

CARDIOLOGY CORNER

Cardiology News / Recent Literature Review / Last Two Quarters 2014*

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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 $\geq 1-2$. 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 are 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 $\geq 0.1\%$ 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 ($\geq 0.1\%$) 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;130:4 308-314).

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;130:7 539-545).

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;130:10 811-819).

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;130:11 872-879).

Rate and Predictors of 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% ($P = \text{NS}$) 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 $\leq 40\%$, 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–Nephrilysin 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 Nephrilysin 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 \pm 9 bpm in the ivabradine group vs 70.6 \pm 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 A₂ - Lp-PLA₂) 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-PLA₂ 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 NSTEMI 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;130:1 87-90), Left atrial appendage closure in patients with AF (Price MJ & Valderrabano M, *Circulation* 2014;130:2 202-212), Cardiovascular management in pregnancy (Brickner ME, *Circulation* 2014;130:3 273-282), Chronic venous insufficiency (Eberhardt RT & Raffetto JD, *Circulation* 2014;130:4 333-346), Chronic thromboembolic pulmonary hypertension (Lang IM & Madani M, *Circulation* 2014;130:6 508-518), Anderson-Fabry disease (Naguch SF, *Circulation* 2014;130:13 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).

Cardiology News / Recent Literature Review / Last Quarter 2014

Antonis S. Manolis, MD, Hector Anninos, MD,
Athens University School of Medicine, Athens, Greece

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

AFFORD study: n-3 Polyunsaturated Fatty Acids (Fish Oil) do not Reduce Atrial Fibrillation Recurrences

In a double-blind, randomized, placebo-controlled trial of fish oil (4 g/day, docosahexaenoic acid - DHA: eicosapentaenoic acid - EPA 1:2) vs safflower oil placebo in 337 patients with symptomatic paroxysmal or persistent AF followed for 9 ± 4 months, the primary endpoint (time to first symptomatic or asymptomatic AF recurrence lasting >30 s) occurred in 64% of patients in the fish oil arm and 63% of patients in the placebo arm (hazard ratio: 1.10; $p = \text{NS}$). hs-CRP and myeloperoxidase - MPO were normal at baseline and decreased to a similar degree at 6 months. The authors concluded that high-dose fish oil does not reduce AF recurrence in patients with a history of AF not receiving AA therapy, and does not reduce inflammation or oxidative stress markers in this population (Nigam A et al, *J Am Coll Cardiol* 2014;64:1441-1448).

N.B.: Another randomized study (VITAL - VITamin D and Omega-3 Trial) is currently examining the effect of 1 g/d of n-3 PUFAs on AF in a much larger population ($N=25,875$) without cardiac disease over 5 years.

RELAX-AHF: Serelaxin Reduces Mainly Cardiovascular & Sudden Deaths, Rather than HF Deaths

The RELAX-AHF study showed that IV serelaxin (recombinant human relaxin-2) compared with placebo reduced mortality at 6 months among 1,161 patients with acute heart failure (HF). In this group there were 107 deaths (9.3%): 37 (35%) from HF, 25 (23%) from sudden death, 15 (14%) from other cardiovascular (CV) causes, 19 (18%) from non-CV causes, and 11 (10%) classified as unknown. The treatment effect of serelaxin was most pronounced on other CV deaths (hazard ratio - HR: 0.29; $p = 0.005$) and sudden death (HR: 0.46; $p = 0.065$), with no effect of serelaxin treatment on HF or non-CV deaths. The authors concluded that the effects of serelaxin on mortality were mainly due to reduced CV causes and sudden death, without apparent effect on HF deaths

(Feleker GM et al, *J Am Coll Cardiol* 2014;64:1591-1598). N.B.: an ongoing large phase III outcome trial (NCT01870778) will further examine serelaxin's effect on mortality.

ARISTOTLE: Anticoagulation Quality was Lower in Warfarin-Treated Patients who Received Amiodarone, and Amiodarone was Associated with Significantly Higher Risk of Thrombo-embolism, while Apixaban had a Benefit over Warfarin in Both Groups

In the ARISTOTLE trial, 2,051 (11.4%) patients received amiodarone. Time in the therapeutic range (TTR) in patients on warfarin and amiodarone was lower than patients not on amiodarone (56.5% vs 63%; $p < 0.0001$). More patients on amiodarone had thromboembolism (stroke or systemic embolism) (1.58%/year vs 1.19%/year; hazard ratio -HR: 1.47; $p = 0.0322$). Mortality and major bleeding rates were higher, albeit not significantly different, in the amiodarone vs the non-amiodarone group. Apixaban, compared with warfarin, decreased systemic embolism, death, and major bleeding in both groups. The authors concluded that amiodarone was associated with significantly increased stroke and systemic embolism risk and a lower TTR when used with warfarin. Apixaban consistently reduced the rate of stroke and systemic embolism, death, and major bleeding compared with warfarin in both (amiodarone and non-amiodarone) groups (Flaker G et al, *J Am Coll Cardiol* 2014;64:1541-1550).

Catheter-Based Transapical Mitral Valve Implantation was Successful in First 2 Cases with Severe Ischemic Cardiomyopathy and Mitral Regurgitation

The first-in-man 2 cases of transapical mitral valve implantation with the Tiara device was successfully performed in a 73-year-old man and a 61-year-old woman with severe functional mitral regurgitation (MR) and heart failure with no need for cardiopulmonary bypass. Systemic arterial pressure and stroke volume increased and pulmonary pressure decreased, immediately after the procedure. Both patients were extubated in the operating room and had an uncomplicated course. Echocardiograms at 48 h, 1 and 2 months demonstrated excellent prosthetic valve function. There was a small paravalvular leak in the first patient at 48 h, which was completely resolved at subsequent studies. The authors concluded that transapical transcatheter mitral valve implantation is technically feasible and can be performed safely (Cheung A et al, *J Am Coll Cardiol* 2014;64:1814-1819).

SECURITY Trial: In a Low-Risk Population, 6-Month Dual Antiplatelet Therapy After Second-Generation Drug Eluting Stent Implantation Appears Acceptable

In the SECURITY trial, 1,399 patients were randomized to receive 6 ($n=682$) vs 12 months ($n=717$) dual antiplatelet therapy (DAPT). The primary endpoint (composite of cardiac

death, myocardial infarction -MI, stroke, definite or probable stent thrombosis, or Bleeding Academic Research Consortium -BARC type 3 or 5 bleeding at 12 months) was not different in the 2 groups. No differences were observed in the occurrence of the secondary endpoint (composite of cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC type 2, 3, or 5 bleeding at 12 and 24 months). Finally, no differences were observed in definite or probable stent thrombosis at 12 months (0.3% vs 0.4%) and between 12 and 24 months of follow-up (0.1% vs 0%). The authors concluded that in a low-risk population, the noninferiority hypothesis of 6 vs. 12 months DAPT following second-generation DES implantation appears acceptable (Colombo A et al, *J Am Coll Cardiol* 2014;64:2086-2097).

MESA Study: Positive Associations Between Baseline-Corrected QT Intervals and Risks of Stroke, Heart Failure, and Cardiovascular Disease (CVD) Events in Middle-Aged Individuals Free of CVD at Baseline

The corrected baseline 12-lead ECG QT interval duration (QTc) was determined in 6,273 participants (mean age 62 ± 10 years; 53% women) in MESA (Multi-Ethnic Study of Atherosclerosis). Cardiovascular events occurred in 291 participants over a mean follow-up of 8 ± 1.7 years. Each 10-ms increase in the baseline QTc was associated with incident heart failure (hazard ratio -HR: 1.25), CVD events (HR: 1.12), and stroke (HR: 1.19). There was no evidence of interaction with gender or ethnicity. The authors concluded that the QT interval was associated with incident cardiovascular events in middle-aged and older adults without prior CVD (Beinart R et al, *J Am Coll Cardiol* 2014;64:2111-2119).

ARREST-AF Study: Aggressive Risk Factor Reduction Improved Outcomes of AF Ablation by Reducing AF Burden and Severity Together With Favorable Changes in Cardiac Remodeling

Risk factor management (RFM) was offered to 149 of 281 consecutive patients undergoing AF ablation who had a body mass index ≥ 27 kg/m² and ≥ 1 cardiac risk factor. After AF ablation, RFM applied in 61 patients resulted in greater reductions in weight ($p = 0.002$) and blood pressure ($p = 0.006$), and better glycemic control ($p = 0.001$) and lipid profiles ($p = 0.01$). At follow-up, AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group compared with the control group ($n = 88$) (all $p < 0.001$). Post-procedural arrhythmia-free survival was greater in RFM patients either with single or multiple procedures ($p < 0.001$). On multivariate analysis, type of AF ($p < 0.001$) and RFM (hazard ratio 4.8; $p < 0.001$) were independent predictors of arrhythmia-free survival. The authors concluded that aggressive RFM improved the long-term success of AF ablation (Pathak RK et al, *J Am Coll Cardiol* 2014;64:2222-2231).

FOCUS Project: Polypill Strategy Improves Adherence Post Myocardial Infarction (MI)

Among 2,118 post-MI patients, in phase 1 of the FOCUS (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) study, overall cardiovascular (CV) medication adherence, was 45.5%. In a multivariate analysis, the risk of being nonadherent was associated with younger age, depression, receiving complex medication regimen, poorer health insurance coverage, and a lower level of social support. In phase 2, 695 patients were randomized to a polypill (aspirin 100 mg, simvastatin 40 mg, and ramipril 2.5, 5, or 10 mg) vs 3 drugs given separately. Over 9 months, the polypill group showed improved adherence: 51% vs 41% ($p = 0.019$; intention-to-treat)/ $\sim 66\%$ vs 56% ($p = 0.012$; per protocol). The authors concluded that for secondary prevention following acute MI, younger age, depression, and a complex drug regimen are associated with lower medication adherence, while a polypill strategy increased adherence (Castellano JM et al, *J Am Coll Cardiol* 2014;64:2071-2082).

Cardiac Deaths After Primary PCI Cluster in the First Month, While Later NonCardiac Deaths Preval and Annual Cardiac Mortality Declines to <1.5%

Among 2,804 consecutive patients with STEMI (age 63 ± 13 y, 72% males) treated with primary PCI and followed up for a median of 4.7 years, 717 patients died. Main causes of death within the first month were cardiogenic shock and anoxic brain injury after cardiac arrest. Age, culprit vessel size and flow, heart failure and diabetes were independent predictors of mortality. After the first month, noncardiac causes of death prevailed (65%; mainly malignancies and pulmonary diseases), while the annual cardiac mortality rate declined to <1.5%. 1-month, 1-year, and 5-year all-cause (and cardiac) mortality rates were $\sim 8\%$, 11%, & 23%, respectively. The authors concluded that patients who survive the first month after STEMI treated with primary PCI have an excellent prognosis, with a <1.5% annual cardiac mortality risk, while noncardiac causes are responsible for the majority of later deaths (Pedersen F et al, *J Am Coll Cardiol* 2014;64:2101-2108).

Multicenter Evaluation of a Third-Generation Balloon-Expandable Transcatheter Aortic Valve: New Valve Addresses Deficiencies of Earlier Transcatheter Valves

The SAPIEN 3 (Edwards Lifesciences Inc., Irvine, California) transcatheter valve claims a low-profile delivery system that facilitates implantation and an external seal that minimizes paravalvular regurgitation. The valve was evaluated in a prospective study of 150 patients at 16 sites in Europe and Canada (aged 83.6 ± 5.0 years; TCT score $7.4 \pm 4.5\%$ and logistic EuroSCORE $21.6 \pm 12.3\%$; transfemoral approach in 64.0%). At 30 days, paravalvular regurgitation was 0 to mild in $\sim 96\%$. Transfemoral approach had low mortality (2.1%),

no disabling stroke (0.0%), and fully percutaneous access and closure in 96%. Nontransfemoral access was associated with higher rates of mortality (11.6%) and stroke (5.6%). The authors concluded that the new valve addresses major deficiencies of earlier valves in terms of ease of use, accuracy of positioning, and paravalvular sealing, with low rates of mortality and stroke via transfemoral access. (Webb J et al, *J Am Coll Cardiol* 2014;64:2235-2243).

ACCOAST-PCI Study: In Patients with NSTEMI, the Data Support Deferring a Loading Dose of Prasugrel until a Decision is Made About PCI

Among 4,033 patients with NSTEMI, 68.7% underwent PCI; 1,394 received pre-treatment with prasugrel (30-mg loading dose), and 1,376 received placebo. At the time of PCI, patients who received pre-treatment with prasugrel received an additional 30-mg dose of prasugrel, and those who received placebo received a 60-mg loading dose of prasugrel. The incidence of the primary endpoint (composite of cardiovascular death, MI, stroke, urgent revascularization, or glycoprotein IIb/IIIa bailout) at 7 days in the pre-treatment group vs the no pre-treatment group was similar (13.1% vs 13.1%). Patients with thrombus on angiography had a 3-fold higher incidence of the primary endpoint than patients without thrombus. There was no impact of pre-treatment with prasugrel on the presence of thrombus before PCI or on occurrence of stent thrombosis after PCI. There was a 3-fold increase in major bleeding and a 6-fold increase in life-threatening bleeding with pre-treatment with prasugrel; same trends persisted in patients who had radial or femoral access even with use of a closure device. The authors concluded that these data support deferring treatment with prasugrel until a decision is made about revascularization in patients with NSTEMI undergoing angiography within 48 h of admission (Montalescot G et al, *J Am Coll Cardiol* 2014;64:2563-2571).

TRA 2°P-TIMI 50 Trial: Vorapaxar, a Novel Antiplatelet Agent Inhibiting Platelet Protease-Activated Receptor (PAR)-1, Reduced Risk of Definite Stent Thrombosis Consistently Over Time not Modified by Background Use of DAPT

TRA 2°P-TIMI 50 (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis In Myocardial Infarction 50) randomized 26,449 patients, with 14,042 (53%) having a history of a coronary stent implantation before randomization, and 449 patients receiving a coronary stent during the trial (total 14,491). During a median 2.5 years, there were 152 definite stent thrombosis (ST) events (majority - 92% occurring late). Vorapaxar reduced definite ST (1.1% vs 1.4%, hazard ratio - HR: 0.71; $p=0.037$) consistently over time after PCI, not modified by diabetes, use of drug-eluting stents, or use

of dual antiplatelet therapy (DAPT). Vorapaxar increased moderate/severe bleeding (HR: 1.57; $p<0.001$). The authors concluded that vorapaxar reduced definite ST (~1.4% at 3 years) in stable patients with coronary stenting receiving standard antiplatelet therapy (Bonaca MP et al, *J Am Coll Cardiol* 2014;64:2309-2317).

PARTNER Trial: TAVI Confers Better Survival and Functional Status in Inoperable Patients with Severe Aortic Stenosis with Durable Benefit Over 3 Years, Albeit with High Residual Mortality

In the Placement of Aortic Transcatheter Valves (PARTNER) study, among the 358 patients randomly assigned to transcatheter aortic valve implantation (TAVI) or standard therapy and all randomly assigned inoperable patients ($n=449$), including the randomized portion of the continued access study ($n=91$), the 3-year mortality rate in TAVI patients was 54.1% and 80.9% in the standard therapy group ($P<0.001$; hazard ratio-HR, 0.53; $P<0.001$). In survivors, there was significant improvement in NYHA functional class sustained at 3 years. The cumulative incidence of strokes at 3-year follow-up was 15.7% in TAVI patients vs 5.5% in patients with standard therapy (HR, 2.81; $P=0.012$); however, the composite of death or strokes was significantly lower after TAVI vs standard therapy (57.4% vs 80.9%, $P<0.001$; HR, 0.60; $P<0.001$). The authors concluded that TAVI resulted in better survival and functional status in inoperable patients with severe aortic stenosis with durable hemodynamic benefit on long-term follow-up. However, there is high residual mortality even in successfully treated TAVI patients (Kapadia SR et al, *Circulation* 2014; 130: 1483-1492).

A 5-Year United States PCI Experience (2005–2009): Significant Impact of Annual Operator and Institutional Volume on PCI Outcomes

According with a Nationwide 5-year sample (2005-2009) of 457,498 percutaneous coronary interventions (PCIs) out of a total of 2,243,209 PCIs performed in the United States, in-hospital, all-cause mortality was 1.08%, and the overall complication rate was 7.10%. The primary (in-hospital mortality) and secondary outcomes (in-hospital mortality and peri-procedural complications) of procedures performed by operators in 4th (>100 annual procedures), 3rd (45–100 procedures), and 2nd quartile (16–44 procedures) were significantly less ($P<0.001$) when compared with those by operators in the 1st quartile (≤ 15 procedures). Similarly operators in the higher quartiles witnessed a significant reduction in length of hospital stay and cost ($P<0.001$). The authors concluded that overall in-hospital mortality after PCI was low. An increase in operator and institutional volume of PCI was found to be associated with a decrease in adverse outcomes, length of hospital stay, and cost of hospitalization (Badheka AO et al, *Circulation* 2014; 130: 1392-1406).

ARIC Study: Most Patients With Incident Heart Failure (HF) Have Pre-Existing Overweight or Obesity and Once they Develop HF, they Have Lower Mortality Compared With Those With Prior Normal BMI / A Significant Component of this Obesity Paradox is Driven by Pre-Morbid Obesity

In the ARIC (Atherosclerosis Risk In Communities) study, among 1,487 patients with incident heart failure (HF), 35% were overweight and 47% were obese before HF diagnosis. Over 10-year follow-up after incident HF, 43% of patients died. Being pre-morbidly overweight (hazard ratio -HR: 0.72; $p=0.004$) or obese (HR: 0.70; $p=0.001$) had a protective association with survival compared with normal BMI. The authors concluded that patients who were overweight or obese before HF development have lower mortality after HF diagnosis compared with patients with normal body mass index (BMI) (Khalid U et al, *J Am Coll Cardiol* 2014;64:2743-2749).

RADAR-AF Trial: In Paroxysmal AF, Localized High-Frequency Source Ablation (HFSA) was Inferior at 6 Months but was as Efficacious as Circumferential Pulmonary Vein Isolation (CPVI) at 1 Year, While in Persistent AF, CPVI+ HFSA Offered no Incremental Value, With a Trend to More Complications

Among 232 patients (age 53 ± 10 y), those with paroxysmal AF ($n=115$) were randomized to circumferential pulmonary vein isolation (CPVI) or localized high-frequency source ablation (HFSA)-only and those with persistent AF ($n=117$) to CPVI or a combined ablation approach (CPVI+HFSA). In paroxysmal AF, HFSA failed to achieve noninferiority at 6 months after a single procedure but, after redo procedures, was noninferior to CPVI at 12 months for freedom from AF with fewer serious adverse events. In persistent AF, there were no significant differences between treatment groups for AF recurrences, but CPVI+HFSA trended toward more serious adverse events (Atienza F et al, *J Am Coll Cardiol* 2014;64:2455-2467).

Improved Survival After Out-of-Hospital Cardiac Arrest and Use of Automated External Defibrillators

According with a population-based cohort study of out-of-hospital cardiac arrest (2006-2012), use of automated external defibrillators (AED) led to an increase in the rates of survival with favorable neurologic outcome ($N=6133$, 16.2% to 19.7%; P for trend=0.021), albeit only in patients presenting with a shockable initial rhythm ($N=2823$; 29.1% to 41.4%; P for trend<0.001). Rates of AED use almost tripled during the study period (21.4% to 59.3%; P for trend <0.001). The authors concluded that increased AED use is associated with increased survival in patients with a shockable initial rhythm, recommending continuous efforts to introduce or extend AED programs (Blom MT et al, *Circulation* 2014; 130: 1868-1875).

Tetralogy of Fallot: Low Late Mortality at Prospective Follow-Up of 40 Years After Surgical Correction

According to a longitudinal cohort study of 136 out of 144 patients with tetralogy of Fallot who underwent surgical repair at <15 years of age (1968-1980), cumulative survival was 72% after 40 years. Late mortality was due to heart failure and ventricular fibrillation. For 72 of 80 survivors participating in further in-hospital investigation, cumulative event-free survival was 25% after 40 years. Although systolic right and left ventricular function declined, peak exercise capacity remained stable. A previous shunt operation (hazard ratio-HR, 2.9), low temperature during surgery (HR 1.1), and early postoperative arrhythmias (HR 2.5) were found to predict late mortality. An increase in QRS duration and worsening exercise tolerance and ventricular dysfunction did not predict mortality. Insertion of a transannular patch was a predictor for late arrhythmias (HR, 4.0) (Cuypers J et al, *Circulation* 2014; 130: 1944-1953).

MADIT-CRT Trial: Left Ventricular Ejection Fraction Normalization in Cardiac Resynchronization Therapy (CRT) Decreases Risk of Ventricular Arrhythmias and Improves Clinical Outcomes

Among 752 patients in the MADIT-CRT trial a total of 7.3% achieved left ventricular ejection fraction (LVEF) normalization (>50%) over 2.2 ± 0.8 years. The risk of ventricular tachyarrhythmias (VTA) was reduced in patients with LVEF >50% (hazard ratio -HR, 0.24; $P=0.023$) and LVEF of 36-50% (HR, 0.44; $P<0.001$). Among patients with LVEF >50%, only 1 patient had $VTA \geq 200$ bpm (HR, 0.16), none were shocked by the ICD, and 2 died of nonarrhythmic causes. The risk of HF or death was reduced with improvements in LVEF. A total of 6 factors were associated with LVEF normalization, and patients with all factors present ($n=42$) did not experience VTAs. The authors concluded that patients who achieve LVEF normalization (>50%) have very low absolute and relative risk of VTAs and a favorable clinical course within 2.2 years of follow-up. They recommend that these patients could be considered for downgrade from CRT-defibrillator to CRT-pacemaker at time of battery replacement if no VTAs have occurred (Ruwald MH et al, *Circulation* 2014; 130: 2278-2286).

X-VeRT: Oral Rivaroxaban an Effective & Safe Alternative to VKA/May Allow Prompter Cardioversion

Among 1504 patients with AF scheduled for cardioversion, the primary efficacy outcome (stroke, TIA, peripheral embolism, MI, and cardiovascular death) occurred in 5 (2 strokes) of 978 patients (0.51%) assigned to rivaroxaban and in 5 (2 strokes) of 492 patients (1.02%) receiving VKA (risk ratio – RR 0.50). In the rivaroxaban group, 4 (0.71%) patients experienced primary efficacy events following early (at 1-5 days) & 1 (0.24%) following delayed (3-8 weeks) cardioversion. In the VKA group, 3 (1.08%) had primary efficacy events fol-

lowing early and 2 (0.93%) following delayed cardioversion. Rivaroxaban was associated with a significantly shorter time to cardioversion compared with VKAs ($P < 0.001$). Major bleeding occurred in 6 (0.6%) in the rivaroxaban group and 4 patients (0.8%) in the VKA group (RR 0.76). The authors concluded that rivaroxaban is an effective and safe alternative to VKAs and may allow prompt cardioversion (Cappato R et al, *Eur Heart J* 2014; 35: 3346-3355).

AMIO-CAT trial: Short-Term Oral Amiodarone Treatment Following Ablation for Paroxysmal or Persistent AF did not Significantly Reduce AF Recurrence at 6-Months, but Prolonged Time to First Recurrence and Reduced Arrhythmia-Related Hospitalization and Cardioversion Rates

A total of 212 patients (median age 61 years) undergoing AF ablation were randomly assigned to 8 weeks of oral amiodarone or placebo post-procedurally. Recurrence was observed in 42/107 (39%) in the amiodarone group vs 48/99 (48%) in the placebo group ($P = \text{NS}$). The amiodarone group had significantly lower rate of arrhythmia-related hospitalizations (rate ratio = 0.43; $P = 0.006$) and cardioversions (rate ratio = 0.36; $P = 0.0004$) within the blanking period. The authors concluded that short-term oral amiodarone treatment following AF ablation did not significantly reduce AF recurrence at 6-months, but it more than halved atrial arrhythmia related hospitalization and cardioversion rates during the blanking period (Darkner S et al, *Eur Heart J* 2014; 35: 3356-3364).

ROCKET AF trial: Every Seventh Patient Had Significant Valvular Disease (SVD) Barring Mitral Stenosis & Prosthetic Valves / AF Patients With SVD Experienced the Same Stroke-Prevention Benefit from Oral Anticoagulants as did AF Patients Without SVD, but Bleeding Rates Were Higher With Rivaroxaban

In the ROCKET AF trial among 14 171 patients with non-valvular AF, defined as the presence of AF in the absence of mitral stenosis or prosthetic valves, 2003 (14.1%) had significant valvular disease (SVD) (mitral regurgitation predominating at ~90%, followed by aortic regurgitation at 25%, and aortic stenosis at 11%, exceeding 100% due to cases with more than one type of valvular lesion). Patients with SVD were older and had more comorbidities. The rate of stroke or systemic embolism with rivaroxaban vs. warfarin was consistent among patients with SVD [2 vs. 2.4%; hazard ratio - HR 0.83] and without SVD (1.96 vs. 2.22%; HR 0.89; $P = \text{NS}$). However, rates of major and non-major clinically relevant bleeding with rivaroxaban vs warfarin were higher in patients with SVD (20% rivaroxaban vs 17% warfarin; HR 1.25) vs those without (14% in both), even when controlling for risk factors and potential confounders. In intracranial hemorrhage, there was no interaction between patients with and without SVD where the overall

rate was lower among those randomized to rivaroxaban. The authors concluded that many patients with 'non-valvular atrial fibrillation' have significant valve lesions. Their risk of stroke is similar to that of patients without SVD after controlling for stroke risk factors. Efficacy of rivaroxaban vs warfarin was similar in patients with and without SVD; however, the observed risk of bleeding was higher with rivaroxaban in patients with SVD but was the same among those without SVD (Breihardt G et al, *Eur Heart J* 2014; 35: 3377-3385).

ADVANCE-ON: In Type 2 Diabetes, Blood-Pressure Lowering but not Glucose Control Lowers Mortality or Macrovascular Events at 6 Years

In the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial, antihypertensive therapy with perindopril and indapamide reduced mortality in patients with type 2 diabetes, but intensive glucose control, (glycated hemoglobin $< 6.5\%$), did not. Among 8494 out of 11,140 patients participating in the post-trial long-term (6-year) follow-up, reductions in the risk of death or cardiovascular death were attenuated in the group receiving anti-hypertensive therapy but remained significant at the end of the post-trial follow-up (hazard ratios 0.91, $P = 0.03$ and 0.88, $P = 0.04$, respectively), while no differences were observed between the intensive-glucose-control group and the standard-glucose-control group. The authors concluded that antihypertensive therapy in diabetics is effective in reducing mortality, an effect attenuated but still evident over 6 years, while there is no evidence that intensive glucose control has any long-term benefits (Zoungas S et al, *N Engl J Med* 2014; 371:1392-1406).

DAPT Study: 30 Instead of 12 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents Reduces Stent Thrombosis and MACCE but Increases Risk of Bleeding

A total of 9961 patients receiving drug-eluting stents (DES) were randomized after 12 months to continue thienopyridine treatment or to receive placebo for another 18 months. Continued treatment with thienopyridine, as compared with placebo, reduced stent thrombosis (0.4% vs 1.4%; hazard ratio-HR, 0.29; $P < 0.001$) and major adverse cardiovascular and cerebrovascular events (MACCE: death, myocardial infarction, or stroke) (4.3% vs 5.9%; HR, 0.71; $P < 0.001$). The rate of bleeding was increased with continued thienopyridine treatment (2.5% vs 1.6%, $P = 0.001$). Risk of stent thrombosis and myocardial infarction increased in both groups during the 3 months after discontinuation of thienopyridine treatment. The authors concluded that dual antiplatelet therapy beyond 1 year after DES significantly reduced the risks of stent thrombosis and MACCE but was associated with an increased risk of bleeding (Mauri L et al, *N Engl J Med* 2014; 371:2155-2166).

ARCTIC-Interruption Trial: No Benefit from Dual-Antiplatelet Treatment Beyond 1 Year After DES

After 1 year of follow-up, 1259 patients having drug-eluting stent (DES) implantation were randomized to interruption of dual antiplatelet therapy (DAPT) while maintaining aspirin (interruption group, n=624) or to DAPT continuation for 6–18 months (continuation group, n=635). After a median of 17 months, the primary endpoint (death, MI, stent thrombosis, stroke, or urgent revascularization) occurred in 27 (4%) patients in the interruption group and 24 (4%) patients in the continuation group (hazard ratio -HR 1.17; p=NS). Major bleeding occurred more often in the continuation group (n=7, 1% vs n=1, <0.5%; HR 0.15; p=0.073). Major or minor bleedings were also more common in the continuation group compared with the interruption group (n=12, 2% vs n=3, 1%; HR 0.26; p=0.04). The authors concluded that extension of DAPT beyond 1 year after stenting with DES confers no apparent benefit but instead harm when no event has occurred within the first year after stenting. N.B.: high-risk patients were not randomized in this study (Collet J et al, *Lancet* 2014;384(9954):1577–1585).

DALLAS Heart Study: HDL Cholesterol Efflux Capacity, a Functional Property of HDL, was Inversely Associated With Incident Atherosclerotic Cardiovascular Disease in a Population-Based Cohort Free from Cardiovascular Disease at Baseline

HDL cholesterol level, HDL particle concentration, and cholesterol efflux capacity were measured at baseline in 2924 adults free from cardiovascular (CV) disease. Over a median follow-up of 9.4 years, cholesterol efflux capacity had minimal association with CV risk factors. Baseline HDL cholesterol level was not associated with CV events, whereas there was a 67% reduction in CV risk in the highest quartile of cholesterol efflux capacity vs the lowest quartile (hazard ratio, 0.33). Adding cholesterol efflux capacity to traditional risk factors was associated with better discrimination and reclassification indexes. The authors concluded that cholesterol efflux capacity, a new biomarker featuring a key step in reverse cholesterol transport, was inversely associated with the incidence of CV events in a population-based cohort. This association persisted after adjustment for traditional CV risk factors, HDL cholesterol level, and HDL particle concentration (Rohatgi A et al, *N Engl J Med* 2014;371:2383-93).

Similar Survival of Bioprosthetic and Mechanical Aortic Valves in Patients Aged 50 to 69 Years

Comparing survival and long-term outcome between bioprosthetic and mechanical valves in 4253 patients (aged 50–69 years; propensity matching yielded 1001 patient pairs) who underwent aortic valve replacement (AVR) (1997–2004) over a median follow-up of 10.8 years, there were no differences

in survival or stroke rates: actuarial 15-year survival 60.6% vs 62.1%; 15-year cumulative incidence of stroke 7.7% vs 8.6%. The 15-year cumulative incidence of reoperation was higher in the bioprosthesis group (12.1% vs 6.9%; hazard ratio-HR, 0.52). The 15-year cumulative incidence of major bleeding was higher in the mechanical prosthesis group (13.0% vs 6.6%; HR, 1.75). The 30-day mortality rate was 18.7% after stroke, 9.0% after reoperation, and 13.2% after major bleeding. The authors concluded that among propensity-matched patients (50–69 years) who had AVR with bioprosthetic compared with mechanical valves, there was no significant difference in 15-year survival or stroke. The bioprosthetic valve group had more reoperations but lower major bleeding. Thus, bioprosthetic valves may be a reasonable choice in patients aged 50 - 69 years (Chiang YP et al, *JAMA* 2014;312:1323-1329).

Nonobstructive Coronary Artery Disease (CAD) Compared With no Apparent CAD, was Associated with a Significantly Greater 1-Year Risk of Myocardial Infarction (MI) and All-Cause Mortality

Among 37 674 US veterans undergoing elective coronary angiography, 8384 (22%) had nonobstructive (≥ 1 stenosis $\geq 20\%$ but no stenosis $\geq 70\%$) CAD, and 20 899 patients (55%) had obstructive (any stenosis $\geq 70\%$ or left main -LM stenosis $\geq 50\%$) CAD. Within 1 year, 845 patients died and 385 were rehospitalized for MI. Among patients with no apparent (no stenosis $>20\%$) CAD, the 1-year MI rate was 0.11% (n=8) and increased progressively by nonobstructive 1-vessel disease (1VD), 0.24%; 2VD, 0.56%; 3VD, 0.59%; obstructive 1VD, 1.18%; 2VD, 2.18%; and 3VD or LM, 2.47%. One-year MI rates increased with increasing CAD extent. Relative to those with no apparent CAD, patients with non-obstructive 1VD had a hazard ratio (HR) for 1-year MI of 2; 2VD HR, 4.6; 3VD HR, 4.5; obstructive 1VD HR, 9.0; 2VD HR, 16.5; and 3VD or LM HR, 19.5. One-year mortality rates were associated with increasing CAD extent (1.38% in patients without apparent CAD to 4.30% in obstructive 3VD or LM). There was no significant association between nonobstructive 1VD or 2VD and mortality, but there were significant associations with mortality for nonobstructive 3VD (HR, 1.6), obstructive 1VD (HR, 1.9), 2VD (HR, 2.8), and 3VD or LM (HR, 3.4). The authors concluded that among patients undergoing coronary angiography, nonobstructive CAD, compared with no apparent CAD, was associated with a greater 1-year risk of MI and all-cause mortality (Maddox TM et al, *JAMA* 2014;312:1754-1763).

CHARGE Consortium: Association of LDL Cholesterol-Related Genetic Variants With Aortic Valve Calcium and Incident Aortic Stenosis

The prevalence of aortic valve calcium across the CHARGE cohorts (n=6942) was 32% (n = 2245). In the Malmö Diet and Cancer Study (MDCS) (n = 28 461), over a median follow-up

of ~16 years, aortic stenosis (AS) developed in 17 per 1000 participants (n = 473) and aortic valve replacement for AS occurred in 7 per 1000 (n = 205). Plasma LDL-C, but not HDL-C or triglycerides (TG), was significantly associated with incident AS (hazard ratio -HR per mmol/L, 1.28; $P=0.02$; AS incidence: 1.3% and 2.4% in lowest and highest LDL-C quartiles, respectively). The LDL-C genetic risk scores (GRS), but not HDL-C or TG GRS, was associated with presence of aortic valve calcium in CHARGE (odds ratio - OR per GRS increment, 1.38; $P=0.007$) and with incident AS in MDCS (HR per GRS increment, 2.78; $P=0.02$; AS incidence: 1.9% and 2.6% in lowest and highest GRS quartiles, respectively). The authors concluded that genetic predisposition to elevated LDL-cholesterol was associated with presence of aortic valve calcium and incidence of AS, supporting a causal association between LDL-C and aortic valve disease (Smith JG et al, *JAMA* 2014;312:1764-1771).

ISAR-CLOSURE Trial: in Trans-Femoral Coronary Angiography, Vascular Closure Devices were Non-Inferior to Manual Compression Regarding Access-Site Complications & Reduced Time to Hemostasis

Of 4524 patients undergoing transfemoral coronary angiography (2011-2014), 3015 were randomly assigned to a vascular closure device (VCD) group (intravascular VCD in 1509, extravascular VCD in 1506) or manual compression group (n=1509). The primary end point (vascular complications at 30 days) was observed in 208 patients (6.9%) in the VCD group and 119 patients (7.9%) in the manual compression group (noninferior). Time to hemostasis was shorter in patients with VCD (1 minute), vs manual compression (10 minutes) ($P < 0.001$). Time to hemostasis was shorter in patients with intravascular VCD (0.5 minute) vs extravascular VCD (2 minutes) ($P < 0.001$) and closure device failure was also lower among those with intravascular vs extravascular VCD (80 patients - 5.3%, vs 184 patients - 12.2%; $P < 0.001$). The authors concluded that in patients undergoing transfemoral coronary angiography, VCDs were noninferior to manual compression in terms of vascular access-site complications and reduced time to hemostasis (Schulz-Schöpfke S et al, *JAMA* 2014;312:1981-1987).

PROTECT AF: Percutaneous Left Atrial Appendage Closure at Least Noninferior to Warfarin for Atrial Fibrillation at 3.8 Years of Follow-up

Among 707 patients with nonvalvular AF and >1 stroke risk factor randomized to left atrial appendage closure (n = 463) or warfarin (n = 244; target INR 2-3), over a mean follow-up of 3.8 years, there were 39 events (8.4%) in the device group and 34 events among 244 patients (13.9%) in the warfarin group (rate ratio, 0.60), meeting prespecified

criteria for both noninferiority and superiority. Patients in the device group had lower rates of both cardiovascular mortality (3.7% vs 9%; hazard ratio -HR, 0.40; $P=0.005$) and all-cause mortality (12.3% vs 18.0%; HR, 0.66; $P=0.04$). The authors concluded that after 3.8 years of follow-up among patients with nonvalvular AF at high risk for stroke, percutaneous LAA closure met criteria for both noninferiority and superiority, compared with warfarin, for preventing stroke, systemic embolism, and cardiovascular death, as well as superiority for cardiovascular and all-cause mortality (Reddy VY et al, *JAMA* 2014;312:1988-1998).

HEAT PPCI Trial: Unfractionated Heparin Superior to Bivalirudin in Primary Percutaneous Coronary Intervention

Among 1812 patients undergoing emergency angiography randomly assigned to bivalirudin (n=905) or heparin (n=907), 751 (83%) and 740 (82%), respectively, had primary percutaneous coronary intervention (PPCI). Rate of GP IIb/IIIa inhibitor use was similar in the 2 groups. The primary efficacy outcome (all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularisation) occurred in 79 (8.7%) patients in the bivalirudin group and 52 (5.7%) in the heparin group (absolute risk difference 3%; relative risk -RR 1.52, $p=0.01$). The primary safety outcome (major bleeding) occurred in 32 (3.5%) in the bivalirudin group and 28 (3.1%) in the heparin group (0.4%; RR 1.15, $p=NS$). The authors concluded that compared with bivalirudin, heparin reduces the incidence of major adverse ischemic events in the setting of PPCI, with no increase in bleeding. Systematic use of heparin rather than bivalirudin would significantly reduce drug costs (Shahzad A et al, *Lancet* 2014;384(9957):1849-1858).

ACCORD Trial: Intensive Glycemic Control Reduces Risk of Ischemic Heart Disease

Over ~5 years (mean 3.7 years of active treatment plus a further mean 1.2 years), among 10 251 adults aged 40-79 years with type 2 diabetes and high mean glycated hemoglobin A_{1c} (HbA_{1c}) (8.3%), and risk factors for ischemic heart disease, assigned to intensive (target $HbA_{1c} < 6%$) or standard therapy (HbA_{1c} 7-7.9%), myocardial infarction (MI) was less frequent in the intensive than in the standard therapy group during active treatment (hazard ratio -HR 0.80; $p=0.015$) and overall (HR 0.84; $p=0.02$). Findings were similar for combined MI, revascularisation, and unstable angina (active treatment HR 0.89, overall HR 0.87) and for coronary revascularisation alone (HR 0.84) and unstable angina alone (HR 0.81) during full follow-up. The authors concluded that glycemia is a modifiable risk factor for ischemic heart disease in middle-aged diabetics and other cardiovascular risk factors (Gerstein HC et al, *Lancet* 2014; 384(9958):1936-1941).

BIOSCIENCE: Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Noninferior to Durable Polymer Everolimus-Eluting Stent

A total of 2119 patients with 3139 lesions were randomly assigned to biodegradable polymer sirolimus-eluting stents (SES) (1063 patients, 1594 lesions) or durable polymer everolimus-eluting stents (EES) (1056 patients, 1545 lesions); 407 (19%) STEMI patients. Target lesion failure with biodegradable polymer SES (69 cases; 6.5%) was non-inferior to durable polymer EES (70 cases; 6.6%) at 1 year. No significant differences were noted in rates of definite stent thrombosis: 9 (0.9%) vs 4 (0.4%), rate ratio -RR 2.26, p=NS). Biodegradable polymer SES were associated with improved outcome compared with durable polymer EES in the subgroup of patients with STEMI: 7 (3.3%) vs 17 (8.7%) (RR 0.38, p=0.024, p for interaction=0.014). The authors concluded that biodegradable polymer SES were non-inferior to durable polymer EES for the combined safety and efficacy outcome target lesion failure at 12 months (Pilgrim T et al, *Lancet* 2014; 384 (9960):2111–2122).

Individual-Patient Data Meta-Analysis of 10 Randomized Trials: No Benefit of β -Blockers in Patients With Heart Failure Plus Atrial Fibrillation

Individual-patient data from 10 randomized controlled trials (N= 18,254) of the comparison of β blockers vs placebo in heart failure, 13,946 (76%) having sinus rhythm and 3066 (17%) atrial fibrillation, showed crude death rates over a mean follow-up of 1.5 years of 16% in patients with sinus rhythm and 21% in patients with atrial fibrillation. β -blocker therapy led to a significant reduction in all-cause mortality in patients with sinus rhythm (hazard ratio-HR 0.73; p<0.001), but not in patients with atrial fibrillation (HR 0.97; p=NS). The authors concluded that β blockers should not be used preferentially over other rate-control medications and not regarded as standard therapy to improve prognosis in patients with concomitant heart failure and atrial fibrillation (Kotecha D et al, *Lancet* 2014; 384(9961):2235–2243).

Systematic Review and Meta-Analysis: Association of Atrial Fibrillation with Silent Cerebral Infarctions

A total of 11 studies including 5317 patients with mean ages from 50 to 83.6 years reported on the association between atrial fibrillation (AF) and silent cerebral infarctions (SCIs). When computed tomography (CT) and magnetic resonance imaging (MRI) studies were combined, AF was associated with SCIs in patients with no history of symptomatic stroke (odds ratio, 2.62). This association was independent of AF type (paroxysmal vs persistent). The results were not altered significantly when the analysis was restricted to studies that met at least 70% of the maximum possible quality score (odds ratio, 3.06). Seventeen studies reported the prevalence of SCIs. The overall prevalence of SCI lesions on MRI and CT among

patients with AF was 40% and 22%, respectively. The authors concluded that atrial fibrillation is associated with more than a 2-fold increase in the odds for silent cerebral infarction (Kalanitarians S et al, *Ann Intern Med* 2014;161:650-658).

Danish Cohort Study: Risk for Serious Bleeding and Thromboembolism in Patients With Atrial Fibrillation (AF) Associated With use of Nonsteroidal Anti-Inflammatory Drugs (NSAID)

Of 150,900 patients with AF (median age, 75 years; 47% female), 53,732 (35.6%) were prescribed an NSAID over 6.2 years. There were 17,187 (11%) occurrences of serious bleeding and 19,561 (13%) events of thromboembolism. At 3 months, the absolute risk for serious bleeding within 14 days of NSAID exposure was 3.5 events per 1000 patients compared with 1.5 events per 1000 patients without NSAID exposure. Use of NSAIDs was associated with increased absolute risks for serious bleeding and thromboembolism across all antithrombotic regimens and NSAID types. The authors concluded that physicians should exercise caution with NSAIDs in patients with AF (Lamberts M et al, *Ann Intern Med* 2014;161:690-698).

A Cohort Study: Renin–Angiotensin System Blockade Therapy Prolongs Survival After Surgical Aortic Valve Replacement (SAVR) for Severe Aortic Stenosis

Comparing 594 matched pairs among patients who were prescribed angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers after SAVR for severe AS (1991-2010) ($n=741$) and those who did not receive these agents ($n=1011$), survival rates at 1, 5, and 10 years were significantly greater in the treated group than in the untreated group (99%, 90%, and 71% vs 96%, 78%, and 49%, respectively; $P < 0.001$). The authors concluded that renin–angiotensin system blockade therapy is associated with increased survival rates in patients after SAVR for severe AS, dictating the need for a randomized trial to further confirm this finding (Goel SS et al, *Ann Intern Med* 2014;161:699-710).

Meta-Analysis: Coronary Artery Bypass Grafting (CABG) is Preferred Over Percutaneous Coronary Intervention (PCI) in Diabetics, Albeit with Increased Risk of Stroke

Meta-analysis of 40 randomized, controlled trials comparing PCI (with drug-eluting or bare-metal stents) with CABG in adults with diabetes with multivessel or left main coronary artery disease indicated that the primary outcome (a composite of all-cause mortality, nonfatal myocardial infarction, and stroke) increased with PCI (odds ratio -OR, 1.33). PCI resulted in increased mortality (OR, 1.44), no change in the number of myocardial infarctions (OR, 1.33), and fewer strokes (OR, 0.56). The authors concluded that CABG seems to be the preferred revascularization technique in diabetics,

however, because of residual uncertainties and increased risk for stroke with CABG, clinical judgment is required (Tu B et al, *Ann Intern Med* 2014;161:724-732).

Coronary Angiography and PCI via Radial vs Femoral Route on Uninterrupted Oral Anticoagulation with Warfarin: Fewer Bleeds with Radial Access in PCI

Among 255 consecutive patients in whom warfarin was continued who underwent coronary angiography (INR >1.8), 97 also underwent percutaneous coronary intervention (PCI) (27% femoral vs 73% radial). No significant difference was seen in bleeds between femoral (2.8%) and radial (1.6%, $P=NS$) during coronary angiography alone. However, PCI via the femoral artery had more bleeding (19.2% vs 1.4%, $P=0.005$) and transfusions (15% vs 0%, $P=0.004$) than via the radial artery. Patients who underwent PCI using radial access were less likely to have any vascular or bleeding complications (1% vs 23%, $P=0.001$) (Baker NC et al, *Am Heart J* 2014; 168:537-544).

Important Review and Other Articles

Scientific statement from AHA/ACC against the use of ECG as a screening tool for sudden death in the young, but in favor of widespread dissemination of automatic external defibrillators in the athletic field and elsewhere (Maron BJ et al, *J Am Coll Cardiol* 2014;64:1479-1514), Expert consensus document (SCAI/AATS/ACC/STS) for transcatheter mitral valve repair (Tommaso CL et al, *J Am Coll Cardiol* 2014;64:1515-1526), Thoracic aortic aneurysm (Goldfinger

JZ et al, *J Am Coll Cardiol* 2014;64:1725-1739), Left ventricular non-compaction (Arbustini E et al, *J Am Coll Cardiol* 2014;64:1840-1850), 2014 ACC/AHA/AATS/PCNA/SCAI/STS Guideline Update for diagnosis and management of patients with stable ischemic heart disease (Fihn HD et al, *J Am Coll Cardiol* 2014;64:1929-1949), 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation (January CT et al, *J Am Coll Cardiol* 2014;64:2246-2280), Vaccine for atherosclerosis (Shah PK et al, *J Am Coll Cardiol* 2014;64:2779-2791), Post-thrombotic syndrome (Kahn SR et al, *Circulation* 2014;130:18 1636-1661), Transcatheter therapy of mitral regurgitation (Herrmann HC & Maisano F, *Circulation* 2014;130:19 1712-1722), Pulmonary hypertension (Rich JD & Rich S, *Circulation* 2014;130:20 1820-1830), Rheumatic fever (Essop MR & Peters F, *Circulation* 2014, 130:24 2181-2188), 2014 ESC Guidelines on pulmonary embolism (Konstantinides S, et al, *Eur Heart J* 2014; 35: 3033-3073), Management of antithrombotic therapy in AF patients presenting with ACS and/or undergoing PCI or valve interventions (Lip G et al, *Eur Heart J* 2014 35: 3155-3179), Acute pericarditis (LeWinter MM, *N Engl J Med* 2014;371:2410-2416), TAVI (Horne A et al, *Am Heart J* 2014;168:414-423),

Just-in (8/1/2015): the U.S. FDA approved Daiichi Sankyo's new oral anticoagulant drug, *edoxaban* (Savaysa) for patients with non-valvular atrial fibrillation, and patients with deep vein thrombosis and/or pulmonary embolism.

9/1/2015: Portola Pharmaceuticals Inc announced that its experimental drug, *andexanet alfa*, met the main goal of reversing the effect of rivaroxaban (Xarelto) and apixaban (Eliquis).