

Cardiology News / Recent Literature Review / Last Quarter 2019

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HCS Working Groups: Thessaloniki, 20-22/2/2020

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

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

HRS Meeting: San Diego, 6-9/5/2020

EuroPCR: Paris, 19-22/5/2020

ESC Meeting: Amsterdam, 29/8-2/9/2020

Childhood Secondhand Smoke Exposure Predicts Increased Risk for Adulthood Atrial Fibrillation (AF) After Adjustment for AF Risk Factors

A study analyzed Framingham Offspring cohort participants with parents in the Original cohort with known smoking status during the offspring's childhood, evaluated every 2-8 years and being under routine surveillance for incident AF. Of 2,816 Offspring cohort participants with at least 1 parent in the Original cohort, 82% were exposed to parental smoking. For every pack/day increase in parental smoking, there was an 18% increase in offspring AF incidence (adjusted hazard ratio - HR: 1.18; $p=0.04$). Additionally, parental smoking was a risk factor for offspring smoking (adjusted odds ratio - OR: 1.34; $p<0.001$). Offspring smoking mediated 17% of the relationship between parental smoking and offspring AF (Groh CA et al, *J Am Coll Cardiol* 2019; 74:1658-64).

When Left Untreated, Severe Aortic Stenosis (AS) is Associated With Poor Long-Term Survival / But Also Moderate AS Confers Poor Survival Rates

Among 16,129 (6.7%), 3,315 (1.4%), and 6,383 (2.6%) patients had mild, moderate, and severe AS, respectively, on an adjusted basis (vs. no AS; 5-year mortality 19%), patients with mild to severe AS had an increasing risk of long-term mortality (adjusted hazard ratio: 1.44-2.09; $p<0.001$ for all comparisons). The 5-year mortality was 56% and 67%, respectively, in those with moderate AS (mean gradient 20.0-39.0 mmHg/peak velocity 3.0-3.9 m/s) and severe AS (≥ 40 mmHg, ≥ 4 m/s, or AV area <1 cm² in low-flow, low-gradient severe AS). A markedly increased risk of death from all causes (5-year mortality $>50\%$) and CV disease was evident from a mean AV gradient >20 mmHg (moderate AS) after adjusting for age, sex, LV systolic or diastolic dysfunction, and aortic

regurgitation (Strange G et al, *J Am Coll Cardiol* 2019; 74:1851-63).

Premature (Age ≤ 45 Years) Acute or Stable Obstructive Coronary Artery Disease (CAD) is an Aggressive Disease Despite the Currently Recommended Prevention Measures, With High Rates of Recurrent Events and Mortality

Among 880 patients with premature CAD, aged 40.1 ± 5.7 years, mainly men, smokers, with a family history of CAD or hypercholesterolemia, at baseline presentation, 91% underwent coronary revascularization, predominantly for acute MI (79%). Over 20 years, one-third ($n = 264$) of patients presented with a total of 399 ischemic events, and 36% had at least a second recurrent event. MI was the most frequent first recurrent event ($n=131$ of 264), mostly related to new coronary lesions (17% vs 8%; $p=0.01$; hazard ratio - HR: 1.45 for new vs initial culprit lesion). All-cause death ($n=55$; 6.3%) occurred at 8.4 years (median time). Ethnic origin (sub-Saharan African vs. Caucasian, adjusted HR - adjHR: 1.95; $p=0.02$), inflammatory disease (adjHR: 1.58; $p=0.03$), and persistent smoking (adjHR: 2.32; $p<0.01$) were the strongest correlates of a first recurrent event. When considering all recurrent events, the same factors and Asian ethnicity predicted poor outcome, but persistent smoking had the greatest impact on prognosis (Collet J-P et al, *J Am Coll Cardiol* 2019; 74:1868-78).

The Absolute Risk of Osteoporotic Fractures is Low Among Patients With Atrial Fibrillation on Oral Anticoagulants, But Direct Oral Anticoagulants (DOAC) Confer Lower Risk of Osteoporotic Fractures Compared With Vitamin K Antagonists (VKA)

Among 37,350 patients, the absolute 2-year risk of any fracture was low among DOAC-treated patients (3.1%) and among VKA-treated patients (3.8%). DOAC was associated with a significantly lower relative risk of any fracture (hazard ratio - HR: 0.85), major osteoporotic fractures (HR: 0.85), and initiating osteoporotic medication (HR: 0.82). A combined endpoint showed that patients treated with DOAC had a significantly lower relative risk of experiencing any fracture or initiating osteoporosis medication (HR: 0.84) (Binding C et al, *J Am Coll Cardiol* 2019;74: 2150-8).

GLASSY Substudy: Ticagrelor Monotherapy After 1-Month DAPT Failed to Decrease Bleeding Risk as Compared With Conventional Treatment

The GLOBAL LEADERS study randomly assigned 15,991 patients undergoing PCI to 1-month dual antiplatelet therapy (DAPT) followed by 23-month

ticagrelor monotherapy or conventional 12-month DAPT followed by 12-month aspirin. A substudy of 7,585 patients (3,794 in the experimental arm and 3,791 in the control arm) indicated that the 2-year coprimary efficacy endpoint (all-cause death, nonfatal MI, nonfatal stroke, or urgent target vessel revascularization) occurred in 271 (7.14%) and in 319 (8.41%) patients in the experimental and conventional groups, respectively (rate ratio-RR: 0.85), fulfilling noninferiority (p noninferiority<0.001), but not superiority (p superiority=0.0465). The rates of BARC 3 or 5 bleeding did not differ (RR: 1.00; p =0.986). A time-dependent treatment effect was observed with the experimental strategy being associated with a lower risk of MI (RR: 0.54; p interaction=0.062) and definite stent thrombosis (RR: 0.14; p interaction=0.007) after 1-year post-PCI (Franzone A et al, *J Am Coll Cardiol* 2019;74:2223-34).

Single-Arterial CABG, Employed in 85% of Patients, Was Associated With Increased Mortality, Myocardial Infarction, and Repeat Revascularization Overall Compared With Multiarterial CABG

Of the 26,124 patients, 3,647 (14%) underwent multiarterial CABG. Single-arterial CABG patients were older (mean 68 vs 61 y; p <0.001), had more comorbidities, and received fewer bypass grafts (3.4 vs 3.6; p <0.001). After adjusting for baseline differences, multiarterial CABG was associated with lower 10-year mortality compared with single-arterial CABG in 3,588 propensity-matched pairs (15.1% vs 17.3%; p =0.01). Multiarterial CABG was associated with lower 10-year myocardial infarction (hazard ratio-HR: 0.81) and lower 10-year reintervention rate (HR: 0.81) (Chikwe J et al, *J Am Coll Cardiol* 2019;74:2238-48).

Worrisome Early Mortality Following AF Ablation Affected Nearly 1 in 200 Patients, With the Majority of Deaths Occurring During 30-Day Readmission / Procedural Complications, Congestive Heart Failure, and Low Hospital AF Ablation Volume Were Predictors of Early Mortality

A total of 60,203 admission records of US (NY) patients undergoing catheter ablation of AF (1/2010 - 8/2015) were analyzed. Early mortality following AF ablation occurred in 0.46% cases, with 54.3% of deaths occurring during readmission. From 2010 to 2015, quarterly rates of early mortality post-ablation increased from 0.25% to 1.35% (p <0.001). Median time from ablation to death was 11.6 days. After adjustment for age and comorbidities, procedural complications (adjusted odds ratio - aOR: 4.06; p <0.001), heart failure (aOR: 2.20; p =0.011) and low AF ablation hospital volume (aOR: 2.35;

p =0.003) were associated with early mortality. Complications due to cardiac perforation (aOR: 2.98; p =0.007), other cardiac (aOR: 12.8; p <0.001), and neurologic etiologies (aOR: 8.72; p <0.001) were also associated with early mortality (Cheng EP et al, *J Am Coll Cardiol* 2019; 74:2254-64).

DC Cardioversion (CV) is Feasible in High-Risk AF Patients With a Left Atrial Appendage Occlusion (LAAO) Device Without Need for Anticoagulation if Pre-Procedural TEE Shows Good Device Position, Absence of Device-Related Thrombus, and Peridevice Leak of ≤ 5 mm

Among 148 patients (aged 72 \pm 7 years; 59% men) with an LAAO device who underwent CV for symptomatic AF or atrial flutter, device-related thrombus was seen by TEE in 2.7%. They were all successfully treated with oral anticoagulation (OAC) and were able to undergo CV after 6-8 weeks. CV restored sinus rhythm in all patients. None of the patients had CV-related thromboembolic complications. A total of 22% of patients were newly started on OAC after CV. There was no difference in CV-related complications between patients treated with or without OAC post-CV. Patients receiving OAC post-CV were found to undergo CV at an earlier time after implantation (3.6 months vs 8.6 months; p =0.003). Three TIAs, unrelated to CV, were found during follow-up. Over a median of 12.8 months, no device or left atrial thrombosis, device dislodgement, or a new device leak were observed. One patient died during follow-up due to noncardiac cause (Sharma SP et al, *J Am Coll Cardiol* 2019; 74:2267-74).

ADVANCE CRT Exposes a Vulnerable Group of Heart Failure Patients: CRT Non-Respondents

Of 1,524 patients (68 \pm 12 years of age, 32% female, ischemic disease 39%), 74.3% received CRT-D devices, using mainly quadripolar LV leads (75%) deployed laterally (78%). Indications for CRT were wider than past trials. Among 1,327 evaluable patients, nonresponse was 20% (greater age, comorbidities, ischemic disease, non-LBBB, and lower %CRT pacing vs responders). Site definitions used mainly clinical criteria, and underestimated nonresponders by 35% compared with independent scoring. Overall, more site-defined nonresponders received treatment (55.9% vs. 38.3% of responders; p < 0.001) using medication changes and heart failure education, but device programming less frequently, while 44% of site-defined nonresponders received no additional treatment. Frequency and duration of hospitalizations, and death, among site-defined

nonresponders was significantly higher than responders (Varma N et al, *J Am Coll Cardiol* 2019; 74:2588-2603).

Rare Genetic Variants Associated With Sudden Cardiac Death (SCD) in Adults

Among the 1,200 SCD cases and controls, the authors identified 5,178 genetic variants and classified 14 as pathogenic or likely pathogenic. These 14 variants were present in 15 individuals, all of whom had experienced SCD, corresponding to a pathogenic variant prevalence of 2.5% in cases and 0% in controls ($p < 0.0001$). Among the 4,525 participants of the prospective cohort study, 41 (0.9%) carried a pathogenic or likely pathogenic variant and these individuals had 3.24-fold higher risk of cardiovascular death over a median follow-up of 14.3 years ($p = 0.02$) (Khera AV et al, *J Am Coll Cardiol* 2019;74:2623–34).

PADIT: In Patients with Implanted Cardiac Devices, Hospitalization for Infection Occurred in 0.90% Within 1 Year / Prior Procedures, Older Age, Reduced Renal Function, Immunocompromised, and Procedure Type Were Significant Predictors of Device Infection

Device procedures were performed in 19,603 patients, and hospitalization for infection occurred in 177 (0.90%) within 1 year of follow-up. The final prediction model identified 5 independent predictors of device infection (prior procedures [P], age [A], depressed renal function [D], immunocompromised [I], and procedure type [T]) with an optimism-corrected C-statistic of 0.704. A PADIT risk score ranging from 0 to 15 points classified patients into low (0 to 4), intermediate (5 to 6) and high (≥ 7) risk groups with rates of hospitalization for infection of 0.51%, 1.42%, and 3.41%, respectively (Birnie DH et al, *J Am Coll Cardiol* 2019;74:2845-54).

CvLPRIT: The Lower Rate of MACE in the Complete Revascularization Group, Previously Seen at 1 Year, is Sustained to a Median of 5.6 Years / A Significant Difference in Composite All-Cause Death/MI Favors Complete Revascularization

Over a median follow-up (achieved in $>90\%$ patients) of 5.6 years, the primary MACE endpoint rate was 24% in the complete revascularization group but 37.7% of the infarct-related artery-only group (hazard ratio-HR: 0.57; $p = 0.0079$). The composite endpoint of all-cause death/MI was 10% in the complete revascularization group vs 18.5% in the infarct-related artery-only group (HR: 0.47; $p = 0.0175$). In a landmark analysis (from 1 year to final follow-up), there was no significant difference between MACE, death/MI, and individual components of the primary endpoint (Gershlick AH et al, *J Am Coll Cardiol* 2019;74: 3083-94).

COMPLETE: Among Patients With STEMI and Multivessel Coronary Artery Disease, Complete Revascularization was Superior to Culprit-Lesion-Only PCI in Reducing the Risk of CV Death or MI, and the Risk of CV Death, MI, or Ischemia-Driven Revascularization

At a median of 3 years, the first coprimary outcome (CV death/MI) had occurred in 158 of the 2016 patients (7.8%) in the complete-revascularization group vs 213 of the 2025 patients (10.5%) in the culprit-lesion-only PCI group (hazard ratio-HR, 0.74; $P = 0.004$). The second coprimary outcome (CV death/MI/revascularization) had occurred in 8.9% vs 16.7% (HR, 0.51; $P < 0.001$). For both coprimary outcomes, the benefit of complete revascularization was consistently observed regardless of the intended timing of nonculprit-lesion PCI (Mehta SR et al, *N Engl J Med* 2019; 381:1411-21)

In RCTs, Triglyceride Lowering Confers a Lower Risk of Major Vascular Events, Even After Adjustment for LDL-C Lowering, Albeit the Effect is Less Than That for LDL-C (Attenuated When REDUCE-IT is Excluded) / The Benefits of Marine-Derived Omega-3 Fatty Acids, Particularly High-Dose Eicosapentaenoic Acid, Appear to Exceed Their Lipid-Lowering Effects

Among 197,270 participants (24 trials) of nonstatin therapy compared with 177,088 participants (25 trials) of statin therapy, starting with non-high-density lipoprotein cholesterol, a surrogate for very-low-density lipoproteins and low-density lipoproteins, the risk ratio (RR) per 1-mmol/L reduction in non-high-density lipoprotein cholesterol was 0.79 ($P < 0.0001$; 0.78 per 40 mg/dL). In a multivariable meta-regression model that included terms for both LDL-C and triglyceride (surrogates for low-density lipoproteins and very-low-density lipoproteins, respectively), the RR was 0.80 ($P < 0.0001$) per 1-mmol/L (0.79 per 40 mg/dL) reduction in LDL-C and 0.84 ($P = 0.0026$) per 1-mmol/L (0.92 per 40 mg/dL) reduction in triglycerides. REDUCE-IT was a significant outlier and strongly influential trial in the meta-regression. When removed, the RRs became 0.79 ($P < 0.0001$) per 1-mmol/L (0.78 per 40 mg/dL) reduction in LDL-C and 0.91 ($P = 0.06$) per 1-mmol/L (0.96 per 40 mg/dL) reduction in triglycerides. In regard to omega-3 dose, each 1 g/d eicosapentaenoic acid administered was associated with a 7% relative risk reduction in major vascular events (RR, 0.93; $P < 0.0001$), whereas there was no significant association between the dose of docosahexaenoic acid and the relative risk reduction in major vascular events (RR 0.96) (Marston NA et al, *Circulation* 2019;140:1308–17).

Targeting Deceleration Zones (DZ) Identified by Propagational Analysis of Ventricular Activation During Sinus Rhythm Using a Voltage-Independent High-Density Mapping Display Can Guide Ablation, Obviating Extensive Radiofrequency Delivery / Regions With Isochronal Crowding During Baseline Rhythm Were Predictive of VT Termination Sites, Providing Mechanistic Evidence that DZ are Highly Arrhythmogenic, Functioning as Niduses for Reentry

In 120 patients (median age 65 years, 15% female, 50% nonischemic, median ejection fraction 31%) undergoing 144 ablation procedures for scar-related VT (57% with prior ablation; epicardial access used in 59%), high-density mapping during baseline rhythm was identified an average of 2 ± 1 DZ, which colocalized to successful termination sites in 95% of cases. The median radiofrequency application duration was 29 min to target DZ, representing ablation of 18% of the low-voltage area. At 12 ± 10 months, 70% freedom from VT recurrence (80% in ischemic cardiomyopathy and 63% in nonischemic cardiomyopathy) was achieved, with an overall survival rate of 87% (Aziz Z et al *Circulation* 2019;140:1383–97).

DAPA-HF: Among Patients With Heart Failure (HF) with Reduced Ejection Fraction, the Risk of Worsening HF or CV Death was Lower among those who Received Dapagliflozin vs Placebo, Regardless of Presence of Diabetes

Among 4744 patients with NYHA class II-IV HF and ejection fraction of $\leq 40\%$, randomized to dapagliflozin (10 mg qd) or placebo, added to recommended therapy, over a median of 18.2 months, the primary outcome (worsening HF or CV death) occurred in 16.3% in the dapagliflozin group and in 21.2% in the placebo group (hazard ratio-HR, 0.74; $P < 0.001$). A first worsening HF event occurred in 10% vs 13.7% (HR, 0.70). Death from CV causes occurred in 9.6% vs 11.5% (HR, 0.82); 11.6% and 13.9%, respectively, died from any cause (HR, 0.83). Findings in patients with diabetes were similar to those in patients without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups (McMurray JJV et al, *N Engl J Med* 2019; 381:1995-2008)

DEFINE-HF: In Patients (With or Without Diabetes) With Heart Failure (HF) and Reduced Ejection Fraction, Use of Dapagliflozin Over 12 Weeks did not Alter NT-ProBNP But Led to Improvement in HF-Related Health Status / Benefits of Dapagliflozin on Clinically Meaningful HF Measures Appear to Extend to Patients Without Type 2 Diabetes Mellitus

Among 263 HF patients with LVEF $\leq 40\%$, NYHA class II-III, eGFR ≥ 30 mL/min/1.73m², and elevated

natriuretic peptides, randomized to dapagliflozin 10 mg daily or placebo for 12 weeks, there was no significant difference in average 6- and 12-week adjusted NT-proBNP with dapagliflozin vs placebo. However, for the second dual-primary outcome of a meaningful improvement in quality of life (QOL) score or NT-proBNP, 61.5% of dapagliflozin-treated patients met this end point vs 50.4% with placebo (adjusted OR 1.8, nominal $P = 0.039$). This was attributable to both higher proportions of patients with ≥ 5 -point improvement in QOL score (42.9 vs 32.5%, adjusted OR 1.73), and $\geq 20\%$ reduction in NT-proBNP (44 vs 29.4%, adjusted OR 1.9) by 12 weeks. Results were consistent among patients with or without type 2 diabetes, and other prespecified subgroups (all P s for interaction = NS) (Nassif ME et al, *Circulation* 2019;140:1463–76).

PARAGON-HF: Sacubitril-Valsartan did not Lower Heart Failure (HF) Hospitalization Rate and CV Death Among Patients With HF and Ejection Fraction $\geq 45\%$

There were 894 primary events in 526 patients in the sacubitril-valsartan group and 1009 primary events in 557 patients in the valsartan group (rate ratio, 0.87; $P = 0.06$). The incidence of death from CV causes was 8.5% in the sacubitril-valsartan group and 8.9% in the valsartan group (hazard ratio-HR, 0.95); there were 690 and 797 total hospitalizations for HF, respectively (rate ratio, 0.85). NYHA class improved in 15% of the patients in the sacubitril-valsartan group and in 12.6% of those in the valsartan group (odds ratio, 1.45); renal function worsened in 1.4% and 2.7%, respectively (HR, 0.50). The mean change in quality of life score at 8 months was 1.0 point higher in the sacubitril-valsartan group. Patients in the sacubitril-valsartan group had a higher incidence of hypotension and angioedema and a lower incidence of hyperkalemia. Among 12 prespecified subgroups, there was suggestion of heterogeneity with possible benefit with sacubitril-valsartan in patients with lower ejection fraction and in women (Solomon SD et al, *N Engl J Med* 2019; 381:1609-20)

Swedish Heart Failure Registry: ICD was Underused for Primary Prevention, Although it was Associated With Reduced Short- and Long-Term All-Cause Mortality Across all Investigated Subgroups

Of 16,702 eligible patients, only 1599 (10%) had an ICD. After matching, 1305 ICD recipients were compared with 1305 nonrecipients. ICD use was associated with a reduction in all-cause mortality risk within 1 year (hazard ratio-HR, 0.73) and 5 years (HR, 0.88). Results were consistent in all subgroups including patients with vs without ischemic heart disease, men vs women, those aged < 75 vs ≥ 75 years, those with earlier vs later enrollment in the Swedish heart failure registry, and patients with vs

without cardiac resynchronization therapy (Schrage B et al, *Circulation* 2019;140:1530–1539).

Patients With Implantable Electronic Devices: There is an Interaction Between AF Duration and CHA₂DS₂-Vasc Score That Can Further Risk-Stratify Patients With AF for Stroke and Systemic Embolism (SSE)

Among 21,768 nonanticoagulated patients with cardiovascular implantable electronic devices (age, 68.6±12.7 years; 63% male), both increasing AF duration ($P<0.001$) and increasing CHA₂DS₂-VAsc score ($P<0.001$) were significantly associated with annualized risk of SSE. SSE rates were low in patients with a CHA₂DS₂-VAsc score of 0 to 1 regardless of device-detected AF duration. However, stroke risk crossed an actionable threshold defined as >1%/y in patients with a CHA₂DS₂-VAsc score of 2 with >23.5 h of AF, those with a CHA₂DS₂-VAsc score of 3–4 with >6 min of AF, and patients with a CHA₂DS₂-VAsc score ≥5 even with no AF. (Kaplan RM et al, *Circulation* 2019;140: 1639–46).

AUGUSTUS Trial: A Regimen of Apixaban and a P2Y₁₂ Inhibitor Without Aspirin Provides Superior Safety and Similar Efficacy in Patients With AF Who Have ACS, Whether Managed Medically or With PCI, and Those Undergoing Elective PCI Compared With Regimens That Include VKAs, Aspirin, or Both

Of 4614 patients enrolled, 1097 (23.9%) had ACS treated medically and 1714 (37.3%) with PCI, while 1784 (38.8%) had elective PCI. Apixaban compared with vitamin K antagonist (VKA) reduced major or clinically relevant nonmajor bleeding in patients with ACS treated medically (hazard ratio-HR, 0.44), patients with ACS treated with PCI (HR, 0.68), and patients having elective PCI (HR, 0.82; $P_{\text{interaction}}=0.052$) and reduced death or hospitalization in the ACS treated medically (HR, 0.71), ACS treated with PCI (HR, 0.88), and elective PCI (HR, 0.87; $P_{\text{interaction}}=0.345$) groups. Compared with VKAs, apixaban resulted in a similar effect on death and ischemic events in all 3 groups ($P_{\text{interaction}}=0.356$). Aspirin had a higher rate of bleeding in all 3 groups. For the same comparison, there was no difference in outcomes among the 3 groups for the composite of death or hospitalization and death and ischemic events (Windecker S et al, *Circulation* 2019;140:1921–32).

EXCEL: In Patients With Left Main Disease of Low or Intermediate Anatomical Complexity, No Significant Difference Between PCI and CABG in Death, Stroke, or Myocardial Infarction at 5 Years

Among 1905 patients with left main disease of low or intermediate anatomical complexity randomized to PCI with everolimus-eluting stents (n=948) or CABG (n=957),

at 5 years, a primary outcome event (death, stroke, or MI) had occurred in 22% vs 19.2% ($P=0.13$). Death from any cause occurred more frequently in the PCI group than in the CABG group (in 13.0% vs 9.9%). In the PCI and CABG groups, the incidences of definite cardiovascular death (5.0% and 4.5%, respectively) and MI (10.6% and 9.1%;) were not significantly different. All cerebrovascular events were less frequent after PCI than after CABG (3.3% vs 5.2%), although the incidence of stroke was not significantly different between the 2 groups (2.9% and 3.7%). Ischemia-driven revascularization was more frequent after PCI than after CABG (16.9% vs 10%) (Stone GW et al, *N Engl J Med* 2019; 381:1820-30).

THEMIS: In Patients With Stable Coronary Artery Disease and Diabetes Without a History of Myocardial Infarction or Stroke, Those Who Received Ticagrelor Plus Aspirin Had a Lower Incidence of Ischemic Cardiovascular (CV) Events But a Higher Incidence of Major Bleeding Compared to Placebo Plus Aspirin

Among 19,220 patients randomized, over a median of 39.9 months, where treatment discontinuation was more frequent with ticagrelor than placebo (34.5% vs. 25.4%), the incidence of ischemic CV events was lower in the ticagrelor than in the placebo group (7.7% vs 8.5%; hazard ratio-HR, 0.90; $P=0.04$), whereas the incidence of TIMI major bleeding was higher (2.2% vs 1.0%; HR, 2.32; $P<0.001$), as was the incidence of intracranial hemorrhage (0.7% vs 0.5%; HR, 1.71; $P=0.005$). There was no difference in the incidence of fatal bleeding (0.2% vs 0.1%). The incidence of an exploratory composite outcome of irreversible harm (death from any cause, myocardial infarction, stroke, fatal bleeding, or intracranial hemorrhage) was similar in the 2 groups (10.1% vs 10.8%) (Steg PG et al, *N Engl J Med* 2019; 381:1309-20).

ISAR-REACT 5: Among Patients With Acute Coronary Syndromes (ACS) With or Without ST-Elevation, the Incidence of Death, MI, or Stroke Was Lower in Those Who Received Prasugrel vs Ticagrelor, and the Incidence of Major Bleeding was Similar

Among 4018 patients randomized, a primary end-point event occurred in 9.3% in the ticagrelor group and in 6.9% in the prasugrel group (hazard ratio-HR, 1.36; $P=0.006$). The respective incidences of the individual components of the primary end point in the ticagrelor group and the prasugrel group were as follows: death, 4.5% vs 3.7%; MI, 4.8% vs 3.0%; and stroke, 1.1% vs 1.0%. Definite or probable stent thrombosis occurred in 1.3% vs 1.0%, and definite stent thrombosis occurred in 1.1% vs 0.6%, respectively. Major bleeding was observed

in 5.4% vs 4.8% (HR, 1.12; P=0.46) (Schüpke S et al, *N Engl J Med* 2019; 381:1524-34).

TWILIGHT: Among High-Risk Patients Who Underwent PCI and Completed 3 Months of Dual Antiplatelet Therapy, Ticagrelor Monotherapy was Associated With a Lower Incidence of Clinically Relevant Bleeding Than Ticagrelor Plus Aspirin, With No Higher Risk of Death, MI, or Stroke

Among 9006 enrolled patients, 7119 underwent randomization after 3 months. Between randomization and 1 year, the incidence of the primary end point was 4% among patients randomized to ticagrelor plus placebo and 7.1% among patients assigned to ticagrelor plus aspirin (hazard ratio-HR, 0.56; P<0.001). The difference in risk between the groups was similar for BARC type 3 or 5 bleeding (1% vs 2.0%; HR, 0.49). The incidence of death from any cause, nonfatal myocardial infarction (MI), or nonfatal stroke was 3.9% in both groups (HR, 0.99; P<0.001 for noninferiority) (Mehran R et al, *N Engl J Med* 2019; 381:2032-2042)

Apple Heart Study: Probability of Receiving an Irregular Pulse Notification by a Smart Watch Was Low, and of Those, Only 34% Had Atrial Fibrillation (AF) on Subsequent ECG Patch Readings

Among 419,297 participants, over a median of 117 days of monitoring, 2161 (0.52%) received notifications of irregular pulse. Among the 450 participants who returned ECG patches, AF was present in 34% overall and in 35% of participants ≥ 65 years of age. Among participants who were notified of an irregular pulse, the positive predictive value was 0.84 for observing AF on the ECG simultaneously with a subsequent irregular pulse notification and 0.71 for observing AF on the ECG simultaneously with a subsequent irregular tachogram. There were no reports of serious app-related adverse events (Perez MV et al, *N Engl J Med* 2019; 381:1909-17).

CRICS-TRIGGERSEP: Among Patients with Coma Resuscitated from Cardiac Arrest With Nonshockable Rhythm (Asystole or Pulseless Electrical Activity), Moderate Therapeutic Hypothermia at 33°C for 24 h Led to a Higher Percentage of Favorable Neurologic Outcome at Day 90 Than Targeted Normothermia

Among 581 patients randomized to moderate therapeutic hypothermia (33°C during the first 24 h) or targeted normothermia (37°C), on day 90, a total of 29 of 284 patients (10.2%) in the hypothermia group were alive with a cerebral performance score of 1 or 2 (lower disability), as compared with 17 of 297 (5.7%) in the normothermia group (P=0.04). Mortality at 90 days did not differ between the 2 groups (81.3% vs 83.2%). The

incidence of prespecified adverse events did not differ between groups (Lascarrou J-B et al, *N Engl J Med* 2019; 381:2327-37).

COLCOT: Among Patients With a Recent Myocardial Infarction (MI), Colchicine (0.5 mg qd) Led to a Lower Risk of Ischemic Cardiovascular Events Than Placebo

Among 4745 MI patients assigned to colchicine (n=2366) or placebo (n=2379), over a median of 22.6 months, the primary end point (CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization) occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (hazard ratio-HR, 0.77; P=0.02). The HRs were 0.84 for CV death, 0.83 for resuscitated cardiac arrest, 0.91 for MI, 0.26 for stroke, and 0.50 for urgent hospitalization for angina leading to coronary revascularization. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group (P=0.35). Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group and in 0.4% of those in the placebo group (P=0.03) (Tardif JC et al, *N Engl J Med* 2019; 381:2497-2505)

BIOSTEMI: Biodegradable Versus Durable Polymer Sirolimus-Eluting Stents Superior in Patients With STEMI Regarding Target Lesion Failure at 1 Year

Among 1300 patients (1623 lesions) with acute MI assigned to biodegradable (649 patients and 816 lesions) or durable polymer everolimus-eluting stents (651 patients and 806 lesions), at 12 months, the primary composite endpoint of target lesion failure occurred in 25 (4%) of 649 patients treated with biodegradable and 36 (6%) of 651 patients treated with durable polymer everolimus-eluting stents (rate ratio 0.59). Cardiac death, target vessel myocardial reinfarction, clinically-indicated target lesion revascularization, and definite stent thrombosis were similar between the two treatment groups (Iglesias JF et al, *Lancet* 2019; 394:1243-53).

SYNTAX/10-Year Follow-Up: At 10 Years, No Difference in All-Cause Death Between PCI Using First-Generation Paclitaxel-Eluting Stents and CABG. However, CABG Provided a Survival Benefit in Patients With 3-Vessel, But not Left Main Disease

Among 1800 patients randomly assigned to PCI (n=903) or CABG (n=897), at 10 years, 27% had died after PCI and 24% after CABG (hazard ratio-HR 1.17, p=0.092). Among patients with 3-vessel disease, 28% had died after PCI vs 21% after CABG (HR 1.41), and among patients with left main disease, 26% had died after PCI vs 28% after CABG (HR 0.90, p_{interaction}=0.019). There was

no treatment-by-subgroup interaction with diabetes ($p_{\text{interaction}}=0.66$) and no linear trend across SYNTAX score tertiles ($p_{\text{trend}}=0.30$) (Thuijs DJFM et al, *Lancet* 2019; 394:1325-34).

EU-CERT-ICD: Periodic Repolarization Dynamics Predict Mortality Reductions Associated With Prophylactic Implantation of ICDs and Could Help Guide Treatment Decisions on Prophylactic ICD

Among 1371 patients, of whom 968 underwent ICD implantation, and 403 were treated conservatively, over a median of 2.7 years in the ICD group and 1.2 years in the control group, death rate was 14% vs 16% respectively. We noted a 43% reduction in mortality in the ICD group compared with the control group (adjusted hazard ratio - HR 0.57; $p=0.0008$). Periodic repolarization dynamics significantly predicted the treatment effect of ICDs on mortality (adjusted $p=0.0307$). The mortality benefits associated with ICD implantation were greater in patients with periodic repolarization dynamics of ≥ 7.5 deg ($n=199$; adjusted HR 0.25 for the ICD group vs the control group; $p<0.0001$) than in those with periodic repolarization dynamics < 7.5 deg ($n=1166$; adjusted HR 0.69; $p=0.0492$; $p_{\text{interaction}}=0.0056$). The number needed to treat was 18.3 in patients with periodic repolarization dynamics < 7.5 deg and 3.1 in those with periodic repolarization dynamics of ≥ 7.5 deg (Bauer A et al, *Lancet* 2019;394: 1344-51)

AMBER: In Patients With Resistant Hypertension and Chronic Kidney Disease, the Potassium Binder, Patiromer, Enabled More Patients to Continue Treatment With Spironolactone With Less Hyperkalemia

Among 295 patients randomly assigned to spironolactone in addition to double-blind treatment with either placebo ($n=148$) or patiromer ($n=147$), at week 12, 66% in the placebo group and 86% in the patiromer group remained on spironolactone (between-group difference 19.5%; $p<0.0001$). Adverse events were mostly mild or moderate in severity and occurred in 53% vs 56% of patients (Agarwal R et al, *Lancet* 2019; 394: 1540-50).

A Comprehensive Framework, Systematic, Large-Scale Cohort Study Supports Equivalence Between Drug Classes for Initiating Monotherapy for Hypertension - In Keeping With Current Guidelines, With the Exception of Thiazide or Thiazide-Like Diuretics Superiority to Angiotensin-Converting Enzyme Inhibitors and the Inferiority of Non-Dihydropyridine Calcium Channel Blockers

A systematic, large-scale cohort study designed to estimate the relative risks of three primary (acute myocardial infarction, hospitalization for heart failure, and

stroke) and six secondary effectiveness and 46 safety outcomes comparing all first-line classes across a global network, used 4.9 million patients, generating 22,000 calibrated, propensity-score-adjusted hazard ratios (HRs) comparing all classes and outcomes across databases. Most estimates revealed no effectiveness differences between classes; however, thiazide or thiazide-like diuretics showed better primary effectiveness than angiotensin-converting enzyme inhibitors (ACEI): acute MI (HR 0.84), hospitalization for heart failure (0.83), and stroke (0.83) risk while on initial treatment. Safety profiles also favored thiazide or thiazide-like diuretics over ACEI. The non-dihydropyridine calcium channel blockers were significantly inferior to the other four classes (Suchard MA et al, *Lancet* 2019;394: 1816-26).

TRILUMINATE: The TriClip System Appears to be Safe and Effective at Reducing Tricuspid Regurgitation by at Least One Grade

Among 85 patients (age 77.8 ± 7.9 years; 66% women) who underwent successful TriClip implantation (clip-based edge-to-edge repair), tricuspid regurgitation severity was reduced by at least one grade at 30 days in 71 (86%) of 83 patients who had available echocardiogram data and imaging. One patient withdrew before 6-month follow-up without having had a major adverse event and was excluded from analysis of the primary safety endpoint. At 6 months, three (4%) of 84 patients experienced a major adverse event, which was less than the prespecified performance goal of 39% ($p<0.0001$). Single leaflet attachment occurred in five (7%) of 72 patients. No periprocedural deaths, conversions to surgery, device embolizations, MIs, or strokes occurred. At 6 months, all-cause mortality had occurred in four (5%) of 84 patients (Nickenig G et al, *Lancet* 2019; 394: 2002-11).

E-VALI or VALI (e-Cigarettes or Vaping Associated Lung Injury) is an Emerging Illness Associated With Severe Lung Injury and Constitutional and Gastrointestinal Symptoms, With a Broad Spectrum of Severity of Illness in Patients Treated With Antibiotics and Steroids / Despite Improvement, at Short-Term Follow-Up Many Patients Have Residual Abnormalities

Of 60 patients presented with EVALI at 13 hospitals or outpatient clinics, 33 (55%) were admitted to an intensive care unit (ICU). 53 (88%) patients presented with constitutional symptoms, 59 (98%) with respiratory symptoms, and 54 (90%) with gastrointestinal symptoms. 54 (90%) of 60 were given antibiotics and 57 (95%) were given steroids. Six (10%) of 60 patients were readmitted to an ICU or hospital within 2 weeks, 3 (50%) of whom had relapsed with vaping or e-cigarette use. Of 26 patients who

were followed up within 2 weeks, despite clinical and radiographic improvement in all, many had residual abnormalities on chest radiographs (10 of 15 or 67%) and pulmonary function tests (6 of 9 or 67%). Two patients died and EVALI was thought to be a contributing factor, but not the cause of death, for both (Blagev DP et al, *Lancet* 2019; 394:2073-83).

AIMS: Irbesartan is Associated With a Reduction in the Rate of Aortic Dilatation in Children and Young Adults With Marfan Syndrome and Could Reduce the Incidence of Aortic Complications

Among 192 participants (median age 18 years; 52% females; mean blood pressure 110/65 mmHg; 56% on β -blockers; mean baseline aortic root diameter 34.4 mm) randomly assigned to irbesartan (n=104) or placebo (n=88), followed for up to 5 years, the mean rate of aortic root dilatation was 0.53 mm per year in the irbesartan group compared with 0.74 mm per year in the placebo group (p=0.030). The rate of change in aortic Z score was also reduced by irbesartan (p=0.035). Irbesartan was well tolerated with no observed differences in rates of serious adverse events (Mullen M et al, *Lancet* 2019;394:2263-70)

A Nationwide Population-Based Study of ~10 Million Persons: Altered Risk for Cardiovascular (CV) Events with Changes in Metabolic Syndrome (MetS) Status / Recovery from MetS was Significantly Associated With Decreased Risk for MACE, whereas Development of MetS was Associated with Increased Risk

The MetS status was determined for 9,553,042 persons. At a median of 3.54 years, the MetS-recovery group (incidence rate, 4.55 per 1000 person-years) had a lower MACE risk (adjusted incidence rate ratios-IRR, 0.85) than that of the MetS-chronic group (incidence rate, 8.52 per 1000 person-years). The MetS-developed group (incidence rate, 6.05 per 1000 person-years) had a significantly higher MACE risk (IRR, 1.36) than that of the MetS-free group (incidence rate, 1.92/1000 person-years). Among the MetS components, change in hypertension was associated with the largest difference in MACE risk (Park S et al, *Ann Intern Med* 2019;171:875–84)

Important Review and Other Articles

ACC/AHA/HRS vs ESC **Syncope Guidelines** (Goldberger ZD et al, *J Am Coll Cardiol* 2019;74:2410-23)

- **Resuscitation Guideline Update** (*Circulation* 2019;140:e826–e938)
- CV toxicities of immune check point inhibitors (Mangieri A et al, *J Am Coll Cardiol* 2019; 74: 2088-2101)
- Thrombotic vs bleeding risk after TAVI (January CT et al, *Circulation* 2019;140:e125–e151)

- Anticoagulation in concomitant chronic kidney disease and AF (Kumar S et al, *Eur Heart J* 2019;74:2204-15)
 - Advanced heart failure therapies for adults with congenital heart disease (Givertz MM et al, *J Am Coll Cardiol* 2019; 74:2295-2312)
 - SGLT2 inhibitors and cardiorenal protection (Cherney DZ et al, *J Am Coll Cardiol* 2019;74:2511-24)
 - Primary aldosteronism (Rossi GP et al, *J Am Coll Cardiol* 2019;74:2799-2811)
 - Left bundle branch pacing (Zhang S et al, *J Am Coll Cardiol* 2019;74:3039-49)
 - Ischemic stroke risk in AF (Alkhouli M et al, *J Am Coll Cardiol* 2019;74:3050-65)
 - Aortic stenosis and cardiac amyloidosis (Ternacle J et al, *J Am Coll Cardiol* 2019;74:2638-51)
 - Chimeric Antigen Receptor (CAR) T-cell therapy for cancer and heart (Ganatra S et al, *J Am Coll Cardiol* 2019;74:3153-63)
 - Mitochondria and CV system (Tian R et al, *Circulation* 2019;140:1205-16)
 - Arterial grafts for coronary bypass (Gaudino M et al, *Circulation* 2019;140:1273-84)
 - Interventional therapies in pulmonary embolism (Giri J et al, *Circulation* 2019;140:e774–e801)
 - Multimodality imaging in infective endocarditis (Erba PA et al, *Circulation* 2019;140:1753–65)
 - Searching for AF post stroke (Schnabel RB, et al, *Circulation* 2019;140:1834–50)
 - Subclinical and device-detected AF (Noseworthy, PA et al, *Circulation* 2019;140:e944–e963)
 - Lipid management for prevention of CVD (Michos ED et al, *N Engl J Med* 2019; 381:1557-1567)
 - Lay responder care for out-of-hospital cardiac arrest (Brady WJ et al, *N Engl J Med* 2019; 381:2242-51)
- Red and processed meat consumption and risk for all-cause mortality and cardiometabolic outcome (Zeraatkar D et al, *Ann Intern Med* 2019;171:703–10)
- Reduction of red and processed meat intake and cancer mortality and incidence (Han MA et al, *Ann Intern Med* 2019;171:711–20)
- European position paper on management of patients with patent foramen ovale (Pristipino C et al, *Eur Heart J* 2019;40:3182-95)
- Treatment of cardiac transthyretin amyloidosis (Emdin M et al, *Eur Heart J* 2019; 40: 3699-3706)
 - Immunotherapy for CV disease (Lutgens E et al, *Eur Heart J* 2019;40:3937-46)
 - Winter swimming: body hardening and cardiorespiratory protection (Manolis AS et al, *Curr Sports Med Rep* 2019;18:401-415)