

Cardiology News / Recent Literature Review / First Quarter 2019

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HRS Meeting: San Francisco, CA, USA, 8-11/5/2019

EuroPCR: Paris, 21-24/5/2019

ESC Meeting: Paris, 31/8-4/9/2019

TCT Meeting: San Francisco, 25-28/9/2019

HCS 40th Congress: Ioannina, 17-19/10/2019

AHA Meeting: Philadelphia, PA, USA, 16-18/11/2019

ACC Meeting: Chicago, IL, USA, 28-30/3/2020

EHRA Meeting: Vienna, 29-31/3/2020

SWEDHEART Registry: Troponinemia is not Innocent and Demands Careful Workup

Among 48,872 patients, a cardiac troponin (cTn) level >99th percentile was found in 9,800 (20.1%) patients. The prevalence of cardiovascular (CV) risk factors as well as CV and nonCV comorbidities increased across higher cTn strata. In total, 7,529 (15.4%) patients had a major adverse event (MAE), defined as the composite of all-cause mortality, MI, readmission for heart failure, or stroke over a median of 4.9 years). MAE risk was associated with higher cTn strata (hazard ratio—HR for highest assay-specific cTn tertile: 2.59; HR 3.57 in patients without CV comorbidities, renal dysfunction, LV dysfunction, or significant coronary stenosis) (Eggers KM et al, *J Am Coll Cardiol* 2019;73: 1–9).

French SCAD Study: the rs9349379 Allele of the PHACTR1/EDN1 Genetic Locus Lying on Chromosome 6q24 is the First Genetic Risk Locus for Spontaneous Coronary Artery Dissection (SCAD)

The previously reported risk allele for fibromuscular dysplasia (FMD) (rs9349379-A) was associated with a higher risk of SCAD in all studies. In a meta-analysis of 1,055 SCAD patients and 7,190 controls, the odds ratio (OR) was 1.67 per copy of rs9349379-A. In a subset of 491 SCAD patients, the OR estimate was higher for the association with SCAD in patients without FMD (OR: 1.89) than in SCAD cases with FMD (OR: 1.60). There was no effect of genotype on age at first event, pregnancy associated SCAD, or recurrence (Adlam D et al, *J Am Coll Cardiol* 2019;73:58-66).

COMPASS-CABG Study: Compared With Aspirin or Rivaroxaban Alone, the Combination of Rivaroxaban and Aspirin Did Not Prevent Early Failure of CABGs but Reduced MACE, Consistent With Outcomes in the Overall COMPASS Trial

Among 1,448 COMPASS trial patients randomized 4-14 days after CABG surgery to receive the combination of rivaroxaban plus aspirin, rivaroxaban alone, or aspirin alone, the combination of rivaroxaban and aspirin and the regimen of rivaroxaban alone did not reduce the graft failure rates compared with aspirin alone (combination vs. aspirin: 9.1% vs 8% failed grafts; odds ratio - OR: 1.13; p=0.45; rivaroxaban alone vs aspirin: 7.8% vs 8% failed grafts; OR: 0.95; p=0.75). Compared with aspirin, the combination was associated with fewer MACE (2.4% vs. 3.5%; hazard ratio-HR: 0.69; p=0.34), whereas rivaroxaban alone was not (3.3% vs 3.5%; HR: 0.99; p=0.98). There was no fatal bleeding or tamponade within 30 days of randomization (Lamy A et al, *J Am Coll Cardiol* 2019;73:121-30)

PFO closure: Durable Efficacy Against Recurrent Ischemic Events for Over a Decade

Among 201 consecutive patients (mean age: 47 ± 12 years, 51% women) who underwent successful PFO closure due to a cryptogenic embolism (76% stroke, 32% TIA, 1% systemic embolism) with 3.3% residual shunt, over a median follow-up of 12 years (range 10-17 years), 13 patients died (all from noncardiovascular causes), and nondisabling stroke and TIA occurred in 2 and 6 patients, respectively. A history of thrombophilia (15%) tended to associate with a higher rate of ischemic events at follow-up (p=0.067). Bleeding events occurred in 13 patients and were major (intracranial bleeding) in 4 patients (all of them under aspirin therapy at the time of the event). A total of 42 patients stopped the antithrombotic treatment at a median of 6 months, and none had any ischemic or bleeding episode after a mean of 10 ± 4 years following treatment cessation (Wintzer-Wehekind J et al, *J Am Coll Cardiol* 2019; 73:278-87).

French TAVI Registry: Anticoagulation Decreases Valve Dysfunction but Increases Mortality

Of 12,804 TAVI patients, 11,469 (aged 82.8±0.07 years; logistic Euroscore 17.8±0.1%; mean follow-up: 1.3 years) were alive at discharge with known antithrombotic treatment. Neither aspirin nor clopidogrel was independently associated with mortality. Male sex (adjusted hazard ratio - aHR: 1.63; p< 0.001), history of atrial fibrillation (1/3 of patients, n=3,836) (aHR: 1.41; p< 0.001), and chronic renal failure (aHR: 1.37; p< 0.001) were the strongest

independent correlates of mortality. Anticoagulation at discharge (adjusted odds ratio - aOR: 0.54; $p=0.005$) and a nonfemoral approach (aOR: 0.53; $p=0.049$) were independently associated with lower rates of bioprosthetic valve dysfunction (BVD), whereas chronic renal failure (aOR: 1.46; $p=0.034$) and prosthesis size ≤ 23 mm (aOR: 3.43; $p < 0.001$) yielded higher risk of BVD (Overtchouk P et al, *J Am Coll Cardiol* 2019;73:13-21).

Long-Term TAVI Valve Function Seems Excellent, With no Increase in Gradient or Regurgitation at a Median of 5.8 Years, up to 10 Years, With Severe Structural Valve Degeneration (SVD) Occurring in $<0.5\%$ of Patients

Among 241 patients (79.3 ± 7.5 years of age; 46% female; 149 patients (64%) treated with a self-expandable valve and 80 (34.7%) with a balloon-expandable valve), more patients had none/trivial aortic regurgitation (AR) (47.5% vs. 33%), and fewer had mild AR (42.5% vs. 57%) at follow-up ($p = 0.02$). There was 1 case (0.4%) of severe SVD (AR) 5.3 years after implantation. There were 21 cases (8.7%) of moderate SVD (mean 6.1 years post-implantation; range 4.9 to 8.6 years). Twelve of these (57%) were due to new AR and 9 (43%) to restenosis. (Blackman DJ et al, *J Am Coll Cardiol* 2019; 73:537-45).

Global Feasibility Study of Trans-Apical Mitral Valve Replacement (TMVR) in First 100 Patients: TMVR (Tendyne, Abbott) Eliminated MR in Nearly All Cases /1-Year Mortality 26% Among Survivors / Improved Functional Status and Quality of Life

In the cohort (mean age 75.4 ± 8.1 years; 69% men), there were no intraprocedural deaths, 1 instance of major apical bleeding, and no acute conversion to surgery or need for cardiopulmonary bypass. Technical success was 96%. The 30-day rates of mortality and stroke were 6% and 2%, respectively. The 1-year survival free of all-cause mortality was 72.4%, with 84.6% of deaths due to cardiac causes. Among survivors at 1 year, 88.5% were NYHA function class I/II, with improvement in 6-min walk distance ($p < 0.0001$) and quality-of-life ($p = 0.011$). (Sorajja P et al, *J Am Coll Cardiol* 2019; 73:1250-60).

First-in-Human Percutaneous Transseptal Balloon-Expandable Mitral Valve Placement in 10 Patients with Severe Mitral Regurgitation (MR) at High Surgical Risk: Feasible in All but 1 Case, and Safe at 30 Days

The new valve was implanted in 9 of 10 (90%) patients with severe MR of various etiologies (4 degenerative, 4 functional, 2 mixed). By transesophageal echo, MR was reduced to \leq trivial in all patients, and mean transmitral

gradient was 2.3 ± 1.4 mmHg. A pericardial effusion occurred in 1 patient managed with pericardiocentesis, and the device was not implanted. Median hospital stay was 1.5 days. At 30 days, there was no stroke, MI, rehospitalization, LVOT obstruction, device migration, embolization, or conversion to mitral surgery. One patient had recurrent MR due to a paravalvular leak, treated with a closure device. All other treated patients had $\leq 1+$ MR. No patients died (Webb JG et al, *J Am Coll Cardiol* 2019;73:1239-46).

PARTNER 2: TAVI is Cost-Effective vs Surgical Aortic Valve Replacement (AVR) in Patients With Severe Aortic Stenosis at Intermediate Risk for the US Healthcare System by Providing Greater Quality-Adjusted Life Expectancy and Lower Long-Term Costs than AVR if Long-Term Data Demonstrate Comparable Late Mortality With TAVI and AVR,

A total of 2032 patients were randomized to receive TAVI using the SAPIEN XT valve (XT-TAVR) or surgery (AVR) in the PARTNER 2A trial, whereas the PARTNER S3i registry included an additional 1078 patients treated with TAVI using the SAPIEN 3 valve (S3-TAVR). Although procedural costs were \approx \$20 000 higher with TAVI than AVR, total cost differences for the index hospitalization were \$2888 higher with XT-TAVR ($P=0.014$) and \$4155 lower with S3-TAVR ($P < 0.001$) due to reductions in length of stay with TAVI. Follow-up costs were lower with XT-TAVR ($\Delta = -\$9304$; $P < 0.001$) and S3-TAVR ($\Delta = -\$11 377$; $P < 0.001$) than with AVR (Baron SJ et al, *Circulation* 2019;139:877-888)

PARTNER 3: Among Patients With Severe Aortic Stenosis Who Were at Low Surgical Risk, the Rate of the Composite of Death, Stroke, or Rehospitalization at 1 Year Was Significantly Lower With TAVI With a Balloon-Expandable Valve Than With Surgery

Among 1000 randomized patients (mean age 73 years, and mean STS risk score 1.9%), the Kaplan-Meier estimate of the rate of the primary composite end point at 1 year was significantly lower in the TAVI group than in the surgery group (8.5% vs. 15.1%; absolute difference, -6.6 percentage points; $P < 0.001$ for noninferiority; hazard ratio, 0.54; $P = 0.001$ for superiority). At 30 days, TAVI resulted in a lower rate of stroke than surgery ($P = 0.02$) and in lower rates of death or stroke ($P = 0.01$) and new-onset atrial fibrillation ($P < 0.001$). TAVI also resulted in a shorter index hospitalization than surgery ($P < 0.001$) and in a lower risk of a poor treatment outcome at 30 days ($P < 0.001$). There were no significant between-group differences in major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation (Mack MJ et al, *New Engl J Med* 2019 March 16; doi: 10.1056/NEJMoa1814052).

NOTION Trial: In Patients With Severe Aortic Stenosis at Low Surgical Risk, Rate of Structural Deterioration of Valves is Greater Within the First 6 Years After Surgical AVR Than TAVI, While Rates of Valve Failure, Endocarditis, and All-Cause Mortality are Low and Similar With Both Methods

Among all-comer patients with severe aortic stenosis and lower surgical risk for mortality randomized 1:1 to TAVI (n=139) or surgical AVR (n=135), at 6 years, the rates of all-cause mortality were similar for TAVI (42.5%) and surgical AVR (37.7%) patients (p=0.58). The rate of structural valve degeneration (SVD) was higher for surgical AVR than TAVI (24.0% vs. 4.8%; p<0.001), whereas there were no differences in NonSVD (57.8% vs 54%; p=0.52) or endocarditis (5.9% vs 5.8%; p=0.95). Valve Failure rates were similar after surgical AVR and TAVI through 6 years (6.7% vs 7.5%; p=0.89) (Sondegaard L et al, *J Am Coll Cardiol* 2019;73:546-53).

STS/ACC TVT Registry: Compared With the Year Before, Non-CV Hospitalizations Increase in the Year Following TAVI / Only Hospitalizations for Heart Failure (HF) Decrease

Among 15,324 patients undergoing TAVI, (median age 84 years, the median STS score 7; 61.1% via transfemoral access), post-TAVI, HF hospitalization rates and hospitalized days were reduced compared with pre-TAVI (rate ratio: 0.87 and 0.95 respectively; p<0.01). However, all-cause, noncardiovascular (non-CV), and bleeding hospitalization rates and hospitalized days were increased (p<0.01). Post-TAVI hospitalizations were reduced the most among those with LVEF<30%. There was only modest reduction in mean post-TAVI costs among all TAVI patients and 1-year survivors (rate ratio: 0.95, p<0.01; and 0.90; p<0.01, respectively) (Vemulapalli S et al, *J Am Coll Cardiol* 2019;73:1135-46).

EVEREST II @ 1 Year: MitraClip in Secondary Mitral Regurgitation (SMR) is Associated With Acceptable Safety, Reduction of MR Severity, Symptom Improvement, and Positive Ventricular Remodeling

A total of 616 patients (482 high risk -HR, 134 non-HR; mean age, 73.3±10.5 years; STS risk, 10.2±6.9%) with SMR received the MitraClip. At baseline, 80.5% of patients were in NYHA class III/IV. Major adverse events at 30 days included death (3.6%), stroke (2.3%), and renal failure (1.5%). At discharge, 88.8% had MR ≤2+. At 1 year, there were 139 deaths, and freedom from mortality was 76.8%. The majority (84.7%) remained with MR ≤2+ and NYHA class I/II (83.0%). Survival at 1 year was

74.1% in HR patients and 86.4% in non-HR patients (P=0.0175). At 1 year, both groups achieved comparable MR reduction (MR ≤2+, 84% vs 87%) and improvement in LV end-diastolic volume (-8.0 mL vs -12.7 mL), whereas NYHA class I/II was found in 80.1% vs 91.8% (P=0.008) of HR and non-HR patients, respectively. In HR patients, the annualized rate of heart failure hospitalizations decreased from 0.68 to 0.46 in the year before to the year after the procedure (P<0.0001) (Ailawadi G et al, *Circulation* 2019;139:37-47).

Fingesture Study/Sudden Cardiac Death (SCD) in Women: Women More Likely to Experience Nonischemic SCD Than Men, With Primary Myocardial Fibrosis (PMF) a More Common Cause of Death Among Women Than in Men

In a cohort of 5869 subjects with SCD, women were older when SCD occurred (70.1±13.1 vs 63.5±11.8 years, P<0.001), and ECGs of females were more likely to be normal than males (22.2% vs 15.3% in men, P<0.001), except for LVH which was more common in women (8.2% vs 4.9%, P=0.036). A normal ECG was even more common among nonischemic females with SCD (27.8% vs 16.2% in men, P=0.009). The most frequently identified cause of death was ischemic heart disease in both sexes: 71.7% vs 75.7%; P=0.005. In contrast, women were more likely to have nonischemic cause of SCD than men (28.3% vs 24.3%, P=0.005). The prevalence of primary myocardial fibrosis (PMF) was higher among women (5.2%) than in men (2.6%; P<0.001) (Haukilahti MAE et al, *Circulation* 2019;139:1012-21).

Cardiac Amyloidosis (CA): In Patients With CA and Atrial Tachyarrhythmias Referred for Cardioversion, the Incidence of Atrial Appendage Thrombus is High Even Among Those who Have Received Anticoagulants

CA patients (n=58, mean age 69 ± 9 years, 81% male) had a significantly higher cardioversion (DCCV) cancellation rate (28% vs. 7%; p<0.001) compared with control patients, mainly due to intracardiac thrombus identified on transesophageal echocardiogram (TEE) (13 of 16 or 81% vs 2 of 8 or 25%; p=0.02); 4 of 13 of the CA patients (31%) with intracardiac thrombus on TEE received adequate anticoagulation ≥3 weeks and another 2 of 13 (15%) had arrhythmia duration <48 h. DCCV success rate (90% vs 94%; p=0.4) was not different. Procedural complications were more frequent in CA vs controls (6 of 42 or 14% vs 2 of 106 or 2%; p=0.007); complications in CA included ventricular arrhythmias in 2 and severe bradyarrhythmias requiring pacemaker implantation in 2. The only complication in the control group was self-limited bradyarrhythmias (El-Am EA et al et al, *J Am Coll Cardiol* 2019;73:589-97).

PRECISE-DAPT: The Risk of Bleeding Rather Than Ischemic Risk Should Determine the Duration of DAPT After PCI / Prolonging DAPT is Associated With a Reduction in Ischemic Events in Patients Undergoing Complex PCI Who are not at High Bleeding Risk (HBR), But Confers No Benefit in Those at HBR, Regardless of PCI Complexity

Among 14,963 patients from 8 RCTs, 3,118 underwent complex PCI and had a higher rate of ischemic, but not bleeding, events. Long-term DAPT in non-HBR patients reduced ischemic events in both complex and noncomplex PCI strata, but not among HBR patients, regardless of complex PCI features. The bleeding risk according to the TIMI scale was increased by long-term DAPT only in HBR patients, regardless of PCI complexity (Costa F et al, *J Am Coll Cardiol* 2019;73: 741-54).

In an Animal Model, Serial Magnetic Resonance Imaging May Identify Early Stages of Anthracycline-Induced Cardiotoxicity

T₂ mapping during treatment identifies intracardiomyocyte edema generation as the earliest marker of anthracycline-induced cardiotoxicity, in the absence of T₁ mapping, extracellular volume, or LV motion defects. The occurrence of these changes at a reversible disease stage shows the clinical potential of this CMR marker for tailored anthracycline therapy (Galán-Arriola C et al, *J Am Coll Cardiol* 2019;73:779–91).

Observational Data Suggest that NOACs May be Effective for Prevention of Thromboembolism in Patients With Mitral Stenosis and Atrial Fibrillation

Among 2,230 AF patients with mitral stenosis (MS) (mean age 69.7 ± 10.5 years; 31% males) receiving oral anticoagulants (propensity score matched; n=1115 in each group), thromboembolic events occurred at a rate of 2.22%/y in the NOAC group, and 4.19%/y in the warfarin group (adjusted hazard ratio-HR for NOAC: 0.28). Intracranial hemorrhage occurred in 0.49% of the NOAC group and 0.93% of the warfarin group (HR for DOAC: 0.53) (Kim JY et al *J Am Coll Cardiol* 2019;73:1123-31).

Large Noncortical or Cortical Infarcts (LNCCIs) in AF Patients Even in Anticoagulated Patients: Most Brain Infarcts Observed are Clinically Silent & Associated With Worse Cognitive Function, Raising the Question of MRI Screening in AF Patients

Among 1,737 AF patients (age of 73 ± 8 years; 28% women, 90% taking oral anticoagulant agents), on MRI, LNCCIs were found in 387 patients (22%), small infarcts in 368 (21%), microbleeds in 372 (22%), and white matter lesions in 1715 (99%). Clinically silent infarcts among the 1,390 patients without a history of stroke or TIA were

found in 201 patients with LNCCIs (15%) and 245 patients with small infarcts (18%). The cognitive testing score was 24.7 ± 3.3 in patients with and 25.8 ± 2.9 in those without LNCCIs (p< 0.001); the difference in score remained similar when only clinically silent LNCCIs were considered (24.9 ± 3.1 vs. 25.8 ± 2.9; p< 0.001). In a multivariable regression model including all vascular brain lesion parameters, LNCCI volume was the strongest predictor of reduced cognition (p< 0.001) (Conen D et al, *J Am Coll Cardiol* 2019;73:989-99).

PRIME Study: Among Patients With Secondary Functional Mitral Regurgitation (MR), Sacubitril/Valsartan Reduced MR to a Greater Extent Than did Valsartan

Among 118 patients with heart failure with chronic functional MR secondary to left ventricular (LV) dysfunction randomly assigned to receive either sacubitril/valsartan or valsartan, in addition to standard medical therapy for heart failure, the decrease in effective regurgitant orifice area was significantly greater in the sacubitril/valsartan group than in the valsartan group (P=0.032) in an intention-to-treat analysis including 117 (99%) patients. Regurgitant volume was also significantly decreased in the sacubitril/valsartan group in comparison with the valsartan group (P=0.009). There was no significant difference in the change of blood pressure between the treatment groups, and 7 patients (12%) in the sacubitril/valsartan group and 9 (16%) in the valsartan group had ≥1 serious adverse events (P=0.54) (Kang D-H et al, *Circulation* 2019;139:1354–1365).

Takotsubo Syndrome (TTS) Registry: Cardiogenic Shock Occurs in 10% and Portends a Worse Prognosis

Of 2078 patients with TTS, 198 (9.5%) had cardiogenic shock (CS) (age 63.4±14.9 y vs 67.2±12.6 y, P<0.001 and more males 14.1% vs 9.3%, p=0.027, than those without CS). Patients with CS more often had physical triggers (66.7% vs 33%, p<0.001), and less often emotional triggers (10.6% vs 31.7%, p<0.001). Apical TTS occurred more often in patients with CS (80.3% vs 70.2%, p<0.001). AF (13.1% vs 5.7%, p<0.001) and lower LVEF (32.7 ± 11.5% vs 41.6±11.3%, p<0.001) were detected more frequently in patients with CS. Patients with CS had a higher prevalence of major CV risk factors, e.g. diabetes (21% vs 14.8%, p=0.023) and smoking (27.4% vs 19.3%, p=0.010). Neurologic disorders were more prevalent in patients with CS (31.7% vs 23.4%, p=0.013). Apical TTS (odds ratio-OR, 1.68; p=0.007), physical stress (OR, 2.84; p<0.001), LVEF <45% (OR, 2.49; p<0.001), diabetes (OR, 1.50; p=0.049), and AF on admission (OR, 2.03; p=0.007) were independently associated with CS. Patients with CS had a higher rate of in-hospital (23.5% vs 2.3%, p<0.001)

and 60-day ($p<0.001$) mortality. Patients with CS who received mechanical support ($n=39$) with intraaortic balloon ($n=39$), Impella ($n=1$), and/or ECMO ($n=1$), had a lower in-hospital mortality than those without mechanical support (12.8% vs 28.3%, $p=0.046$) (Di Vece D et al, *Circulation* 2019;139: 413-5).

ECG Monitoring of Emergency Room (ER) Patients with Syncope: Serious Arrhythmia Was Often Identified Within the First 2h of ER Arrival for CSRS* Low-Risk Patients and Within 6h for CSRS Medium- and High-Risk Patients/ Outpatient Rhythm Monitoring for 15 Days for Selected Medium-Risk Patients and All High-Risk Patients Discharged from the Hospital Should be Considered

Among 5581 patients (mean age, 53.4 years; 54.5% females; 11.6% hospitalized) presenting within 24 h of syncope in the emergency room (ER), 417 patients (7.5%) experienced serious outcomes, 207 of which (3.7%) were arrhythmic (161 arrhythmias, 30 cardiac device implantations, 16 unexplained deaths). Overall, 4123 (73.9%) were classified as CSRS* low risk, 1062 (19%) medium risk, and 396 (7.1%) high risk. The CSRS accurately stratified subjects as low risk (0.4% risk for 30-day arrhythmic outcome), medium risk (8.7% risk), and high risk (25.3% risk). One-half of arrhythmic outcomes were identified within 2 hours of ER arrival in low-risk patients and within 6 h in medium- and high-risk patients, and the residual risk after these cut points were 0.2% for low-risk, 5% for medium-risk, and 18.1% for high-risk patients. Overall, 91.7% of arrhythmic outcomes among medium- and high-risk patients, including all ventricular arrhythmias, were identified within 15 days. None of the low-risk patients experienced ventricular arrhythmia or unexplained death, whereas 0.9% of medium-risk patients and 6.3% of high-risk patients experienced them ($P<0.0001$) (Thiruganasambandamoorthy V et al, *Circulation* 2019;139:1396–1406).

* **Canadian Syncope Risk Score (CSRS)** / The 9 predictors and their associated point values: ER diagnosis of *vasovagal syncope*, **minus 2**; predisposition to *vasovagal* symptoms, **minus 1**; abnormal *QRS* axis, *QRS* duration >130 ms, and *history of heart disease*, **plus 1** each; any *systolic BP* recorded in the ER of <90 mm Hg or >180 mm Hg, elevated *troponin* level, *QTc* >480 ms, and ER diagnosis of *cardiac syncope*, **plus 2** each / Low risk: -3 to 0; medium: 1-3; high: 4-5; very high: 6-11.

P₂-CHA₂DS₂-VASc is a Better Prediction Tool for AF-Related Ischemic Stroke than CHA₂DS₂-VASc: Abnormal P-Wave Axis-an ECG Correlate of Left Atrial Abnormality- Improves Stroke Prediction in AF

Among 2229 participants from the ARIC study and 700 participants from MESA with incident AF who were not

on anticoagulants within 1 year of AF diagnosis, abnormal P-wave axis was associated with increased ischemic stroke risk (hazard ratio, 1.84) independent of CHA₂DS₂-VASc variables, and resulted in meaningful improvement in stroke prediction. The β estimate was approximately twice that of the CHA₂DS₂-VASc variables, and thus abnormal P-wave axis was assigned 2 points to create the P₂-CHA₂DS₂-VASc score. This improved the C-statistic from 0.60 to 0.67 in ARIC and 0.68 to 0.75 in MESA (validation cohort). In ARIC and MESA, the categorical net reclassification improvements were 0.25 and 0.51, respectively, and the relative integrated discrimination improvements were 1.19 and 0.82, respectively (Maheshwari A et al, *Circulation* 2019;139:180–191).

Noninvasive Electrophysiology-Guided Cardiac Radioablation: Reduced Ventricular Arrhythmia Burden With Modest Short-Term Risks/Reduced Antiarrhythmic Drug Use/Improved Quality of Life

Among 19 patients submitted to radioablation (17 VT, 2 for PVC-cardiomyopathy; median ablation time 15.3 min), over 3 months, 2/19 patients (10.5%) had a treatment-related adverse event. The median number of VT episodes was reduced from 119 to 3 ($p<0.001$). Reduction was observed for both ICD shocks and anti-tachycardia pacing. VT episodes or PVC burden were reduced in 17/18 evaluable patients (94%). The frequency of VT episodes or PVC burden was reduced by 75% in 89% of patients. Survival was 89% at 6 and 72% at 12 months. Use of dual antiarrhythmic drugs decreased from 59% to 12% ($p=0.008$). Quality of life improved at 6 months (Robinson CG et al, *Circulation* 2019;139:313–21).

Meta-Analysis: Catheter Ablation of AF in HF Patients was Superior to Drug Therapy in Improving Mortality, HF Hospitalizations, LVEF, 6-Minute Walk Test Distance, Vo₂max, and Quality of Life, with no Significant Increase in Adverse Events.

In 6 RCTs involving 775 HF patients, compared with drug therapy, AF ablation reduced all-cause mortality (9.0% vs 17.6%; risk ratio-RR, 0.52) and HF hospitalizations (16.4% vs 27.6%; RR, 0.60). Ablation improved LVEF (mean difference, 6.95%), 6-minute walk test distance (mean difference, 20.93 m), peak oxygen consumption (Vo₂max) (mean difference, 3.17 mL/kg per minute), and quality of life (mean difference in Minnesota Living with Heart Failure Questionnaire score, -9.02 points). Serious adverse events were more common in the ablation groups, although differences between the ablation and drug therapy groups were not statistically significant (7.2% vs 3.8%; RR, 1.68) (Turagam MK et al, *Ann Intern Med* 2019;170:41-50).

IABP-SHOCK II: IABP Had no Effect on All-Cause Mortality at 6-Year Follow-Up / Mortality is Still Very High, With 2/3 Dying Despite Revascularization

Follow-up was performed 6.2 years after initial randomization and was completed for 591 of 600 patients (98.5%). Mortality was not different between the IABP and the control group (66.3% vs 67%; relative risk, 0.99; $P=0.98$). There were also no differences in recurrent MI, stroke, repeat revascularization, or rehospitalization for cardiac reasons (all $P>0.05$). Survivors' quality of life and the NYHA class did not differ between groups (Thiele H et al, *Circulation* 2019;139:395–403).

APOLLO Study: Patisiran May Halt or Reverse the Progression of Cardiac Manifestations of Hereditary Transthyretin-Mediated Amyloidosis (hATTR)

Patients with hATTR were randomized 2:1 to IV 0.3 mg/kg patisiran or placebo every 3 weeks for 18 months. In the cardiac subpopulation ($n=126$), patisiran reduced mean LV ($p=0.017$), septal, posterior, and relative wall thickness at month 18. Patisiran also led to increased end-diastolic volume (8.3 ± 3.9 mL, $p=0.036$), decreased global longitudinal strain ($-1.4\pm 0.6\%$, $p=0.015$), and increased cardiac output (0.38 ± 0.19 L/min, $p=0.044$) compared with placebo at month 18. It lowered NT-proBNP at 9 and 18 months ($p<0.001$). At a median of 18.7 months, patisiran reduced the rates of cardiac hospitalizations and all-cause death (10.1 vs 18.7 per 100 patient-years; hazard ratio, 0.54) (Solomon SD et al, *Circulation* 2019;139:431–43)

Influenza Vaccination in Heart Failure (HF) Patients: Reduces Risk of All-Cause and Cardiovascular (CV) Death / Frequent Vaccination and Vaccination Earlier in the Year Confers Larger Reductions

Among HF patients ($n=134,048$) over a median of 3.7 years, with vaccination coverage ranging from 16% to 54%, after adjustment for inclusion date, comorbidities, medications, income, and education level, receiving ≥ 1 vaccinations conferred an 18% reduced risk of death (all-cause: hazard ratio-HR, 0.82; $p<0.001$; CV causes: HR, 0.82; $p<0.001$). Annual vaccination, vaccination early in the year (September to October), and greater cumulative number of vaccinations were associated with larger reductions in the risk of death compared with intermittent vaccination (Modin D et al, *Circulation* 2019; 139:575-86)

REDUCE-IT: In Patients With High Triglycerides Despite Use of Statins, the Risk of Ischemic Events, Including CV Death, was Lower in Those Who Received 2 g of Icosapent Ethyl bid Than Those Who Received Placebo

A total of 8179 patients with established CV disease or diabetes and other risk factors, who had been on statin

therapy and who had a fasting triglyceride level of 135-499 mg/dl and a LDL cholesterol level of 41-100 mg/dl were randomly assigned to receive 2 g of icosapent ethyl bid (total daily dose, 4 g) or placebo (70.7% for secondary prevention of CV events) and were followed for a median of 4.9 years. A primary end-point event (composite of CV death, MI, stroke, coronary revascularization, or unstable angina) occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22% in the placebo group (hazard ratio-HR, 0.75; $P<0.001$); the corresponding rates of the key secondary end point (composite of CV death, MI, or stroke) were 11.2% and 14.8% (HR, 0.74; $P<0.001$). The rates of additional ischemic end points were lower in the icosapent ethyl group than in the placebo group, including the rate of CV death (4.3% vs 5.2%; HR, 0.80; $P=0.03$). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs 2.1%, $P=0.004$). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group ($P=0.06$) (Bhatt DL et al, *N Engl J Med* 2019; 380:11-22).

CLEAR Harmony Trial: Over 52 Weeks, Bempedoic Acid Added to Maximally Tolerated Statin Therapy did not Lead to a Higher Incidence of Overall Adverse Events Than Placebo and Led to Lower LDL Levels

Among 2230 patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both on maximally tolerated statin therapy and $LDL\geq 70$ mg/dl (mean 103.2 ± 29.4 mg/dl), of whom 1488 were randomized to bempedoic acid and 742 to placebo, the incidence of adverse events (78.5% in the bempedoic acid group and 78.7% in the placebo group) and serious adverse events (14.5% and 14%, respectively) did not differ substantially between the two groups during the intervention period, but the incidence of adverse events leading to discontinuation of the regimen was higher in the bempedoic acid group than in the placebo group (10.9% vs 7.1%), as was the incidence of gout (1.2% vs 0.3%). At week 12, bempedoic acid reduced the mean LDL cholesterol level by 19.2 mg/dl, representing a change of -16.5% from baseline (difference vs. placebo in change from baseline, -18.1 percentage points; $P<0.001$). Safety and efficacy findings were consistent, regardless of the intensity of background statin therapy (Ray KK et al, *N Engl J Med* 2019;380:1022-32).

ODYSSEY Outcomes: The Price of Alirocumab Would Have to be Reduced Drastically to be Cost-Effective

Compared with a statin alone, the addition of ezetimibe cost \$81,000 per QALY. Compared with a statin alone, the addition of alirocumab cost \$308,000 per QALY. Compared with the combination of statin and

ezetimibe, replacing ezetimibe with alirocumab cost \$997,000 per QALY. The price of alirocumab would have to decrease from its original cost of \$14,560 to \$1974 annually to be cost-effective relative to ezetimibe (Kazi DS et al, *Ann Intern Med* 2019;170:221-229).

FOURIER Trial: Higher Lipoprotein(a) - Lp(a) Levels are Associated with Increased Risk of CV Events in Patients with CV Disease Irrespective of LDL Cholesterol / Evolocumab Reduced Lp(a) Levels, and Patients With Higher Baseline Lp(a) Experienced Greater Absolute Reductions in Lp(a) and Tended to Derive Greater Benefit from PCSK9 Inhibition

The median baseline Lp(a) concentration was 37 nmol/L. In the placebo arm, patients with baseline Lp(a) in the highest quartile had a higher risk of CAD death, MI, or urgent revascularization (adjusted hazard ratio quartile 4: quartile 1, 1.22) independent of LDL cholesterol. At 48 weeks, evolocumab reduced Lp(a) by a median of 26.9%. The percent change in Lp(a) and LDL cholesterol at 48 weeks in patients taking evolocumab was moderately positively correlated ($r=0.37$; $p<0.001$). Evolocumab reduced the risk of CAD death, MI, or urgent revascularization by 23% (hazard ratio-HR, 0.77) in patients with a baseline Lp(a) >median, and by 7% (HR, 0.93; p interaction=0.07) in those \leq median. Coupled with the higher baseline risk, the absolute risk reductions, and number needed to treat over 3 years were 2.49% and 40 vs 0.95% and 105, respectively (O'Donoghue ML et al, *Circulation* 2019;139:1483-92).

VITAL Trial: Supplementation With Vitamin D or ω -3 Fatty Acids did not Result in a Lower Incidence of Cancer or Cardiovascular Events Than Placebo

Among 25,871 individuals (men \geq 50 years/ women \geq 55 years) randomized to vitamin D₃ (cholecalciferol) (2000 IU/d) and ω -3 fatty acids (1 g/d), supplementation with vitamin D or ω -3 fatty acids was not associated with a lower risk of either of the primary end points (cancer of any type and major cardiovascular - CV events) during a median follow-up of 5.3 years. No excess risks of hypercalcemia or other adverse events were identified with vitamin D and no excess risks of bleeding or other serious adverse events were observed with ω -3 free fatty acids. (Manson JF et al, *N Engl J Med* 2019; 380:33-44 & 23-32).

CARMELINA: In Patients With Type 2 Diabetes and Cardiovascular (CV) Disease and/or Kidney Disease, Linagliptin did not Affect the Risk of Heart Failure (HF) Hospitalization (hHF) or Other Selected HF-Related Outcomes

Among 6979 participants (mean age, 65.9 years; eGFR, 55 mL/min per 1.73m²; hemoglobin A1c, 8%;

62.9% men), including 1873 (26.8%) with a history of HF at baseline, over a median of 2.2 years, linagliptin vs placebo did not affect the incidence of hHF (6% vs 6.5%, respectively; hazard ratio -HR, 0.90), the composite of CV death/hHF (HR, 0.94), or risk for recurrent hHF events (326 vs 359 events, respectively; rate ratio, 0.94) (Sharma A et al, *Circulation* 2018;138:1666-1676).

DECLARE-TIMI 58: In Patients With Type 2 Diabetes Who Had or Were at Risk for Atherosclerotic Cardiovascular (CV) Disease (CVD), Treatment With Dapagliflozin did not Change MACE Rate vs Placebo But Did Result in a Lower Rate of CV Death or Heart Failure (HF) Hospitalization, Reflecting a Lower Rate of HF Hospitalization

Among 17,160 patients, including 10,186 without atherosclerotic CVD, followed for a median of 4.2 years, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (upper boundary of the 95% confidence interval, <1.3; $P<0.001$ for noninferiority). In the two primary efficacy analyses, dapagliflozin did not result in a lower rate of MACE (8.8% vs 9.4%; hazard ratio-HR, 0.93; $P=0.17$) but did result in a lower rate of CV death or HF hospitalization (4.9% vs. 5.8%; HR, 0.83; $P=0.005$), which reflected a lower rate of HF hospitalization (HR, 0.73); there was no between-group difference in CV death (HR, 0.98). A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (HR, 0.76), and death from any cause occurred in 6.2% and 6.6%, respectively (HR, 0.93). Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs 0.1%, $P=0.02$), as was the rate of genital infections that led to discontinuation of the regimen or that were considered to be serious adverse events (0.9% vs 0.1%, $P<0.001$) (Wiviott SD et al, *N Engl J Med* 2019; 380:347-357).

EMPA-REG OUTCOME Trial: Empagliflozin Reduced Mortality and Hospitalization for Heart Failure Across the Spectrum of Cardiovascular Risk

Of 7020 patients who received empagliflozin, 65% had a prior MI or stroke, 12% were at low, 40% at intermediate, 30% at high, and 18% were at highest cardiovascular (TIMI) risk. In the placebo group, 3-point MACE occurred during the trial in 7.3%, 9.4%, 12.6%, and 20.6% of patients at low, intermediate, high, and highest estimated baseline risk, respectively. Relative reductions in risk of CV death, all-cause mortality, 3-point MACE and hospitalization for heart failure with empagliflozin vs placebo were consistent in patients with and without prior MI and/or stroke and across subgroups by TIMI Risk Score at baseline ($P>0.05$) (Fitchett D et al, *Circulation* 2019; 139:1384-1395).

Meta-Analysis: SGLT2 Inhibitors (SGLT2i) Have Moderate Benefits on Major Adverse CV Events (MACE) Confined to Patients With Established Atherosclerotic CV Disease (CVD) / They Also Have Robust Benefits on Reducing Hospitalization for Heart Failure (HF) and Progression of Renal Disease Regardless of Existing CVD or a History of HF

Data from 3 trials (EMPA-REG, CANVAS, and DECLARE-TIMI 58) and 34,322 patients (60.2% with established atherosclerotic CVD), with 3342 MACE, 2028 CV deaths or HF hospitalization, and 766 renal composite outcomes, indicated that SGLT2i reduced MACE by 11% (HR 0.89, $p=0.0014$), with benefit only seen in patients with CVD (HR 0.86) and not in those without (HR 1.00, p for interaction= 0.0501). SGLT2i reduced the risk of CV death or HF hospitalization by 23% (HR 0.77, $p<0.0001$), with a similar benefit in patients with and without CVD and with and without a history of HF. SGLT2i reduced the risk of progression of renal disease by 45% (HR 0.55, $p<0.0001$), with a similar benefit in those with and without CVD. The magnitude of benefit of SGLT2i varied with baseline renal function, with greater reductions in HF hospitalizations (p for interaction= 0.0073) and lesser reductions in progression of renal disease (p for interaction = 0.0258) in patients with more severe kidney disease at baseline (Zelniker TA et al, *Lancet* 2019;393:31-39).

CASSINI Trial: In High-Risk Ambulatory Patients With Cancer, Rivaroxaban Did Not Result in a Lower Incidence of VTE or Death Due to VTE Over 6-Months / However, During the Pre-specified Intervention Period, Rivaroxaban Led to a Lower Incidence of Such Events, With a Low Incidence of Major Bleeding

Among 841 high-risk ambulatory patients with cancer (Khorana score of ≥ 2), randomized to rivaroxaban (10 mg) or placebo daily for up to 3 months, the primary end point (composite of DVT in a lower limb, pulmonary embolism, symptomatic DVT in an upper limb or distal DVT in a lower limb, and death from VTE) occurred in 6% (rivaroxaban) vs 8.8% (placebo) (hazard ratio-HR, 0.66; $P=0.10$). In the prespecified intervention-period (first receipt of trial agent to last dose plus 2 days) analysis, the primary end point occurred in 2.6% vs 6.4% (HR, 0.40). Major bleeding occurred in 2% vs 1% (HR, 1.96) (Khorana AA et al, *N Engl J Med* 2019; 380:720-728).

AVERT Trial: Apixaban Conferred a Lower Rate of Venous Thromboembolism Than Did Placebo Among Intermediate-To-High-Risk Ambulatory Patients With Cancer Who Were Starting Chemotherapy, Albeit with a Higher Rate of Major Bleeding Episodes

An RCT assessed the efficacy and safety of apixaban (2.5 mg bid) for thromboprophylaxis in ambulatory

patients with cancer who were at intermediate-to-high risk for venous thromboembolism (VTE) (Khorana score, ≥ 2) and were initiating chemotherapy. Of the 574 patients who underwent randomization, 563 were included in the modified intention-to-treat analysis. Over 6 months, VTE occurred in 4.2% in the apixaban group and in 10.2% in the placebo group (hazard ratio-HR, 0.41; $P<0.001$). In the modified intention-to-treat analysis, major bleeding occurred in 3.5% vs 1.8% (HR, 2.00; $P=0.046$). During the treatment period, major bleeding occurred in 2.1 vs 1.1% (HR, 1.89) (Carrier M et al, *New Engl J Med* 2019; 380:711-719).

PIONEER-HF: Among Patients With Heart Failure (HF) With Reduced Ejection Fraction (HFrEF) Who Were Hospitalized for Acute Decompensated HF, Initiation of Sacubitril–Valsartan Led to a Greater Reduction in NT-ProBNP Than Enalapril with Similar Rates of Worsening Renal Function, Hyperkalemia, Symptomatic Hypotension, and Angioedema

Among 881 HFrEF patients randomized to sacubitril–valsartan (target dose 97/103 mg, $n=440$) or enalapril (target dose 10 mg bid, $n=441$), the time-averaged reduction in the NT-proBNP was greater in the sacubitril–valsartan group; the ratio of the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53 vs 0.75 (percent change, -46.7% vs -25.3% ; ratio of change, 0.71; $P<0.001$). The greater reduction in the NT-proBNP concentration with sacubitril–valsartan was evident as early as week 1 (ratio of change, 0.76). The rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ between the two groups (Velazquez EJ et al, *N Engl J Med* 2019; 380:539-548).

POET: In Patients With Left-Sided Endocarditis Who Were in Stable Condition, Changing to Oral Antibiotic Treatment Was Noninferior to Continued Intravenous (IV) Antibiotic Treatment

Among 400 adults in stable condition who had left-sided endocarditis caused by streptococcus, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci and who were being treated with IV antibiotics for at least 10 days and then randomized to continue IV treatment (199 patients) or to switch to oral antibiotic treatment (201 patients), who finally completed treatment after a median of 19 days (IV group) vs 17 days (oral group), the primary composite outcome (all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia) occurred in 24 patients (12.1%) in the intravenous group and in 18 (9%) in the oral group (between-group difference, 3.1 percentage points;

P=0.40), which met noninferiority criteria (Iversen K et al, *N Engl J Med* 2019; 380:415-424).

TRED-HF: Patients Who Have Recovered from Dilated Cardiomyopathy (DCM) Will Relapse Following Treatment Withdrawal / Until Robust Predictors of Relapse are Defined, Treatment Should Continue Indefinitely

Of 51 patients with DCM, 25 were randomly assigned to the treatment withdrawal group and 26 to continue treatment. Over the first 6 months, 11 (44%) patients had a relapse compared with none of those assigned to continue treatment (Kaplan-Meier estimate of event rate 45.7%; p=0.0001). After 6 months, 25 (96%) of 26 patients assigned initially to continue treatment attempted withdrawal. During the following 6 months, 9 patients had a relapse (Kaplan-Meier estimate of event rate 36%). No deaths were reported in either group (Halliday BP, *Lancet* 2019;393(10166):61-73).

Meta-Analysis: Statin Therapy Produces Significant Reductions in Major Vascular Events Irrespective of Age, But There is Less Direct Evidence of Benefit Among Patients Older Than 75 Years Who Do Not Already Have Evidence of Occlusive Vascular Disease

A total of 14,483 (8%) of 186,854 participants in 28 statin trials were older than 75 years. Over a median of 4.9 years, statin therapy produced a 21% proportional reduction in major vascular events per 1.0 mmol/L reduction in LDL cholesterol. A significant reduction was observed in major vascular events in all age groups. Proportional reductions in major vascular events diminished slightly, albeit not statistically, with age. Overall, statin or more intensive therapy yielded a 24% proportional reduction in major coronary events per 1.0 mmol/L reduction in LDL cholesterol, and with increasing age, a trend was observed towards smaller proportional risk reductions. There was a 25% proportional reduction in the risk of coronary revascularization procedures with statin therapy per 1.0 mmol/L lower LDL cholesterol, similar across age groups. There were similar proportional reductions in stroke of any type across age groups. There were smaller proportional risk reductions with increasing age. The proportional reduction in major vascular events was similar, irrespective of age, among patients with pre-existing vascular disease, but appeared smaller among older than among younger individuals not known to have vascular disease. A 12% proportional reduction was observed in vascular mortality, with a trend towards smaller proportional reductions with older age, which did not persist after exclusion of the heart failure or dialysis trials. Statin therapy had no effect at any age on non-

vascular mortality, cancer death, or cancer incidence (Cholesterol Treatment Trialists, *Lancet* 2019;393:407-415).

Predicting ~1% Median 5-Year Bleeding Risk to Guide Aspirin Use for the Primary Prevention of Cardiovascular Disease (CVD)

In a study cohort comprising 385,191 persons aged 30-79 years whose CVD risk was assessed, during 1,619,846 person-years of follow-up, 4442 persons had major bleeding events (of which 7% were fatal). The main models predicted a median 5-year bleeding risk of 1% in women and 1.1% in men. Plots of predicted-against-observed event rates showed good calibration throughout the risk range (Selak V et al, *Ann Intern Med* 2019;170:357-368).

Important Review and Other Articles

- **Electric car** EMI in patients with CIEDs (Turagam MK et al, *J Am Coll Cardiol* 2019;73:210-3)
- Use of medication for cardiovascular disease during **pregnancy** (Halpern DG et al, *J Am Coll Cardiol* 2019;73:457-76)
- 2018 AATS/ACC/SCAI/STS Expert Consensus Systems of Care Document: Operator and Institutional Recommendations and Requirements for **TAVI** (Bavaria JE et al, *J Am Coll Cardiol* 2019;73:340-74)
- **AF** and cognitive function (Diener H-C et al, *J Am Coll Cardiol* 2019;73:612-19)
- **HFpEF** and diabetes (McHugh K et al, *J Am Coll Cardiol* 2019;73:602-11)
- **Lyme** carditis (Yeung C & Baranchuk A, *J Am Coll Cardiol* 2019;73:717-26)
- Non-alcoholic **fatty liver disease** and the heart (Stahl EP et al, *J Am Coll Cardiol* 2019;73:948-63)
- **Anticoagulation** in cancer patients (Mosarla RC et al, *J Am Coll Cardiol* 2019;73:1336-49)
- Postural orthostatic tachycardia syndrome (**POTS**) (Bryarly M et al, *J Am Coll Cardiol* 2019;73:1207-28)
- **Autonomic nervous system** dysfunction (Goldberger JJ et al, *J Am Coll Cardiol* 2019;73:1189-206)
- **Cardio-Oncology**: vascular & metabolic perspectives (Campia U et al, *Circulation* 2019;139:e579-e602)
- Mitochondrial dysfunction in **HFpEF** (Kumar AA et al, *Circulation* 2019;139:1435-1450)
- Acute infection and **MI** (Musher DM et al, *N Engl J Med* 2019; 380:171-176)