Cardiology News / Recent Literature Review / Third Quarter 2018

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HCS 39th Meeting: Athens, 18-20/10/2018

AHA Meeting: Chicago, IL, USA, 10-12/11/2018

ACC.19 Meeting: New Orleans, LA, USA, 16-18/3/2019

EHRA Congress: Lisbon, 17-19/3/2019

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

EuroPCR: Paris, 21-24/5/2019

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

NOACs are All Associated With a Significant Standardized Absolute Risk Reduction of MI Compared With VKA

Among 31,739 patients with atrial fibrillation (AF) (median age, 74 years; 47% females), the standardized 1-year risk of MI for VKA was 1.6%, 1.2% for apixaban, 1.2% for dabigatran, and 1.1% for rivaroxaban. No significant risk differences were observed in the standardized 1-year risks of MI among the NOACs: dabigatran vs apixaban (0.04%), rivaroxaban versus apixaban (0.1%), and rivaroxaban versus dabigatran (−0.1%). The risk differences for NOACs vs VKA were all significant: −0.4% for apixaban, −0.4% for dabigatran, and −0.5% for rivaroxaban (Lee CJ-Y et al, *J Am Coll Cardiol* 2018;72: 17–26).

ATLAS ACS 2-TIMI 51 Trial: In Patients With ACS, Addition of Rivaroxaban, 2.5 mg bid, to Dual Antiplatelet Therapy With Aspirin and Clopidogrel Was Associated With a Net Reduction in Fatal or Irreversible Events Compared to Dual Antiplatelet Therapy Alone

Rivaroxaban, 2.5 mg bid, in ACS patients treated with aspirin and clopidogrel/ticlopidine was associated with 115 fewer fatal or irreversible ischemic events (663 for placebo vs 548 for therapy) and 10 additional fatal or irreversible seriously harmful events (33 vs 23 for placebo) per 10,000 patient-years of exposure. Thus, there would be 105 fatal or irreversible events prevented per 10,000 patient-years of exposure to rivaroxaban compared with placebo, with 11 (10 of 115) fatal or irreversible ischemic events prevented for each fatal or irreversible seriously harmful event caused. If only nonbleeding cardiovascular death is included as a fatal or irreversible event, then 95 events would be prevented per 10,000 patient-years of exposure in the group taking 2.5 mg bid (Gibson CM et al, *J Am Coll Cardiol* 2018;72: 129-36).

XANTUS Program: In a Pooled Analysis of Several Practice-Based Registries, AF Patients on Rivaroxaban Had Generally Low Rates of Stroke, Bleeding, and Treatment Discontinuation and Results Were Broadly Consistent Across Different Regions of the World

Among 11,121 AF patients receiving rivaroxaban (mean age 70.5±10.5 years; female 42.9%) with comorbidities including heart failure (21.2%), hypertension (76.2%), and diabetes (22.3%), event rates were: events/100 patient-years: major bleeding 1.7 (lowest: Latin America 0.7; highest: Western Europe, Canada, and Israel 2.3); all-cause death 1.9 (lowest: Eastern Europe 1.5; highest: Latin America, Middle East, and Africa 2.7); and stroke or systemic embolism 1.0 (lowest: Latin America 0; highest: East Asia 1.8). One-year treatment persistence was 77.4% (lowest: East Asia 66.4%; highest: Eastern Europe 84.4%) (Kirchhof P et al, *J Am Coll Cardiol* 2018;72:141-53).

In Patients With AMI Complicated by Cardiogenic Shock (CS) Who Have Undergone Successful Primary Angioplasty, Shock is Less Refractory When Arterial Pressure is Supported With Norepinephrine Rather Than With Epinephrine

Patients (N=57) with CS were randomized into 2 study arms, epinephrine (n=27) and norepinephrine (n=30). For the primary efficacy endpoint, cardiac index evolution was similar between the 2 groups from baseline (H0) to H72. For the main safety endpoint, the observed higher incidence of refractory shock in the epinephrine group (37% vs norepinephrine 7%; p=0.008) led to early termination of the study. Heart rate increased significantly with epinephrine from H2 to H24 while it remained unchanged with norepinephrine (p<0.0001). Several metabolic changes were unfavorable to epinephrine compared with norepinephrine, including an increase in cardiac double product (p=0.0002) and lactic acidosis from H2 to H24 (p< 0.0001) (Levy B et al, *J Am Coll Cardiol* 2018; 72:173-82)

Valve-in-Valve (ViV)-TAVI Can be a Safe and Effective Alternative to Cardiac Reoperation for High-Risk Patients With Degenerated Bioprosthetic Aortic Valves

Patients who underwent ViV-TAVI (n=1,150) were matched 1:2 to patients undergoing native valve (NV)-

TAVI (n=2,259). A lower 30-day mortality (2.9% vs 4.8%; p< 0.001), stroke (1.7% vs 3.0%; p=0.003), and heart failure hospitalizations (2.4% vs 4.6%; p<0.001) were observed in the ViV-TAVI compared with NV-TAVI group. A lower 30-day mortality (hazard ratio-HR: 0.503; p=0.008), 1-year mortality (HR: 0.653; p=0.001), and hospitalization for heart failure (HR: 0.685; p=0.019) were noted in the ViV-TAVI group. Patients in the ViV-TAVI group had higher post-TAVI mean gradient (16 vs 9 mmHg; p< 0.001), but less moderate or severe aortic regurgitation (3.5% vs 6.6%; p<0.001). Post-TAVI gradients were highest in small AVRs and stenotic AVRs (Tuzcu EM et al, *J Am Coll Cardiol* 2018; 72:370-82).

NODE-1: Intra-Nasal Etripamil, a Short-Acting Calcium Channel Blocker, with a Rapid Onset of Action, was More Effective Than Placebo in Terminating Induced SVT, Though a High Dose was Associated With Lowering of Blood Pressure

Among 104 patients with induced SVT, conversion rates were between 65% and 95% in the etripamil nasal spray groups and 35% in the placebo group; differences were significant in the 3 highest active compound dose groups versus placebo. In patients who converted, the median time to conversion with etripamil was <3 min. Adverse events were mostly related to the intranasal route of administration or local irritation. Reductions in blood pressure occurred predominantly in the highest etripamil dose (Stambler BS et al, *J Am Coll Cardiol* 2018; 72:489-97).

Contemporary Medical Treatment of Heart Failure (HF) With Depressed Ejection Fraction is Associated With an Early Rise in LVEF, Followed by a Plateau for About a Decade and a Slow Decline Thereafter

Measurements (3.6±1.7) of left ventricular ejection fraction (LVEF) trajectories among 1,160 HF patients projected by Loess spline curves showed an inverted U shape with a marked rise in LVEF during the first year, maintained up to a decade, and a slow LVEF decline thereafter (p <0.001). This pattern was more pronounced in HF of nonischemic origin and in women. Patients with new-onset HF (≤1 year) had a higher early increase in LVEF, whereas patients with ischemic HF showed a lower LVEF increase at 1 year; both groups had a relative plateau thereafter. Patients with HF with mid-range LVEF had less of an increase (3±9%) than those with HF with reduced LVEF (9±12%) during the first year (p< 0.001), but the groups overlapped after 15 years. Patients who died had lower final LVEF and worse LVEF dynamics in the immediately preceding period than survivors (Lupon J et al, *J Am Coll Cardiol* 2018;72:591-601).

APACE & BACC Studies: The European Society of Cardiology 0/1-h Algorithm Based on High-Sensitivity Cardiac Troponin T 0r I, Used in Conjunction With All Other Clinical Information Including Chest Pain Characteristics and the ECG, is Safe and Effective in Triaging Patients With Suspected NSTEMI

Prevalence of NSTEMI among patients presenting to the emergency room was 17%. Among 4,368 patients with serial hs-cTnT measurements available, safety of rule-out (negative predictive value-NPV 99.8%), accuracy of rule-in (positive predictive value-PPV 74.5%), and overall efficacy were high by assigning 3/4 of patients either to rule-out (57%) or rule-in (18%). Similarly, among 3,500 patients with serial hs-cTnI measurements, safety of rule-out (NPV 99.7%), accuracy of rule-in (PPV 62.3%), and overall efficacy were high by assigning >2/3 of patients either to rule-out (44%) or rule-in (23%). Excellent safety was confirmed in multiple subgroup analyses including patients presenting early (≤3 h) after chest pain onset. (Twerenbold R et al, *J Am Coll Cardiol* 2018;72:620-32).

RAID Trial: In High-Risk Patients With Heart Failure and Implanted Defibrillators (ICDs), Ranolazine Failed to Reduce the Primary Endpoint of VT, VF, or Death; in Secondary Analyses, Ranolazine Reduced Recurrent VT or VF Requiring ICD Therapy, Mainly Through Reduction in Episodes of VT Without Increasing Proarrhythmia or Associated Mortality

Among 1,012 ICD patients (510 on ranolazine and 502 on placebo; aged 64±10 years; 18% women), over 28±16 months, there were 372 (37%) patients with primary endpoint, 270 (27%) patients with VT or VF, and 148 (15%) deaths. The study drug was stopped in 199 (39.6%) patients receiving placebo and in 253 (49.6%) receiving ranolazine (p=0.001). The hazard ratio-HR for ranolazine vs placebo was 0.84 (p=0.117) for VT, VF, or death. In a pre-specified secondary analysis, patients randomized to ranolazine had a marginally significant lower risk of ICD therapies for recurrent VT or VF (HR: 0.70; p=0.028) (Zareba W et al, *J Am Coll Cardiol* 2018;72: 636-45).

In Low-/Intermediate-Risk Patients With Hypertrophic Cardiomyopathy (HCM) (Obstructive, Myectomy, Nonobstructive Groups) With Preserved Systolic Function, %LGE was Associated With a Higher Rate of Composite Endpoint (Sudden Death/ Appropriate ICD Discharge)

Among 1,423 low-/intermediate-risk patients with HCM (age ≥18 years) with preserved left ventricular ejection fraction (mean age 66 ± 14 years, 60% men), mean 5-year SCD risk score of 2.3±2.0, 50% had late gadolinium enhancement (LGE) on CMR (458 nonobstructive and 965

obstructive of whom 686 had myectomy). At 4.7±2.0 years, 60 (4%) met the composite endpoint (sudden death/appropriate ICD discharge). On quadratic spline analysis, LGE ≥15% was associated with increased risk of composite events. In the obstructive subgroup, ≥15% LGE (subhazard ratio: 3.04) was associated with a higher rate and myectomy (subhazard ratio: 0.44) with a lower rate of composite endpoints (both p< 0.01). Association of %LGE with composite events was similar in myectomy and nonobstructive subgroups (Mentias A et al, *J Am Coll Cardiol* 2018;72:857–70).

Takotsubo Syndrome (TTS): Long-Term Outcome Highly Variable / Prognosis is More Favorable When the Syndrome is Triggered by Emotional Events Than When it Develops in Response to Physical or Neurologic Conditions

Overall, TTS patients had a comparable long-term mortality risk with acute coronary syndrome (ACS) patients. Of 1,613 TTS patients, emotional trigger was detected in 485 patients (30%); of 630 patients (39%) related to physical triggers, 98 patients (6%) had acute neurologic disorders, while in the other 532 patients (33%), physical activities, medical conditions, or procedures were the triggering conditions. The remaining 498 patients (31%) had no identifiable trigger. TTS patients related to physical stress showed higher mortality rates than ACS patients during long-term follow-up, whereas patients related to emotional stress had better outcomes compared with ACS patients (Ghadri JR et al *J Am Coll Cardiol* 2018;72:874–82).

SUMMIT Trial: In Patients With COPD and High Cardiovascular (CV) Risk, Plasma Cardiac Troponin I (cTnI) Concentrations were an Indicator of Future CV Events and CV Death / Inhaled Therapies Did not Affect cTnI Levels Consistent With Their Neutral Effect on Mortality and CV Outcomes

Among 16,485 COPD patients with CV disease or risk factors, randomized to once daily inhaled placebo, fluticasone furoate (100 μg), vilanterol (25 μg), or their combination, plasma high-sensitivity cTnI was measured in a subgroup of 1,599 patients. Baseline cTnI levels were above the limit of detection (1.2 ng/l) in 1,542 (96%) patients. Concentrations were unaffected by inhaled therapies at 3 months (p > 0.05). Compared with the lowest quintile (<2.3 ng/l), patients in the highest quintile (≥7.7 ng/l) were at greater risk of CV events (hazard ratio-HR 3.7; p=0.012) and CV death (HR: 20.1; p=0.005) after adjustment for risk factors. By contrast, there were no differences in exacerbations between quintiles (HR: 1.1; p=0.548) (Adamson PD et al, *J Am Coll Cardiol* 2018;72:1126-37).

Chronic Coronary Artery Disease (CAD): Low Diastolic Blood Pressure (DBP) May Precipitate or Worsen Angina / Should Consider Reducing Antihypertensive Medications in Patients With CAD and Low DBP Who Have Angina

Among 1,259 outpatients with CAD, 411 (33%) reported angina in the prior month, with higher rates in the lowest DBP quartile (40-64 mmHg: 37%). In the unadjusted model, DBP was associated with angina with a J-shaped relationship (p=0.017, p for nonlinearity=0.027), with a progressive increase in odds of angina as DBP decreased below ~70-80 mmHg. This association remained significant after sequential adjustment for demographic characteristics (p=0.002), comorbidities (p=0.002), heart rate (p=0.002), systolic BP (p=0.046), and antihypertensive antianginal medications (p=0.045) (Peri-Okonny PA et al, *J Am Coll Cardiol* 2018;72:1227-32).

Atrial Fibrillation (AF) Patients Treated for Hypertension: There is a U-Shaped Relationship Between BP and CV Events, With Optimum Outcomes Associated With a BP Range of 120-129/<80 mmHg

Among 298,374 Korean adults with AF, 62.2% had hypertension (HTN) according with the old guidelines; applying the 2017 ACC/AHA guideline, 79.4% had HTN, including 17.2% with newly redefined HTN (130-139/80-89 mmHg). Those with newly redefined hypertension had greater risks of major CV events (hazard ratio: 1.07; p< 0.001), ischemic stroke, intracranial hemorrhage, and heart failure admission, compared with non-hypertensive patients (<130/80 mmHg). Among patients with AF receiving HTN treatment, patients with BP≥130/80 mmHg or <120/80 mmHg were at significantly higher risks of major CV events than patients with BP of 120-129/<80 mmHg (Kim D et al, *J Am Coll Cardiol* 2018;72:1233–45).

LIMA-Radial Artery (RA)-Y Graft Technique is Superior Compared to LIMA+SVG in Achieving Total Arterial Revascularization (TAR)

Survival was compared between 346 LIMA-RA-Y patients and 534 patients who received LIMA+ SVG, and 5,800 patients who received TAR with different grafting configurations. Survival was worse for LIMA+SVG vs LIMA-RA-Y (27.9% vs 53.5 still alive at 15 years) in the unmatched groups (KM, p< 0.001) and for propensity score matching (PSM) groups (KM, p=0.043; Cox proportional hazards ratio: 1.3; p=0.038). Survival did not differ between LIMA-RA-Y and other TAR (n=5,800) patients before, or after, PSM (n=332 pairs) (Royse AG et al, *J Am Coll Cardiol* 2018;72:1332–40).

Fluoroquinolones are Associated With a 2.5-Fold Increased Risk of Aortic Aneurysm and Dissection (AA/AD)

Among 1,213 hospitalized AA/AD patients, exposure to fluoroquinolone was more frequent during the hazard periods than during the referent periods (1.6% vs 0.6%; odds ratio-OR: 2.71). In the sensitivity analysis, after adjustment for infections and co-medications, the risk remains significant (OR: 2.05). An increased risk of AA/AD was observed for prolonged exposure to fluoroquinolones (OR: 2.41 for 3- to 14-day exposure; OR: 2.83 for >14-day exposure). Susceptible period analysis revealed that the use of fluoroquinolone within 60 days was associated with the highest risk of AA/AD. In the case-time-control analysis, there was no evidence that the observed association is due to temporal changes in fluoroquinolone exposure (Lee C-C et al, *J Am Coll Cardiol* 2018;72:1369–78).

Very Elderly (≥90 Years) AF Patients: Warfarin was Associated With a Lower Risk of Ischemic Stroke and Positive Net Clinical Benefit / Compared With Warfarin, NOACs were Associated With a Lower Risk of Intracranial Hemorrhage (ICH)

In the era without NOACs, risks of ischemic stroke and ICH were compared between 14,658 very elderly patients without AF and without antithrombotic therapy and 15,756 AF patients who were divided into 3 groups: no treatment (n=11,064), antiplatelet agents (n=4,075), and warfarin (n=617). In the era with NOACs, AF patients receiving warfarin (n=768) were compared with those receiving NOACs (n=978). Compared with patients without AF, AF patients had an increased risk of ischemic stroke (hazard ratio-HR, 1.93) and similar risk of ICH (HR, 0.85). Among patients with AF, warfarin use was associated with a lower stroke risk (HR, 0.69), with no difference in ICH risk compared with nontreatment. When compared with no antithrombotic therapy or antiplatelet drugs, warfarin was associated with a positive net clinical benefit. These findings persisted in propensity-matched analyses. Compared with warfarin, NOACs were associated with a lower risk of ICH (4/978, 0.42%/y vs 19/768, 1.63%/y; HR, 0.32), with no difference in risk of ischemic stroke (Chao T-F et al, *Circulation* 2018;138:37-47.

H_2FPEF Score Enables Discrimination of HFpEF from Noncardiac Causes of Dyspnea

A new score (H_2FPEF: **H**eavy, BMI>30 kg/m^2, 2 points; **H**ypertensive, ≥2 drugs, 1 point; atrial **F**ibrillation, 3 points; **P**ulmonary hypertension, >35 mmHg by Doppler, 1 point; **E**lder, >60 years, 1 point; **F**illing pressure, E/e´>9, 1 point) (0-9 points) was derived from 414 consecutive patients (derivation cohort) with unexplained dyspnea (267 cases with HFpEF and 147 controls; HFpEF prevalence, 64%) and tested in 100 patients (test cohort) (61 with HFpEF; prevalence, 61%). The odds of HFpEF doubled for each 1-unit score increase (odds ratio, 1.98; P<0.0001), with an area under the curve of 0.841 (P<0.0001). The H_2FPEF score was superior to a currently used algorithm based on expert consensus (increase in area under the curve of 0.169; P<0.0001). Performance in the independent test cohort was maintained (area under the curve, 0.886; P<0.0001) (Reddy YNV et al, *Circulation* 2018;138:861–870).

CANVAS Program: In High Cardiovascular (CV) Risk Patients With Type 2 Diabetes (T2DM), Canagliflozin Reduced Risk of CV Death or Hospitalized HF / Benefits May Be Greater in Those With a History of Heart Failure (HF) at Baseline

Among 10,142 participants with T2DM and high CV risk, randomly assigned to canagliflozin or placebo and followed for a mean of 3.6 years, the primary end point (CV death or hospitalized HF) was reduced in those treated with canagliflozin (16.3 vs 20.8 per 1000 patient-years; hazard ratio - HR, 0.78), as was fatal or hospitalized HF (HR, 0.70) and hospitalized HF alone (HR, 0.67). The benefit on CV death or hospitalized HF may be greater in patients with a prior history of HF (HR, 0.61) constituting 14.4% of the whole group. The effects of canagliflozin compared with placebo on other CV outcomes and key safety outcomes were similar in participants with and without HF at baseline, except for a possibly reduced absolute rate of events attributable to osmotic diuresis among those with a prior history of HF (P=0.03) (Radholm K et al, *Circulation* 2018;138:458–468).

After Left Atrial Appendage (LAA) Closure With Watchman, Device-Related Thrombus (DRT) was Observed in ≈3.7% and was Associated With a Higher Rate of Stroke and Systemic Embolism

Of 1739 patients in 4 studies (PROTECT-AF / PREVAIL / CAP / CAP2) who received an implant (7159 patient-years follow-up; CHA_2DS_2-VASc=4.0), DRT was seen in 65 patients (3.74%). The rates of stroke or systemic embolism (SSE) with and without DRT were 7.46 and 1.78 per 100 patient-years (rate ratio - RR, 3.55; P<0.001), and ischemic SSE rates were 6.28 and 1.65 per 100 patient-years (RR, 3.22, P<0.001). Predictors of DRT were: history of TIA or stroke (odds ratio - OR, 2.31; P=0.007), permanent AF (OR, 2.24; P=0.012); vascular disease (OR, 2.06; P=0.028); LAA diameter (OR, 1.06 per mm increase; P=0.019); left ventricular ejection fraction (OR, 0.96 per 1% increase; P=0.009). DRT and SSE both occurred in 17

of 65 patients (26.2%). Of the 19 SSE events in these patients with DRT, 9 of 19 (47.4%) and 12 of 19 (63.2%) occurred within 1 and 6 months of DRT detection. After LAA closure, most SSEs (123/142, 86.62%) occurred in patients without DRT (Dukkipati SR et al, *Circulation* 2018;138:874–85).

Acute Myocarditis (AM): In a Contemporary Study, Overall Serious Adverse Events After AM Were Lower Than Previously Reported / Patients With Left Ventricular Ejection Fraction (LVEF) <50%, Ventricular Arrhythmias, or Low Cardiac Output Syndrome at Presentation Were at Higher Risk

Among 443 patients (median age, 34 years; 19.4% female) with AM diagnosed by either endomyocardial biopsy (12.6%) and/or increased troponin plus edema and late gadolinium enhancement at cardiac magnetic resonance (CMR) (93.7%), at presentation, 118 patients (26.6%) had LVEF <50%, sustained ventricular arrhythmias, or a low cardiac output syndrome. Cardiac mortality plus heart transplantation rates at 1 and 5 years were 3% and 4.1%. Cardiac mortality plus heart transplantation rates were 11.3% and 14.7% in patients with complicated presentation and 0% in uncomplicated cases (log-rank P<0.0001). Major AM-related cardiac events after the acute phase occurred in 2.8% at the 5-year follow-up, with a higher incidence in patients with complicated forms (10.8% vs 0% in uncomplicated AM; log-rank P<0.0001). β-blockers were the most frequently used medications. After a median time of 196 days, 200 patients had follow-up CMR, and 8 of 55 (14.5%) with complications at presentation had LVEF <50% compared with 1 of 145 (0.7%) of those with uncomplicated presentation (Ammirati E et al, *Circulation* 2018;138: 1088–99).

Only the *SCN5A* Gene was Classified as Having Definitive Evidence as a Cause for Brugada Syndrome (BrS)

Of 21 genes curated for clinical validity, biocurators classified only 1 gene (*SCN5A*) as definitive evidence of its association with BrS, whereas all other genes were classified as limited evidence. After comprehensive review by a clinical Expert panel, all 20 genes classified as limited evidence were reclassified as disputed with regard to any assertions of disease causality for BrS (Hosseini SM et al, *Circulation* 2018;138:1195–1205).

FAME-2: Favorable 5-Year Outcomes of PCI Guided by Fractional Flow Reserve (FFR)

Among 888 patients (FFR-guided PCI) undergoing randomization (447 patients in the PCI group and 441 in the medical-therapy group), at 5 years, the rate of the primary end point (death, MI, urgent revascularization) was lower in the PCI group than in the medical-therapy group (13.9% vs 27%; hazard ratio - HR, 0.46; P<0.001). The difference was driven by urgent revascularizations, which occurred in 6.3% of the patients in the PCI group vs 21.1% in the medical group (HR, 0.27). There were no significant differences between the PCI group and the medical-therapy group in the rates of death (5.1% and 5.2%, respectively; HR, 0.98) or MI (8.1% and 12.0%; HR, 0.66). There was no significant difference in the rate of the primary end point between the PCI group and the registry cohort (13.9% and 15.7%, respectively; HR, 0.88). Relief from angina was more pronounced after PCI than after medical therapy (Xaplanteris P et al, *N Engl J Med* 2018; 379:250-259.

PAREMEDIC 2 Trial: In Out-Of-Hospital Cardiac Arrest, Epinephrine Conferred Higher Rate of 30-Day Survival vs Placebo, But with no Difference in Neurologic Outcome

Concern about the use of epinephrine as a treatment for out-of-hospital cardiac arrest led to a randomized trial involving 8014 patients with out-of-hospital cardiac arrest in the UK, where paramedics administered either parenteral epinephrine (4015 patients) or saline placebo (3999 patients), along with standard care. At 30 days, 130 patients (3.2%) in the epinephrine group and 94 (2.4%) in the placebo group were alive (odds ratio – OR for survival, 1.39; P=0.02). There was no evidence of a significant difference in the proportion of patients who survived until hospital discharge with a favorable neurologic outcome (2.2% vs 1.9%; OR, 1.18). At the time of hospital discharge, severe neurologic impairment (a score of 4 or 5 on the modified Rankin scale) had occurred in more of the survivors in the epinephrine group than in the placebo group (31% vs 17.8%) (Perkins GD et al, *N Engl J Med* 2018; 379:711-721).

ATTR-ACT: Tafamidis is an Effective Therapy for Transthyretin Amyloid Cardiomyopathy

Tafamidis, a benzoxazole derivative lacking non-steroidal anti-inflammatory drug activity that binds to the thyroxine-binding sites of transthyretin and inhibits the dissociation of tetramers into monomers, was tested in 441 patients with transthyretin amyloid cardiomyopathy. All-cause mortality and rates of cardiovascular-related hospitalizations were lower among the 264 patients who received tafamidis than among the 177 patients who received placebo (P<0.001). Tafamidis was associated with lower all-cause mortality (29.5% vs 42.9%; hazard ratio, 0.70) and a lower rate of cardiovascular-related hospitalizations, with a relative risk ratio of 0.68 (0.48 vs 0.70 per year). At month 30, tafamidis was also associated

with a lower rate of decline in distance for the 6-minute walk test (P<0.001) and better quality of life (P<0.001). The incidence and types of adverse events were similar in the two groups (Maurer MS et al, *N Engl J Med* 2018; 379:1007-16).

CAMELLIA–TIMI 61: In High-Risk Overweight or Obese Patients, Lorcaserin Facilitated Sustained Weight Loss Without a Higher Rate of Major Cardiovascular (CV) Events

Among 12,000 overweight or obese patients with atherosclerotic CV disease or multiple CV risk factors, randomly assigned to receive either lorcaserin (10 mg bid) or placebo, at 1 year, weight loss of at least 5% had occurred in 38.7% in the lorcaserin group and in 17.4% in the placebo group (odds ratio, 3.01; P<0.001). Patients in the lorcaserin group had slightly better values with respect to CV risk factors. During a median of 3.3 years, the rate of the primary safety outcome (CV death, MI, or stroke) was 2% per year in the lorcaserin group and 2.1% per year in the placebo group (hazard ratio-HR, 0.99; P<0.001 for noninferiority); the rate of extended major CV events was 4.1% per year and 4.2% per year, respectively (HR, 0.97; P=0.55). Except for a higher number of patients with serious hypoglycemia in the lorcaserin group (13 vs. 4, P=0.04), other adverse events were similar (Bohula EA et al, *N Engl J Med* 2018; 379:1107-17).

VEST: Among Patients With a Recent Myocardial Infarction (MI) and an Ejection Fraction (LVEF) ≤35%, the Wearable Cardioverter–Defibrillator (WCD) did not Lower Arrhythmic Death

Among 2302 MI patients with LVEF ≤35%, 1524 randomly assigned to the device (WCD) group (wearing it for a median of 18 h/d) and 778 to the control group, arrhythmic death occurred in 1.6% in the device group and in 2.4% in the control group (relative risk, 0.67; P=0.18). Death from any cause occurred in 3.1% vs 4.9% respectively (relative risk-RR, 0.64; P=0.04), and non-arrhythmic death in 1.4% and 2.2%, respectively (RR, 0.63; P=0.15). Of the 48 participants in the device group who died, 12 were wearing the device at the time of death. Twenty patients in the device group (1.3%) received an appropriate shock and 9 (0.6%) received an inappropriate shock (Olgin JE et al, *N Engl J Med* 2018; 379:1205-15).

Electric Cars did not Affect CIED Function or Programming / However, Vigilance is Recommended to Monitor for Rare Events, Especially Those Associated With Charging and Proposed "Supercharging" Technology

Among 108 patients fitted with cardiac implantable electronic devices (CIEDs; 34 pacemakers, 74 ICDs) for several indications who were tested for electromagnetic interference (EMI) by electric cars, no evidence of EMI with CIEDs was found. There were no episodes of over- or under-sensing, inappropriate pacing or pacing inhibition, or device reprogramming (incidence of EMI, 0%). Postexposure testing also revealed that pacing thresholds, sensing, and lead impedance remained unchanged. The electrocardiographic recorder did observe EMI, but CIED function and programming were unaffected (Lennerz C et al, *Ann Intern Med* 2018;169: 350-52).

Tailored (Weight-Adjusted) Strategy for Aspirin in Primary Prevention: Low Doses (75–100 mg) are Only Effective in Preventing Cardiovascular (CV) Events in Patients Weighing <70 kg / Higher Doses are Only Effective in Patients Weighing ≥70 kg

Among 10 eligible trials of aspirin in primary prevention (117,279 participants), the ability of 75–100 mg aspirin to reduce CV events decreased with increasing weight ($p_{interaction}$=0·0072), with benefit seen in people weighing 50–69 kg (hazard ratio - HR 0.75) but not in those weighing ≥70 kg (HR 0.95; 1.09 for CV death). The case fatality of a first CV event was increased by low-dose aspirin in people weighing ≥70 kg (odds ratio 1.33, p=0·0082). Higher doses of aspirin (≥325 mg) had the opposite interaction with bodyweight, reducing CV events only at higher weight ($p_{interaction}$=0.017). Findings were similar in men and women, in people with diabetes, in trials of aspirin in secondary prevention, and in relation to height ($p_{interaction}$=0.0025 for CV events). Aspirin-mediated reductions in long-term risk of colorectal cancer were also weight dependent ($p_{interaction}$=0.038). Stratification by body size also revealed harms due to excess dosing: risk of sudden death was increased by aspirin in people at low weight for dose ($p_{interaction}$=0.0018) and risk of all-cause death was increased in people weighing less than 50 kg who were receiving 75–100 mg aspirin (HR 1.52, p=0·031). In participants aged ≥70 years, the 3-year risk of cancer was also increased by aspirin (HR 1.20, p=0.02), particularly in those weighing <70 kg (1.31, p=0.009) and consequently in women (HR 1.44, p=0.0069) (Rothwell PM JL et al, *Lancet* 2018;392:387-99).

PURE: Sodium Intake was Associated With Cardiovascular (CV) Disease (CVD) and Strokes Only in Communities Where Mean Intake was >5 g/d

WHO recommends consuming <2 g/day sodium as a preventive measure against CVD, but this target has not been achieved in any country. Among 95,767 participants in 369 communities/18 countries assessed for BP and 82,544 in 255 communities for CV outcomes over a median of 8.1 years, overall, mean systolic BP increased

by 2.86 mmHg per 1 g increase in mean sodium intake, but positive associations were only seen among the communities in the highest tertile of sodium intake (p<0.0001). The association between mean sodium intake and major CV events showed significant deviations from linearity (p=0.043) due to a significant inverse association in the lowest tertile of sodium intake (lowest tertile <4.43 g/d, p=0.0497), no association in the middle tertile (middle tertile 4.43–5.08 g/day, p=0.8391), and a positive but non-significant association in the highest tertile (highest tertile >5.08 g/d, p=0.0712). A strong association was seen with stroke in China (mean sodium intake 5.58 g/day, 0.42 events per 1000 years, p=0.0020) compared with in other countries (4.49 g/day, –0.26 events, p=0.0124; p<0.0001 for heterogeneity). All major CV outcomes decreased with increasing potassium intake in all countries (Mente A et al, *Lancet* 2018;392:496-506).

MATRIX: In Patients With Acute Coronary Syndrome, Radial Access was Associated With Lower Rates of Net Adverse Clinical Events Compared With Femoral Access, but not Major Adverse Cardio-vascular Events (MACE) at 1 Year. Bivalirudin did not Confer Any Benefit Over Heparin

Among 8404 patients randomly assigned to radial (4197 patients) or femoral (4207 patients) access, and 7213 randomly assigned to bivalirudin (3610 patients) or heparin (3603 patients), at 1 year, MACE did not differ (14.2% vs 15.7%; rate ratio-RR 0.89; p=0.0526), but net adverse clinical events were fewer with radial than with femoral access (15.2% vs 17.2%; RR 0·87; p=0.0128). Compared with heparin, bivalirudin was not associated with fewer MACE (15.8% vs 16.8%; RR 0.94; p=0.28) or net adverse clinical events (17% vs 18.4%; RR 0.91; p=0.10) (Valgimigli M et al, *Lancet* 2018; 392:835-48).

BASKET-SMALL 2: In Small Native Coronary Artery Disease, Drug-Coated Balloons (DCB) was Non-Inferior to DES Regarding MACE up to 1 Year, With Similar Event Rates for Both Treatment Groups

Among 382 patients randomly assigned to the DCB group and 376 to DES group, non-inferiority of DCB vs DES was shown. After 1 year, the proportions of MACE were similar in both groups (MACE was 7.5% for the DCB vs 7.3% for the DES group; hazard ratio -HR 0.97, p=0.9180). There were 5 (1.3%) cardiac-related deaths in the DES group and 12 (3.1%) in the DCB group. Probable or definite stent thrombosis (0.8% in the DCB vs 1.1% in the DES group; HR 0.73) and major bleeding (1.1% in the DCB vs 2.4% in the DES group; HR 0.45) were the most common adverse events (Jeger RV, *Lancet* 2018;392:849-56).

ASCOT Legacy Study: Long-Term Beneficial Effects on Mortality of Antihypertensive and Hypolipidemic Treatment / Patients on Amlodipine-Based Treatment Had Fewer Stroke Deaths and Patients on Atorvastatin Had Fewer Cardiovascular (CV) Deaths >10 Years After Trial Closure

Over 16 years, among 8580 UK-based patients in ASCOT, in the BP lowering arm (BPLA), there were significantly fewer deaths from stroke (adjusted HR 0.71, p=0.0305) in the amlodipine-based treatment group than in the atenolol-based treatment group. In the 3975 patients in the non-lipid-lowering arm (LLA) group, there were fewer CV deaths (adjusted HR 0.79, p=0.0046) among those assigned to amlodipine-based treatment (p=0.022). In the LLA, significantly fewer CV deaths (HR 0.85, p=0.0395) occurred among patients assigned to statin than among those assigned placebo (Gupta A et al, *Lancet* 2018;392:1127-37).

Higher Dose of β-Blocker Therapy (>25 mg/d for Carvedilol or >100 mg/d For Metoprolol) and a Lower Achieved Heart Rate (HR) (Mean 64-77 bpm) Were Independently Associated With a Reduction in Mortality in HFrEf Patients

A total of 36,168 patients on low-dose β-blocker (carvedilol <25 mg/d or metoprolol <100 mg/d) were matched with 36,168 patients on high dose β-blocker using propensity score matching. High β-blocker dose was associated with lower overall mortality as compared with a low dose of β blocker (hazard ratio 0.75, p <0.01) independent of the HR achieved. The results held for all 4 quartiles of average HR. A higher β-blocker dose or a lower HR were independently and jointly associated with lower mortality for all quartiles of HR (Ajam T et al, *Am J Cardiol* 2018;122:994-8).

Meta-Analysis: Catheter Ablation of Atrial Fibrillation (AF) in Patients with Heart Failure (HF) is Associated With Improved Survival and HF Hospitalizations Compared With Medical Therapy

Among 775 ambulatory AF patients from 6 trials with HF and a mean LVEF of 31% (mean NYHA class 2.5), over 26 months, ablation was associated with lower incidences of all-cause mortality (RR 0.50, p <0.0001), and HF hospitalizations (RR 0.58, p = 0.002), with similar incidences of stroke. Improvement in LVEF and quality of life were also noted, with no change in 6-minute walk test. The incidence of all reported procedural complications (including major and minor) was 7.3% (Elgendy LY et al, *Am J Cardiol* 2018;122:806-13).

TAVI for Aortic Regurgitation (AR): Feasible in Selected High-Risk Patients Albeit With Considerable Risk of Valve Malpositioning and Residual AR

Among 254 AR patients (age 74 ± 12 years, STS score 6.6±6.2%) undergoing TAVI, success was higher with newer (82%) vs early generation (47%) devices ($p < 0.001$), driven by lower rates of device malpositioning (9% vs 33%) and AR ≥ moderate (4% vs 31%), translating into higher clinical efficacy at 30 days in patients treated with newer devices (72% vs 56%, $p = 0.041$). Both device under- and oversizing were associated with an increased risk of malpositioning (De Baker O et al, *Am J Cardiol* 2018;122:1028-35).

DETO2X-AMI Trial: No Benefit of Routine Use of Supplemental Oxygen in Normoxemic Patients With STEMI Undergoing Primary PCI

Among 2807 patients with STEMI undergoing PCI randomized to receive oxygen at 6 L/min for 6–12 h or ambient air, the pre-specified primary composite endpoint of all-cause death, rehospitalization with MI, cardiogenic shock, or stent thrombosis at 1 year occurred in 6.3% vs 7.5% (hazard ratio - HR 0.85; $P = 0.27$). There was no difference in the rate of death from any cause (HR 0.86; $P = 0.41$), rate of rehospitalization for MI (HR 0.92; $P = 0.73$), rehospitalization for cardiogenic shock (HR 1.05; $P = 0.95$), or stent thrombosis (HR 1.27; $P = 0.64$) (Hoffman R et al, *Eur Heart J* 2018;39:2730-39).

Continuing Apixaban Peri-Procedurally was "Safe" in Patients Undergoing Atrial Fibrillation (AF) Ablation / But ¼ Had Ablation-Related Acute Brain Lesions

Overall, 674 AF patients (median age 64 years, 33% female, 42% non-paroxysmal AF) undergoing ablation were randomized; 633 received study drug (apixaban at 5 mg bid or vitamin K antagonists - VKA, INR 2–3); 335 had MRI. The primary outcome (death, stroke, or bleeding) was observed in 22/318 patients randomized to apixaban, and in 23/315 randomized to VKA (difference −0.38%, non-inferiority $P = 0.0002$), including 2 (0.3%) deaths, 2 (0.3%) strokes, and 24 (3.8%) major bleeds. Acute small brain lesions were found in a similar number of patients in each arm (apixaban 27.2%, VKA 24.8%; $P = 0.64$). Cognitive function increased at the end of follow-up without differences between study groups (Kirchhof P et al, *Eur Heart J* 2018;39:2942-55).

Important Review and Other Articles

- 2018 ESC/ESH Hypertension Guidelines (Williams B et al, *Eur Heart J* 2018;39:3021-3104)
- Neoplasia and the heart (Maleszewski JJ et al, *J Am Coll Cardiol* 2018;72:202–27)
- Therapies targeting left atrial appendage (Turagam MK et al, *J Am Coll Cardiol* 2018;72:448-63)
- Fourth universal definition of MI (Thygesen K et al, *J Am Coll Cardiol* 2018 Aug;72:xx)
- Mechanical unloading in heart failure (Nir U et al, *J Am Coll Cardiol* 2018;72:569-80)
- Arrhythmogenic RV dysplasia (Gandjbakhch E et al, *J Am Coll Cardiol* 2018;72:784-804)
- Telomere length as CV aging biomarker (De Meyer T et al, *J Am Coll Cardiol* 2018;72:805-13)
- Brugada syndrome (Brugada J et al, *J Am Coll Cardiol* 2018;72:1046-59)
- Orthostatic hypotension (Freeman R et al, *J Am Coll Cardiol* 2018;72:1294-309)
- Anemia and iron deficiency in heart failure (Anand IS & Gupta P, *Circulation* 2018;138:80-98)
- Management of intraprocedural anticoagulation with NOACs during AF ablation (Martin A-C et al, *Circulation* 2018;138:627-33)
- Primary aldosteronism (Byrd JB et al, *Circulation* 2018;138:823–835)
- Cardiorenal syndrome (Zannad F & Rossignol P, *Circulation* 2018;138:929-44)
- Ventricular arrhythmias in cardiac sarcoidosis (Okada DR et al, *Circulation* 2018;138:1253–64)
- Hypertrophic cardiomyopathy (Maron BJ, *New Engl J Med* 2018; 379:655-668)
- Adverse effects of statin therapy (Mach F et al, *Eur Heart J* 2018; 39:2526–39)
- TAVI (Cahill TJ et al, *Eur Heart J* 2018; 39:2625–34)
- 2018 ESC Guidelines for management of CV diseases during pregnancy (Regitz-Zagrosek V et al, *Eur Heart J* 2018;39:3165-3241)
- Management of antithrombotic therapy in AF patients presenting with ACS and/or undergoing PCI (Lip GYH et al, *Eur Heart J* 2018;39:2847-50)
- ESC Position paper on spontaneous coronary dissection (Adlam D et al, *Eur Heart J* 2018;39:3353-68)
- New-onset arrhythmias following TAVI (Siontis GCM et al, *Heart* 2018;104:1208-15)
- Optimal CRT (Chousou PA & Pugh PJ, *Heart* 2018;104:1300-07)
- Cardiovascular safety of oncologic agents (Manolis AA et al, *Exp Opin Drug Saf* 2018;17: 875-92 & 893-915)
- Perioperative management of anticoagulant and anti-platelet therapy (Tafur A & Duketis J, *Heart* 2018;104: 1461-67)