patients with STEMI was safe but did not improve pre-PCI coronary reperfusion (Montalescot G et al, ***N Engl J Med*** 2014; 371:1016-1027).

SIGNIFY: No Benefit of Ivabradine in Patients With Stable Coronary Artery Disease Without Clinical Heart Failure

A total of 19,102 patients with stable coronary artery disease (CAD) and heart rate ≥70 bpm without heart failure were randomized to ivabradine (10 mg bid) to achieve a heart rate of 55 - 60 bpm. At 3 months, heart rate was 60.7±9 bpm in the ivabradine group vs 70.6±10.1 bpm in the placebo group. After a median follow-up of 27.8 months, there was no significant difference between the 2 groups in the primary end point (composite of death from

cardiovascular causes or nonfatal myocardial infarction) (6.8% and 6.4%, respectively; hazard ratio, 1.08; P=NS). The incidence of bradycardia was higher with ivabradine (18% vs 2.3%, P<0.001). The authors concluded that in patients with stable CAD without clinical heart failure, the addition of ivabradine to standard therapy to reduce the heart rate did not improve outcomes (Fox K et al, ***N Engl J Med*** 2014; 371:1091-1099).

TASTE at 1 Year: No Benefit of Thrombus Aspiration for Myocardial Infarction (MI)

A total of 7244 patients with STEMI were randomly assigned to undergo manual thrombus aspiration followed by PCI or PCI alone, in a registry-based, randomized clinical trial. Mortality at 1 year was 5.3% in the thrombus-aspiration group vs 5.6% in the PCI-only group (hazard ratio-HR, 0.94; P=NS). Re-hospitalization for MI at 1 year occurred in 2.7% and 2.7% of the patients (HR, 0.97; P=NS), and stent thrombosis in 0.7% and 0.9%, respectively (HR, 0.84; P=NS). The composite of death from any cause, rehospitalization for MI, or stent thrombosis occurred in 8.0% and 8.5% of patients, respectively (HR, 0.94; P=NS). The authors concluded that routine thrombus aspiration before PCI in patients with STEMI did not reduce the rate of death from any cause or the composite of death from any cause, rehospitalization for myocardial infarction, or stent thrombosis at 1 year (Lagerqvist B et al, ***N Engl J Med*** 2014; 371:1111-1120).

FAME 2: Favorable Results From Fractional Flow Reserve–Guided PCI in Stable Coronary Disease

In 1220 patients with stable coronary artery disease, fractional flow reserve (FFR) was assessed in all coronary stenoses. Patients with ≥1 stenosis with an FFR of ≤0.80 were randomly assigned to undergo FFR-guided PCI plus medical therapy or to receive medical therapy alone. Patient with all stenoses having FFR >0.80 received medical therapy alone (included in a registry). The primary end point (composite of death from any cause, nonfatal MI, or urgent revascularization within 2 years) was significantly lower in the PCI group (8.1% vs 19.5%; hazard ratio-HR, 0.39; P<0.001), driven by a lower rate of urgent revascularization (4.0% vs 16.3%; HR, 0.23; P<0.001); there were no between-group differences in rates of death and MI. Urgent revascularizations were less frequent in the PCI group (3.4% vs 7.0%, P=0.01). Rate of death or MI from 8 days to 2 years was lower in the PCI group (4.6% vs 8.0%, P=0.04). In the registry patients, the rate of the primary end point was 9.0% at 2 years. The authors concluded that in patients with stable coronary artery disease, FFR-guided PCI improved the outcome. Patients without ischemia (normal FFR) had a favorable outcome with medical therapy alone (De Bruyne B et al, ***N Engl J Med*** 2014; 371:1208-1217).

ARIC: an Elevated (≥140 mmHg) Systolic BP Carries the Highest Risk for Cardiovascular Events / BP <120 Confers no Additional Benefit Compared With BP<140

Among 4480 individuals with hypertension (HTN) but without prevalent cardiovascular (CV) disease at baseline, a total of 1622 incident CV events (heart failure, ischemic stroke, myocardial infarction, or death related to coronary heart disease) occurred over a median follow-up of ~22 years. Elevated (≥140 mmHg) systolic blood pressure (SBP) conferred significantly more CV events than low BP (<120 mmHg) (hazard ratio -HR, 1.46), with no difference noted in the standard (120-140 mmHg) vs low SBP group (HR, 1.00). No effect related to BP medication use or diastolic BP was observed. The authors concluded that among patients with HTN, an elevated SBP carries the highest risk for CV events, but once SBP was <140 mmHg, an SBP <120 mmHg did not appear to lessen the risk (Rodriguez CJ, ***JAMA Intern Med*** 2014;174:1252-1261).

83% 1-Year Survival after Transcatheter Valve-in-Valve Implantation

A multinational registry included 459 patients with degenerated bioprosthetic valves undergoing valve-in-valve implantation (2007 – 2013) with both balloon- and self-expandable valves. Within 1 month, 35 (7.6%) patients died, 8 (1.7%) had major stroke, and 313 (92.6%) of surviving patients had good functional status (New York Heart Association class I/II). Overall 1-year survival rate was 83.2% (62 death events; 228 survivors). Patients in the stenosis group had worse survival (76.6%) in comparison with the regurgitation (91.2%) and the combined group (83.9%) ($P = 0.01$). Patients with small valves had worse 1-year survival (74.8%) vs with intermediate-sized valves (81.8%) and with large valves (93.3%) ($P = .001$). Factors associated with 1-year mortality included small surgical bioprosthesis (≤21 mm; hazard ratio, 2.04; $P = .02$) and baseline stenosis (vs regurgitation; hazard ratio, 3.07; $P = .008$). The authors concluded that in this registry of patients who underwent transcatheter valve-in-valve implantation for degenerated bioprosthetic aortic valves, overall 1-year survival was 83%. Survival was lower among patients with small bioprostheses and those with predominant surgical valve stenosis **(**Dvir D et al, ***JAMA*** 2014;312:162-170).

Perioperative Atrial Fibrillation (AF) Confers High Long-term Risk of Ischemic Stroke

In a retrospective study (2007-2011) of 1,729,360 patients hospitalized for surgery, 24,711 (1.43%) had new-onset perioperative AF and 13,952 (0.81%) had a stroke

after discharge. At 1 year after *cardiac* surgery, stroke rate was 0.99% in those with perioperative AF and 0.83% in those without AF. At 1 year after *noncardiac* surgery, stroke rate was 1.47% in those with perioperative AF and 0.36% in those without AF. Perioperative AF was associated with subsequent stroke both after cardiac (hazard ratio-HR, 1.3) and noncardiac surgery (HR, 2.0). The authors concluded that among patients having surgery, perioperative AF conferred an increased long-term risk of ischemic stroke, especially after noncardiac surgery (Gialdini G et al, ***JAMA*** 2014;312:616-622).

SOLID-TIMI 52: No Benefit of Darapladib on Major Coronary Events After an Acute Coronary Syndrome

A total of 13 026 patients were randomized (2009-2013) within 30 days of an acute coronary syndrome (ACS) to either once-daily darapladib (160 mg) (an oral, selective inhibitor of lipoprotein-associated phospholipase A_2 - Lp-PLA_2) or placebo. During a median of 2.5 years, major coronary events occurred in 903 patients in the darapladib group and 910 in the placebo group (16.3% vs 15.6% at 3 years; hazard ratio - HR, 1.00; *P* = NS). There was no difference between the treatment groups in all-cause mortality (7.3% vs 7.1% at 3 years; HR, 0.94; *P* = NS). Darapladib caused more diarrhea and an odor-related concern. The authors concluded that in patients with ACS, direct inhibition of Lp-PLA_2 with darapladib added to optimal medical therapy and initiated within 30 days of hospitalization did not reduce the risk of major coronary events (O'Donoghue ML et al, ***JAMA*** 2014;312:1006-1015).

Meta-Analysis: Bivalirudin Increases MACE Compared With Heparin in Patients Planned for Percutaneous Coronary Intervention (PCI)

Data from 16 trials involving 33,958 patients indicated an increase in the risk of major adverse cardiac events (MACE) with bivalirudin-based regimens compared with heparin-based regimens (risk ratio-RR 1.09; p=0·0204), largely driven by increases in myocardial infarction (MI) (RR 1.12) and ischemia-driven revascularisation (RR 1.16), with no effect on mortality (RR 0.99). Bivalirudin increased the risk of stent thrombosis (RR 1.38; p=0.0074), primarily due to an increase in acute cases of MI (RR 4.27; p<0·0001). Overall, bivalirudin-based regimens lowered the risk of major bleeding (RR 0.62; p<0·0001), but the magnitude of this effect varied (p<0·0001) depending on whether glycoprotein IIb/IIIa inhibitors were used. The authors concluded that compared with a heparin-based regimen, a bivalirudin-based regimen increases the risk of MI and stent thrombosis, but decreases the risk of bleeding (Cavender MA & Sabatine MS, ***Lancet*** 2014; 384 (9943): 599 – 606).

Important Review and Other Articles

Renal denervation for treatment of cardiac arrhythmias (Kosiuk J et al, *J Cardiovasc Electrophysiol* 2014 Sep 18. doi: 10.1111/jce.12553. [Epub ahead of print], 2014 AHA/ ACC Guideline for the management of patients with NSTE ACS (Amsterdam EA et al, *J Am Coll Cardiol* 2014; doi: 10.1016/j.jacc.2014.09.017), The MOGE(S) classification of cardiomyopathy (*J Am Coll Cardiol* 2014;64:304-318), Hypertrophic cardiomyopathy (Baron et al, *J Am Coll Cardiol* 2014;64:83-99), Aspirin in primary cardiovascular disease prevention (Halvorsen S et al, *J Am Coll Cardiol* 2014;64:319-327), Rhythm control in heart failure patients with AF (Trulock KM et al, *J Am Coll Cardiol* 2014;64:710-721), Carotid artery stenting (White CJ, *J Am Coll Cardiol* 2014;64:722-731), AF ablation (Nishida K et al, *J Am Coll Cardiol* 2014;64:823-831), Fibromuscular dysplasia involving coronary arteries (Michelis KC et al, *J Am Coll Cardiol* 2014;64:1033-1046), CRT (Leyva F et al, *J Am Coll Cardiol* 2014;64:1047-1058), ICDs in patients not included or not well represented in clinical trials (Kusumoto FM et al, *J Am Coll Cardiol.* 2014;64(11):1143-1177), Triple therapy for AF and PCI (Dewilde W et al, *J Am Coll Cardiol* 2014;64:1270-1280), Chronic total occlusions (Strauss BH et al, *J Am Coll Cardiol* 2014;64:1281-1289), Superresponse to CRT (Steffel J & Ruschitzka F**,** *Circulation* 2014;130:87-90), Left atrial appendage closure in patients with AF (Price MJ & Valderrabano M, *Circulation* 2014;130:202-212), Cardiovascular management in pregnancy (Brickner ME, *Circulation* 2014;130:273-282), Chronic venous insufficiency (Eberhardt RT & Raffetto JD, *Circulation* 2014;130:333-346), Chronic thromboembolic pulmonary hypertension (Lang IM & Madani M, *Circulation* 2014;130:508-518), Anderson-Fabry disease (Nagueh SF, *Circulation* 2014;130:1081-1090), Risk stratification for sudden cardiac death (Wellens HJJ et al, *Eur Heart J* 2014;35: 1642-1651), Edoxaban (Lip G & Agnelli G, Eur Heart J 2014;35: 1844-1855), Post-infarct ventricular septal rupture (Jones BM et al, *Eur Heart J* 2014;35: 2060-2068), Aortic stenosis and coronary artery disease (Paradis J et al, *Eur Heart J* 2014;35: 2069-2082), Cardiac tamponade (Ristic AD et al, *Eur Heart J* 2014;35: 2279-2284), Catheter ablation of AF (Haegeli LM & Calkins H, *Eur Heart J* 2014;35: 2454-2459), Aortic stenosis (Otto CM & Prendergast B, *N Engl J Med* 2014; 371:744-756), Screening for abdominal aortic aneurysm (LeFevre ML et al, *Ann Intern Med* 2014; 161: 281-290), Screening for asymptomatic carotid artery stenosis (Jonas DE et al, *Ann Intern Med* 2014;161:336-346; LeFevre ML et al, *Ann Intern Med* 2014;161:356-362).