Cardiology News /Recent Literature Review / Last Quarter 2014

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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= 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

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)/ ~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 Prevail 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 ~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 ± 4.5% and logistic EuroSCORE 21.6 ± 12.3%; transfemoral approach in 64.0%). At 30 days, paravalvular regurgitation was 0 to mild in ~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 ≥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 following 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 = 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=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 Diamicron 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 revascularisation) 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 ≥20% but no stenosis ≥70%) CAD, and 20 899 patients (55%) had obstructive (any stenosis ≥70% or left main -LM stenosis ≥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-Schüpke S et al, ***JAMA*** 2014;312:1981-1987).

PROTECT AF: Percutaneous Left Atrial Appendage Closure at Least Noninferior to Warfarin for Atrial Fibrillation 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 hadd 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 (Kalantarian 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;130:1636-1661), Transcatheter therapy of mitral regurgitation (Herrmann HC & Maisano F, *Circulation* 2014;130:1712-1722), Pulmonary hypertension (Rich JD & Rich S, *Circulation* 2014;130:1820-1830), Rheumatic fever (Essop MR & Peters F, *Circulation* 2014, 130:2181-2188), 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 Hear 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).