Cardiology News / Recent Literature Review / Second Quarter 2020

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ESC Meeting/Digital Experience: 29/8-1/9/2020

TCT/ Virtual Event: 14-18/10/2020

HCS/Panhellenic (41st) Congress of Cardiology: Athens, 22-24/10/2020

AHA Meeting 2020: cancelled

ACC Meeting: Atlanta, 20-22/3/2021

EHRA Meeting: Barcelona, 28-30/3/2021

Women Have a Higher Risk of MACE and Ischemia-Driven Target Lesion Revascularization (ID-TLR) Compared With Men at 5 Years Post-PCI

Among 32,877 patients, 9,141 (27.8%) were women who were older and had higher body mass index, more frequent hypertension and diabetes, and less frequent history of surgical or percutaneous revascularization compared with men. Lesions in women had smaller reference vessel diameter and shorter lesion length. At 5 years, women had a higher rate of MACE (18.9% vs 17.7%; p=0.003), all-cause death (10.4% vs 8.7%; p=0.0008), cardiac death (4.9% vs 4.0%; p=0.003) and ID-TLR (10.9% vs 10.2%; p=0.02) compared with men. By multivariable analysis, female sex was an independent predictor of MACE (hazard ratio [HR:]: 1.14; p=0.04) and ID-TLR (HR: 1.23; p=0.009) but not all-cause death (HR: 0.91; p=0.30) or cardiac death (HR: 0.97; p=0.85) (Kosmidou I et al, *J Am Coll Cardiol* 2020; 75:1631-40).

PARAGON-HF: Baseline and Mean Achieved Systolic Blood Pressure (SBP) of 120-129 mmHg Identified the Lowest Risk Patients With Heart Failure With Preserved Ejection Fraction Treated With Sacubitril/ Valsartan

Among 4,795 trial participants (age 73 ± 8 years, 52% women), multivariable analysis indicated that baseline and mean achieved SBP of 120-129 mmHg demonstrated the lowest risk for all outcomes. Sacubitril/valsartan reduced SBP by 5.2 mmHg compared with valsartan at 4 weeks, which was not modified by baseline SBP. However, sacubitril/valsartan reduced SBP more in women (6.3 mmHg) than men (4 mmHg) (interaction p=0.005). Change in SBP was directly associated with change in NT-proBNP (p<0.001) but not symptom score (p=0.40) (Selvaraj S et al, *J Am Coll Cardiol* 2020; 75:1644-56).

Evolocumab Added to Statin Had no Impact on Cognition after a Mean of 2.2 years, Even Among Patients with LDL-C<20 mg/dl

A total of 22,655 patients in the FOURIER trial completed a survey on memory (ECog) after a median duration of 2.2 years. The proportions of patients reporting cognitive decline (ECog score ≥2) at the end of the study were similar for placebo vs evolocumab, both for total score 3.6% vs 3.7% (p=NS) and for subdomains (memory, 5.8% vs 6%; total executive, 3.6% vs 3.7%). The proportion of patients reporting a decline in total cognitive score was similar among the 2,338 patients who achieved very low LDL-C levels (<20 mg/dl) compared to the 3,613 patients with LDL-C ≥100 mg/dl (3.8% vs 4.5%, p = 0.57). (Gencer B et al, *J Am Coll Cardiol* 2019; 75:2283-93).

Higher Olive Oil Intake Conferred Lower Risk of Coronary Artery Disease (CAD) and Total Cardiovascular Disease (CVD) in 2 Large Prospective Cohorts of U.S. Patients/ The Substitution of Margarine, Butter, Mayonnaise, and Dairy Fat With Olive Oil Could Lead to Lower Risk of CAD and CVD

Over 24 years, this study documented 9,797 incident cases of CVD, including 6,034 CAD cases and 3,802 stroke cases. After adjusting for major diet and lifestyle factors, compared with nonconsumers, those with higher olive oil intake (>0.5 tablespoon/day or >7 g/day) had 14% lower risk of CVD (pooled HR: 0.86) and 18% lower risk of CAD (pooled HR: 0.82). No significant associations were observed for total or ischemic stroke. Replacing 5 g/day of margarine, butter, mayonnaise, or dairy fat with the equivalent amount of olive oil was associated with 5% to 7% lower risk of total CVD and CAD. (Guasch-Ferré M et al, *J Am Coll Cardiol* 2020;75: 1729-39).

First Direct Evidence that KCNQ1 Antibodies Act as Agonists on I_{ks} Channels / KCNQ1 Antibodies Restored Alterations in Cardiac Repolarization and Suppressed Arrhythmias in LQTS2/Thus, KCNQ1 Antibody May Present a Novel Therapeutic Approach for LQTS2

The authors purified KCNQ1 antibodies and performed whole-cell patch clamp experiments and single-channel recordings on Chinese hamster ovary cells overexpressing I_{Ks} channels. The effect of purified KCNQ1 antibodies on human cardiomyocytes derived from induced pluripotent stem cells was then studied. The study demonstrated that KCNQ1 antibodies underlie the previously observed increase in repolarizing I_{Ks} current. The antibodies shift the voltage dependence of activation and slow the deactivation of I_{Ks}. At the single-channel level, KCNQ1 antibodies increase the open time and probability of the channel. In models of LQTS type 2 (LQTS2) using human induced pluripotent stem cell-

derived cardiomyocytes, KCNQ1 antibodies reverse the prolonged cardiac repolarization and abolish arrhythmic activities (Maguy A et al, *J Am Coll Cardiol* 2020;75: 2140-52).

In Patients With PFO-Associated Stroke, Atrial Septal Aneurysm (ASA) is a More Important Predictor of Recurrent Stroke Than Shunt Size

Of 898 patients (mean age 45.3 years), 178 (19.8%) had ASA with large PFO, 71 (7.9%) ASA with nonlarge PFO, 397 (44.2%) large PFO without ASA, and 252 (28.1%) nonlarge PFO without ASA. Over a median of 3.8 years, 47 (5.2%) patients experienced a recurrent stroke. In a model accounting for age, hypertension, antithrombotic therapy, and PFO anatomy, ASA was independently associated with recurrent stroke (adjusted hazard ratio-HR: 3.27; p<0.0001), whereas large PFO was not (HR: 1.43; p=0.50) (Turc G et al, *J Am Coll Cardiol* 2020;75:2312-20).

TWILIGHT Study: Among Patients Undergoing Complex PCI Who Completed 3 Months of Ticagrelor Plus Aspirin, Continuation of Ticagrelor Monotherapy Was Associated With Lower Incidence of Bleeding Without Increasing the Risk of Ischemic Events

Among 2,342 patients having complex PCI, compared to ticagrelor plus aspirin, ticagrelor plus placebo resulted in significantly lower rates of bleeding (4.2% vs 7.7%; hazard ratio -HR: 0.54). There were no significant between-group differences in death, MI, or stroke (3.8% vs. 4.9%; HR: 0.77), nor in stent thrombosis (Dangas G et al, *J Am Coll Cardiol* 2020; 75:2414-24).

TWILIGHT: Compared With Ticagrelor Plus Aspirin, the Effect of Ticagrelor Monotherapy in Reducing the Risk of Bleeding Without Increase in Ischemic Events Was Consistent Among Patients With or Without DM Undergoing PCI

The incidence of BARC 2, 3, or 5 bleeding was 4.5% and 6.7% among patients with DM (n=2620) randomized to ticagrelor plus placebo vs ticagrelor plus aspirin (hazard ratio-HR: 0.65; p=0.012). Ticagrelor monotherapy did not increase ischemic events compared with ticagrelor plus aspirin (4.6% vs. 5.9%; HR: 0.77; p=0.14). In the overall trial population, there was no significant interaction between DM status and treatment group for the primary bleeding or ischemic endpoints (Angiolillo DJ et al, *J Am Coll Cardiol* 2020; 75:2403-13).

Single-Dose sc Selatogrel in Patients With AMI Was Safe and Induced a Profound, Rapid, and Dose-Related Antiplatelet Response

Among 47 patients receiving selatogrel (a potent, highly selective, and reversible $P2Y_{12}$ receptor antagonist with rapid onset and short duration of action.) 8 mg (n=24) or 16 mg (n=23) followed by ticagrelor (n=43) or clopidogrel (n=1). The proportion of responders 30 min post-dose was 91% and 96% with 8 and 16 mg, respectively. Response rates were independent from type of AMI presentation, age, or sex. A similar response rate was observed at 15 min, which was sustained at 60 min post-dose. Selatogrel was well tolerated, without major bleeding complications (Sinnaeve P et al, *J Am Coll Cardiol* 2020; 75:2588-97).

MAVERICK-HCM (Phase II): Mavacamten, a Novel Myosin Inhibitor, Was Well Tolerated in Most Patients With Symptomatic nHCM and Produced a Significant Reduction in NT-ProBNP and cTnI, Suggesting Improvement in Myocardial Wall Stress

Among 59 participants randomized to 200 ng/ml (n=19) or 500 ng/ml (n=21) of mavacamten, or placebo (n=19) (mean age 54 years, 58% women), serious adverse events occurred in 10% with the drug and in 21% with placebo. Five participants on mavacamten had reversible reduction in LVEF ≤45%. NT-proBNP geometric mean decreased by 53% in the pooled mavacamten group vs 1% in the placebo group (p=0.0005). Cardiac troponin I (cTnI) geometric mean decreased by 34% in the pooled mavacamten group vs a 4% increase in the placebo group (p=0.009) (Ho CY et al, *J Am Coll Cardiol* 2020; 75:2649-60).

DAEDALUS: At 3 Years, Drug-Coated Balloon (DCB) Angioplasty and Re-stenting with DES are Similarly Affective and Safe in Bare Metal Stent Restenosis (BMS-ISR), but DCB is Less Effective than Repeat DES in DES-ISR, and Associated with a Nonsignificant Reduction in Safety Endpoint / Overall, DES-ISR is Associated with Higher Treatment Failure and Similar Safety Compared with BMS-ISR

A total of 710 patients with BMS-ISR (722 lesions) and 1,248 with DES-ISR (1,377 lesions) were included. In patients with BMS-ISR, no significant difference between treatments was observed in efficacy (9.2% vs. 10.2%; hazard ratio-HR: 0.83) and safety endpoints (8.7% vs. 7.5%; HR: 1.13). In patients with DES-ISR, the risk of the primary efficacy endpoint was higher with DCB angioplasty than with repeat DES implantation (20.3% vs. 13.4%; HR: 1.58), whereas the risk of the primary safety endpoint was numerically lower (9.5% vs. 13.3%; HR: 0.69). Regardless of the treatment used, the risk of TLR was lower in BMS- vs DES-ISR (9.7% vs. 17.0%; HR: 0.56), whereas safety was not significantly different between ISR types (Giacoppo D et al, *J Am Coll Cardiol* 2020;75:2664–78).

Infective Endocarditis After TAVI Most Frequently Occurs in the Early Period, is Commonly Caused by *Enterococcus Species*, and Results in Significant Mortality and Stroke Risk

Among 7,203 patients undergoing TAVI at 15 hospitals in Switzerland, endocarditis occurred in 149 patients. The incidence for peri-procedural, delayed-early, and late endocarditis after TAVI was 2.59, 0.71, and 0.40 events per 100 person-years, respectively. Among patients with early endocarditis, *Enterococcus species* were the most frequently isolated microorganisms (30%). Among those with peri-procedural endocarditis, 47.9% of patients had a pathogen that was not susceptible to the peri-procedural antibiotic prophylaxis. Younger age (subhazard ratio-SHR: 0.969), male sex (SHR: 1.989), lack of pre-dilatation (SHR: 1.485), and treatment in a catheterization laboratory as opposed to hybrid operating room (SHR: 1.648) were independently associated with endocarditis. In a case-control matched analysis, patients with endocarditis were at increased risk of mortality (hazard ratio-HR: 6.55) and stroke (HR: 4.03) (Stortecky S et al, *J Am Coll Cardiol* 2020;75:3020-30).

***SHaRe Registry:* Hypertrophic Cardiomyopathy (HCM) With Left Ventricular (LV) Systolic Dysfunction (EF<50%) (*HCM-LVSD)* Affects ≈8% of Patients With HCM / Despite Variable Natural History, 75% Had Adverse Events (a Death Equivalent in 35%) at a Median of 8.4 Years After Developing Systolic Dysfunction / In Addition to Clinical Features, Genetic Substrate Appears to Play a Role in Prognosis (Multiple Sarcomeric Variants) and Risk for Incident HCM-LVSD (Thin Filament Variants)**

Among 6793 patients with HCM, 553 (8%) had HCM-LVSD. Overall, 75% of patients with HCM-LVSD experienced clinically relevant events, and 35% met the composite outcome (all-cause death, n=128; cardiac transplantation, n=55; or LVAD implantation, n=9). After recognition of HCM-LVSD, the median time to composite outcome was 8.4 years. There was substantial individual variation in natural history. Significant predictors of the composite outcome included the presence of multiple pathogenic/likely pathogenic sarcomeric variants (hazard ratio-HR, 5.6), AF (HR, 2.6), and LVEF <35% (HR, 2.0). The incidence of new HCM-LVSD was ≈7.5% over 15 years. Significant predictors of developing incident HCM-LVSD included greater LV cavity size (HR, 1.1) and wall thickness (HR, 1.3), LVEF of 50-60% (HR, 1.8-2.8) at baseline evaluation, the presence of late gadolinium enhancement on cardiac magnetic resonance imaging (HR, 2.3), and the presence of a pathogenic/likely pathogenic sarcomeric variant, particularly in thin filament genes (HR, 1.5 and 2.5, respectively) (Marstrand P et al, *Circulation* 2020;141:1371–83).

End-Stage (ES) Hypertrophic Cardiomyopathy (HCM): Contemporary Treatment Strategies, Including ICDs and Heart Transplant, are Associated with Lower Mortality Than Previously Considered / ICDs Should be Considered When EF is <50%

Among 2,447 patients, 118 (4.8%) had ES-HCM (EF 39 ± 9%) at age 48 ± 15 years. Notably, over follow-up, 57 patients (48%) achieved clinical stability in NYHA classes I/II with medical treatment (or cardiac resynchronization therapy). In total, 61 other patients (52%) developed refractory heart failure to disabling NYHA classes III/IV (5.2%/year); 67% have survived, including 31 with heart transplant. Of the 118 ES patients, 21 had appropriate ICD therapy. With all available treatment modalities, ES-related mortality was 1.9%/year, with 10-year survival of 85%. Mortality was 4-fold lower than previously reported for ES (8.0%/year), but exceeded 10-fold HCM with preserved EF (0.2%/year; p<0.001) (Rowin EJ et al, *J Am Coll Cardiol* 2020;75:3033-43).

CABANA: Catheter Ablation Was Effective in Reducing AF Recurrence by ~50% Compared With Drug Therapy over 5 Years / AF Burden Was Also Significantly Reduced by Catheter Ablation

Among 1,240 patients (median age 68 years, 34.4% women, 43% PAF), over 5 years, first recurrence of *any* AF (hazard ratio-HR: 0.52; p<0.001) or first *symptomatic-only* AF (HR: 0.49; p < 0.001) were significantly reduced in the catheter ablation group. Baseline Holter AF burden in both treatment groups was 48%. At 12 months, AF burden in ablation patients averaged 6.3%, and in drug-therapy patients, 14.4%. AF burden was significantly less in catheter ablation (p<0.001) (Poole JE et al, *J Am Coll Cardiol* 2020;75:3105-18).

PRAGUE-17: Among Patients at High Risk for Stroke and Bleeding, Left Atrial Appendage Closure (LAAC) was Noninferior to Direct Oral Anticoagulants (DOAC) in Preventing Major AF-Related Events

A high-risk patient cohort (CHA_2DS_2-VASc: 4.7±1.5) was randomized to receive LAAC (n=201, successful in 90%) or DOAC (n=201, apixaban in 95.5%). At a median 19.9 months, the annual rates of the primary outcome were 11% with LAAC and ~13% with DOAC (subdistribution hazard ratio-sHR: 0.84; p=0.44; p=0.004 for noninferiority). There were no differences between groups for the components of the composite endpoint: all-stroke/TIA (sHR: 1.00), clinically significant bleeding (sHR: 0.81), and cardiovascular death (sHR: 0.75). Major

LAAC-related complications occurred in 4.5% (Osmacik P et al, *J Am Coll Cardiol* 2020;75:3122-35).

MARINER: Extended-Duration Rivaroxaban in Hospitalized Medically Ill Patients Conferred 28% Reduction in Fatal and Major Thromboembolic Events Without a Significant Increase in Major Bleeding

Among 4,909 patients assigned to rivaroxaban (10 mg) and 4,913 assigned to placebo (mean age 67.8 years, 55.5% men, mean baseline creatinine clearance 87.8 ml/min, mean duration of hospitalization 6.7 days) at hospital discharge for 45 days, the pre-specified composite efficacy endpoint (symptomatic VTE, myocardial infarction, non-hemorrhagic stroke, and cardiovascular death) occurred in 1.28% and 1.77% of patients, respectively (hazard ratio-HR: 0.72; p=0.049), whereas major bleeding occurred in 0.27% and 0.18%, respectively (HR: 1.44; p=0.398) (Spyropoulos AC et al, *J Am Coll Cardiol* 2020;75:3140-7).

Unsafe Transesophageal Echocardiography (TEE) to Guide Structural Cardiac Interventions: Most Patients Had Some Form of Injury Associated With TEE, With Longer Procedural Time and Poor or Suboptimal Image Quality Determining an Increased Risk

Post-procedural esophagogastroduodenoscopy (EGD) in 50 patients undergoing structural cardiac interventions with TEE guidance (mitral and tricuspid valve repair, left atrial appendage closure, and paravalvular leak closure) showed a new injury in 86% (n=43 of 50) of patients, with complex lesions accounting for 40% (n=20 of 50) of cases. Patients with complex lesions presented more frequently with an abnormal baseline EGD (70% vs. 37%; p=0.04) and had a higher incidence of post-procedural dysphagia or odynophagia (40% vs. 10%; p=0.02). Independent factors associated with an increased risk of complex lesions were a longer procedural time under TEE manipulation (for each 10-min increment in imaging time, odds ratio: 1.27) and poor or suboptimal image quality (odds ratio: 4.93) (Freitas-Ferraz AB et al, *J Am Coll Cardiol* 2020;75:3164-73).

ATTR-ACT: Cost of Treatment of Transthyretin Amyloid Cardiomyopathy (ATTR) With Tafamidis is Prohibitive as it May Produce Substantial Clinical Benefit But Exceeds Cost-Effectiveness Thresholds Even in the US, Limiting Access to and Uptake of this Effective Therapy Unless There is a Large Reduction in Drug Cost

Compared with usual care, tafamidis was projected to add 1.29 quality-adjusted life-years (QALYs) at an incremental cost of $1,135,000, resulting in an incremental cost-effectiveness ratio (ICER) of $880,000 per QALY gained. A 92.6% price reduction from $225 000 to $16 563 would be necessary to make tafamidis cost-effective at $100 000/QALY. Treating all eligible patients with transthyretin amyloid cardiomyopathy in the US with tafamidis (n=120 000) was estimated to increase annual healthcare spending by $32.3 billion (Kazi DS et al, Circulation. 2020;141:1214–1224).

DECLARE-TIMI 58 Trial: Dapagliflozin Decreased Episodes of Atrial Fibrillation/Flutter (AF/AFL) in High-Risk Patients with Type 2 Diabetes

Dapagliflozin reduced the risk of AF/AFL events by 19% (264 vs 325 events; 7.8 vs 9.6 events per 1000 patient-years; hazard ratio-HR, 0.81; *P*=0.009). The reduction in AF/AFL events was consistent regardless of presence or absence of a history of AF/AFL at baseline (previous AF/AFL: HR, 0.79; no AF/AFL: HR, 0.81; *P* for interaction 0.89). Similarly, presence of atherosclerotic cardiovascular disease (HR, 0.83) vs multiple risk factors (HR, 0.78; *P* for interaction 0.72) or a history of heart failure (HF) (HF: HR, 0.78; No HF: HR, 0.81; *P* for interaction 0.88) did not modify the reduction in AF/AFL events observed with dapagliflozin. Dapagliflozin also reduced the total number (first and recurrent) of AF/AFL events (337 vs 432; incidence rate ratio, 0.77; *P*=0.005) (Zelniker TA et al, *Circulation* 2020;141:1227-34).

Apixaban vs Warfarin in Patients With AF and Advanced Chronic Kidney Disease (CKD): Among Patients with AF and CrCl 25-30 mL/min, Apixaban Caused Less Bleeding than Warfarin, with even Greater Reductions in Bleeding than in Patients with CrCl >30 mL/min / Substantial Overlap in the Range of Exposure to Apixaban 5 mg bid for Patients with or without Advanced CKD Supporting Conventional Dosing in Patients with CrCl 25-30 mL/min

Among patients with CrCl 25-30 mL/min, apixaban caused less major bleeding (hazard ratio-HR, 0.34) and major or clinically relevant nonmajor bleeding (HR, 0.35) compared with warfarin. Patients with CrCl 25-30 mL/min randomized to apixaban demonstrated a trend toward lower rates of major bleeding when compared with those with CrCl >30 mL/min (*P* interaction=0.08) and major or clinically relevant nonmajor bleeding (*P* interaction=0.05). Median daily steady-state areas under the curve for apixaban 5 mg bid were 5512 ng/(mL·h) and 3406 ng/(mL·h) for patients with CrCl 25-30 mL/min or >30 mL/min, respectively. For apixaban 2.5 mg bid, the median exposure was 2780 ng/(mL·h) for patients with CrCl 25-30 mL/min. The area under the curve values for patients with CrCl 25-30 mL/min fell within the ranges demonstrated for patients with CrCl >30 mL/min (Stanifer JW et al, *Circulation* 2020;141:1384–92).

PRECOMBAT Trial: 10-Year Follow-up of Patients With Left Main Coronary Artery Disease Randomized to PCI or CABG did not Demonstrate Significant Difference in Major Adverse Cardiac or Cerebrovascular Events (MACCE)

Among patients with unprotected left main disease randomly assigned to PCI with sirolimus-eluting stents (n=300) or CABG (n=300), at 10 years, a primary outcome event occurred in 29.8% of the PCI group and in 24.7% of the CABG group (hazard ratio-HR with PCI vs CABG, 1.25). Although the study is underpowered, the 10-year incidence of the composite of death, MI, or stroke (18.2% vs 17.5%; HR 1.00) and all-cause mortality (14.5% vs 13.8%; HR 1.13) were not significantly different between the 2 groups. Ischemia-driven target-vessel revascularization was more frequent after PCI (16.1% vs 8%; HR 1.98) (Park D-W et al, *Circulation* 2020;141:1437–1446).

Desmoplakin (DSP) Cardiomyopathy: A Distinct Form of Arrhythmogenic Cardiomyopathy Characterized by Episodic Myocardial Injury, Left Ventricular (LV) Fibrosis That Precedes Systolic Dysfunction, and a High Incidence of Ventricular Arrhythmias (VAs)

Comparing 107 patients with pathogenic *DSP* mutations and 81 patients with pathogenic plakophilin 2 (*PKP2*) mutations, LV predominant cardiomyopathy (CM) was exclusively present among patients with *DSP* (55% vs 0% for *PKP2*, $P<0.001$), whereas right ventricular (RV) CM was present in only 14% of patients with *DSP* vs 40% for *PKP2* ($P<0.001$). Arrhythmogenic RV CM diagnostic criteria had poor sensitivity for *DSP* CM. LV late gadolinium enhancement (LGE) was present in a primarily subepicardial distribution in 40% of patients with *DSP*. LV LGE occurred with normal LV systolic function in 35% (8/23) of patients with *DSP*. Episodes of acute myocardial injury (chest pain with troponin elevation and normal coronary angiography) occurred in 15% of patients with *DSP* and were strongly associated with LV LGE (90%), even in cases of acute myocardial injury with normal ventricular function (4/5, 80% with LGE). In 4 *DSP* cases with 18F-fluorodeoxyglucose PET scans, acute LV myocardial injury was associated with myocardial inflammation misdiagnosed initially as cardiac sarcoidosis or myocarditis. LVEF <55% was strongly associated with severe VAs for *DSP* cases ($P<0.001$, sensitivity 85%, specificity 53%). RV EF <45% was associated with severe arrhythmias for *PKP2* cases ($P<0.001$) but was poorly associated for *DSP* cases ($P=0.8$). Frequent PVCs were common among patients with severe arrhythmias for both *DSP* (80%) and *PKP2* (91%) groups (P=NS) (Smith ED et al, *Circulation* 2020;141:1872-84).

Infective Endocarditis: Despite Changes in Antibiotic Prophylaxis Guidelines, the Crude Incidence of Infective Endocarditis has Remained Stable, but Has Doubled in the Elderly / *Staphylococcus Aureus* and Enterococcus Bacteremia Were Associated With Worse Outcomes

Analysis of 7638 hospitalizations (65±17 years, 51% females) with infective endocarditis indicated that the estimated crude hospitalization rate increased from 5.3 to 8.6/100 000 between 1990 and 1995 but remained stable thereafter. There was no change in crude incidence following the 2008 change in antibiotic prophylaxis guidelines (relative risk of change 1.06). The incidence rate in patients >80 years of age doubled from 1990 to 2014 (17.7 to 37.9/100 000). The predicted 1-year age- and comorbidity-adjusted case fatality rate for a 65-year-old patient decreased in women (27.3% to 23.7%) and men (30.7% to 26.8%) from 1990 to 2014. Blood culture data were available from 2008 (n=2267/7638, 30%), with positive blood cultures recorded in 42%. Staphylococcus (42.4%) and streptococcus (35.5%) species were most common. *Staphylococcus aureus* and enterococcus had the highest 1-year mortality (adjusted odds ratio 4.34 and 3.41, respectively) (Shah ASV et al, *Circulation* 2020;141:2067-77).

ISCHEMIA Trial: Among Patients With Stable Coronary Artery Disease (CAD) and Moderate or Severe Ischemia, There Was No Difference in Initial Invasive Strategy vs Initial Conservative Strategy, Regarding the Risk of Cardiovascular (CV) Events or Any Death Over a Median of 3.2 Years

Among 5179 patients with stable CAD randomized to initial invasive (angiography and revascularization when feasible; n=2295) or initial conservative strategy of medical therapy alone and angiography if medical therapy failed (n=2322), over a median of 3.2 years, 318 primary outcome events (CV death, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest) occurred in the invasive-strategy group and 352 in the conservative-strategy group. At 6 months, the cumulative event rate was 5.3% vs 3.4%; at 5 years, the cumulative event rate was 16.4% and 18.2%, respectively. Results were similar with respect to the key secondary outcome (CV death/MI). The incidence of the primary outcome was sensitive to the definition of MI; a secondary analysis yielded more procedural MIs of uncertain clinical importance. There were 145 deaths in the invasive-strategy group and 144 deaths in the conservative-strategy group (hazard ratio, 1.05) (Maron DJ et al, *N Engl J Med* 2020; 382:1395-1407).

ISCHEMIA Trial: In the Overall Trial Population Including 35% Without Angina at Baseline, Patients Assigned to the Invasive Strategy Had Greater Improvement in Angina-Related Health Status Than Those Assigned to the Conservative Strategy

Seattle Angina Questionnaire (SAQ) summary scores increased in both treatment groups, with increases at 3, 12, and 36 months that were 4.1 points, 4.2 points, and 2.9 points higher with the invasive strategy than with the conservative strategy. Differences were larger among participants who had more frequent angina at baseline (Spertus JA et al, *N Engl J Med* 2020; 382:1408-19).

ORION Trials: Reductions in LDL Cholesterol of ~50% Were Obtained With Inclisiran (Inhibitor of Hepatic Synthesis of PCSK9), Administered Subcutaneously Every 6 Months

Among 1561 and 1617 patients randomized in the ORION-10 and ORION-11 trials, respectively, mean LDL cholesterol levels at baseline were 104.7±38.3 mg/dl and 105.5±39.1 mg/dl, respectively. At day 510, inclisiran reduced LDL cholesterol levels by 52.3% in the ORION-10 trial and by 49.9% in the ORION-11 trial, with corresponding time-adjusted reductions of 53.8% and 49.2% (P<0.001 for all comparisons vs placebo). Adverse events were generally similar in the inclisiran and placebo groups in each trial, although injection-site adverse events were more frequent with inclisiran than with placebo (2.6% vs. 0.9% in the ORION-10 trial and 4.7% vs. 0.5% in the ORION-11 trial); such reactions were generally mild, and none were severe or persistent (Ray KK et al, *N Engl J Med* 2020; 382:1507-1519).

ORION-9: Among Adults With Heterozygous Familial Hypercholesterolemia, Those Who Received Inclisiran Had Significantly Lower Levels of LDL Cholesterol Than Those Who Received Placebo, With Infrequent Dosing Regimen and Acceptable Safety Profile

Among 482 adults with heterozygous familial hypercholesterolemia (median age 56 years; 47% men; baseline LDL 153 mg/dl) randomly assigned to subcutaneous injections of 300 mg inclisiran sodium (small interfering RNA shown to inhibit hepatic synthesis of PCSK9) or matching placebo on days 1, 90, 270, and 450, at day 510, the percent change in the LDL cholesterol level was a reduction of 39.7% in the inclisiran group and an increase of 8.2% in the placebo group (P<0.001). The time-averaged percent change in the LDL cholesterol level between day 90 and day 540 was a reduction of 38.1% in the inclisiran group and an increase of 6.2% in the placebo group (P<0.001). There were robust reductions in LDL cholesterol levels in all genotypes of familial hypercholesterolemia. Adverse events and serious adverse events were similar in the two groups (Raal FJ et al, *N Engl J Med* 2020; 382:1520-30).

VICTORIA: Among Patients With High-Risk Heart Failure (HF), Incidence of CV Death or HF Hospitalization Was Lower in Those Who Received Vericiguat (Oral Soluble Guanylate Cyclase Stimulator) vs Placebo

Over a median of 10.8 months, a primary-outcome event (CV death/HF hospitalization) occurred in 897 of 2526 patients (35.5%) in the vericiguat group and in 972 of 2524 patients (38.5%) in the placebo group (hazard ratio-HR, 0.90; P=0.02). A total of 691 patients (27.4%) vs 747 patients (29.6%), respectively, were hospitalized for heart failure (HR, 0.90). Death from CV causes occurred in 414 patients (16.4%) vs 441 patients (17.5%) (HR, 0.93). The composite of death from any cause or HF hospitalization occurred in 957 patients (37.9%) vs 1032 patients (40.9%) (HR, 0.90; P=0.02). Symptomatic hypotension occurred in 9.1% vs 7.9% (P=0.12), and syncope occurred in 4% vs 3.5% (P=0.30) (Armstrong PW et al, *N Engl J Med* 2020; 382:1883-93).

RAS Blockers and COVID-19: Use of ACE Inhibitors and ARBs, More Frequent Among Patients With Covid-19 Because of Higher Prevalence of CV Disease, did not Affect the Risk Of COVID-19

Among 6272 case patients with COVID-19 infection (mean age 68±13 years, 37% women) compared with 30,759 matched controls, the use of ACE inhibitors and ARBs was more common among case patients than among controls, as was the use of other antihypertensive and non-antihypertensive drugs, and case patients had a worse clinical profile. Use of ARBs or ACE inhibitors did not show any association with Covid-19 among case patients overall (adjusted odds ratio-OR, 0.95 for ARBs and 0.96 for ACE inhibitors) or among patients who had a severe or fatal course of the disease (OR, 0.83 for ARBs and 0.91 for ACE inhibitors), and no association between these variables was found according to gender (Mancia G et al, *N Engl J Med* 2020; 382:2431-40).

COVID-19: No Substantial Increase in the Likelihood of a Positive Test for Covid-19 or in the Risk of Severe Covid-19 Among Patients Who Tested Positive in Association With 5 Common Classes of Antihypertensive Medications

Among 12,594 patients who were tested for Covid-19, a total of 5894 (46.8%) were positive; 1002 of these patients (17.0%) had severe illness. A history of hypertension was present in 4357 patients (34.6%), among whom 2573 (59.1%) had a positive test; 634 of these

patients (24.6%) had severe illness. There was no association between any single medication class and an increased likelihood of a positive test. None of the medications examined (ACE inhibitors, ARBs, beta-blockers, calcium-channel blockers, or thiazide diuretics) was associated with a substantial increase in the risk of severe illness among patients who tested positive (Reynolds HR et al, *N Engl J Med* 2020;382:2441-8).

RAAS Inhibitors Do Not Increase the Risk of COVID-19 Requiring Admission to Hospital, Including Fatal Cases and ICU Admissions, and Should Not Be Discontinued to Prevent a Severe Case of COVID-19

Data for 1139 cases (39% women, mean age 69 years; preexisting CV disease: OR 1.98 & risk factors: OR 1.46) and 11 390 population controls, indicated that compared with users of other antihypertensive drugs, users of RAAS inhibitors had an adjusted OR for COVID-19 requiring admission to hospital of 0·94. No increased risk was observed with either ACE inhibitors (adjusted OR 0.80) or ARBs (OR 1.10). Sex, age, and background CV risk did not modify the adjusted OR between use of RAAS inhibitors and COVID-19 requiring admission to hospital, whereas a decreased risk of COVID-19 requiring admission to hospital was found among patients with diabetes who were users of RAAS inhibitors (adjusted OR 0.53). The adjusted ORs were similar across severity degrees of COVID-19 (de Abajo FJ et al, *Lancet* 2020; 395(10238):1705-14).

HUNT3 Study: Higher Physical Activity (PA) and Cardiorespiratory Fitness (CRF) are Associated With Lower Long-Term Risk of CVD and All-Cause Mortality in Individuals With Atrial Fibrillation (AF)

Among 1117 AF patients, those meeting PA guidelines had lower risk of all-cause (hazard ratio-HR 0.55) and CVD mortality (HR 0.54) compared with inactive patients. The respective HRs for CVD morbidity and stroke were 0.78 and 0.70. Each 1-metabolic equivalent task (MET) higher eCRF was associated with a lower risk of all-cause (HR 0.88), CVD mortality (HR 0.85), and morbidity (HR 0.88) (Garnvik LE et al, *Eur Heart J* 2020; 41:1467-75).

***POPular AGE Trial*: In Patients Aged ≥70 Years With NSTE-ACS, Clopidogrel is a Favorable Alternative to Ticagrelor, as it Leads to Fewer Bleeding Events Without an Increase in the Combined Endpoint of All-Cause Death, MI, Stroke, and Bleeding**

Among 1002 patients randomly assigned to clopidogrel (n=500) or ticagrelor or prasugrel (n=502, 95% received ticagrelor) (premature discontinuation of the study drug: 22% in clopidogrel group and 47% in ticagrelor group), primary bleeding outcome was significantly lower in the clopidogrel group (18%) than in the ticagrelor group (24%) (hazard ratio-HR 0·71; p=0.02 for superiority). Co-primary net clinical benefit outcome was non-inferior for the use of clopidogrel (28%) vs ticagrelor (32%) (p=0.03 for non-inferiority). The most important reasons for discontinuation were occurrence of bleeding (n=38), dyspnea (n=40), and the need for treatment with oral anticoagulation (n=35) (Gimbel M et al, *Lancet* 2020;395 (10233): 1374-1381).

***SPYRAL HTN-OFF MED (SPYRAL Pivotal) Trial*: Superiority of Catheter-Based Renal Denervation Compared With a Sham Procedure to Safely Lower Blood Pressure in Absence of Antihypertensive Drugs**

Among 331 patients randomly assigned to either renal denervation (n=166) or sham procedure (n=165), the primary and secondary efficacy endpoints were met, with posterior probability of superiority more than 0.999 for both. The treatment difference between the two groups for 24-h systolic blood pressure was −3·9 mm Hg and for office systolic blood pressure the difference was −6·5 mm Hg. No major device-related or procedural-related safety events occurred up to 3 months (Bohm M et al, *Lancet* 2020;395(10234):1444-51).

Compared With Aspirin Monotherapy, $P2Y_{12}$ Inhibitor Monotherapy is Associated With a Risk Reduction for MI, Albeit With a High Number Needed to Treat (NNT) and no Effect on Mortality, and a Comparable Risk of Stroke in the Patients With Atherosclerosis for Secondary Prevention

According to a systematic review and meta-analysis of 9 randomized trials comprising 42,108 patients allocated to a $P2Y_{12}$ inhibitor (n=21,043) or aspirin (n=21,065), patients who received a $P2Y_{12}$ inhibitor had a borderline reduction for the risk of MI compared with those who received aspirin (OR 0.81; I^2=10.9%). Risks of stroke (OR 0.93; I^2=34.5%), all-cause death (OR 0.98; I^2=0%), and vascular death (OR 0.97; I^2=0%) did not differ between patients who received a $P2Y_{12}$ inhibitor and those who received aspirin. Similarly, the risk of major bleeding (OR 0.90; I^2=3·9%) did not differ between patients who received a $P2Y_{12}$ inhibitor and those who received aspirin. The number needed to treat (NNT) to prevent one MI with $P2Y_{12}$ inhibitor monotherapy was 244 patients. Findings were consistent regardless of the type of $P2Y_{12}$ inhibitor used (Chiarito M et al, *Lancet* 2020; 395(10235):1487-95).

Adults With Atrial Fibrillation (AF) on Apixaban Had Lower Rate of Ischemic Stroke or Systemic Embolism and Bleeding Compared With Those on Rivaroxaban

Among 39,351 AF patients newly prescribed apixaban and propensity score matched 39,351 patients newly

prescribed rivaroxaban (mean age 69 years, 40% women, mean follow-up ~290 days), the incidence rate of ischemic stroke or systemic embolism was 6.6 per 1000 person-years vs 8.0 per 1000 person-years, respectively (hazard ratio -HR, 0.82). Adults prescribed apixaban also had a lower rate of gastrointestinal bleeding or intracranial hemorrhage (12.9 per 1000 person-years) compared with those prescribed rivaroxaban (21.9 per 1000 person-years), corresponding to an HR of 0.58 (Fralick M, *Ann Int Med* 2020;172: 463-73).

Dual vs Triple Therapy for Atrial Fibrillation (AF) After Percutaneous Coronary Intervention (PCI): Dual Therapy Reduces Risk for Bleeding Compared With Triple Therapy, Whereas its Effects on Risks for Death and Ischemic End Points Remain Unclear

Meta-analysis of 4 trials encompassing 7953 patients indicated that at the median of 1 year, high-certainty evidence showed that dual therapy was associated with reduced risk for major bleeding compared with triple therapy (risk difference-RD, −0.013). Low-certainty evidence showed inconclusive effects of dual vs triple therapy on risks for all-cause mortality (RD, 0.004), CV mortality (RD, 0.001), MI (RD, 0.003), stent thrombosis (RD, 0.003), and stroke (RD, −0.003). The upper bounds of the CIs for these effects were compatible with possible increased risks with dual therapy (Khan SU et al, *Ann Intern Med* 2020;172: 474-83)

Among Patients Undergoing PFO Closure, Residual Shunt, Especially a Moderate or Large Residual Shunt, Was Associated With an Increased Risk for Stroke or TIA Recurrence

In 1078 consecutive patients (mean age, 49.3 years) with PFO-attributable cryptogenic stroke undergoing PFO closure, followed for up to 11 years, compared with complete closure, the presence of residual shunt, as evaluated by transthoracic echocardiography with saline contrast, was associated with an increased incidence of recurrent stroke or TIA: 2.32 vs 0.75 events per 100 patient-years (hazard ratio-HR, 3.05; $P<0.001$). This result remained robust after adjustment for important covariates (age, study period, device, presence of atrial septal aneurysm, hypertension, hyperlipidemia, diabetes, hypercoagulability, or hypermobile septum, and medication use) (HR, 3.01; $P<0.001$). Further stratification based on shunt size revealed that moderate or large residual shunts were associated with a higher risk for stroke or TIA recurrence (HR, 4.50; $P < 0.001$); the result for small residual shunts was indeterminate (HR, 2.02; $P=0.102$) (Deng W et al, *Ann Intern Med* 2020;172:717-725).

DASH Trial: Diets Rich in Fruits and Vegetables Given Over 8 Weeks Were Associated With Lower Levels of Markers for Subclinical Cardiac Damage and Strain In Adults Without Preexisting CVD

Among 326 trial participants (mean age 45.2 years, 48% were women, 49% were black, and mean baseline BP was 131/85 mm Hg), compared with the control diet, the fruit-and-vegetable diet reduced hs-cTnI levels by 0.5 ng/L and NT-proBNP levels by 0.3 pg/mL. Compared with the control diet, the DASH diet reduced hs-cTnI levels by 0.5 ng/L and NT-proBNP levels by 0.3 pg/mL. Levels of hs-CRP did not differ among diets. None of the markers differed between the fruit-and-vegetable and DASH diets. (Juraschek SP et al, *Ann Intern Med* 2020;172:786-794).

SOLVE-TAVI Trial: In Patients With Aortic Stenosis Undergoing Transfemoral TAVI, Newer Generation Self-Expandable (SEV) and Balloon-Expandable Valves (BEV) are Equivalent With Some Specific Preferences Based on Individual Valve Anatomy

Among 447 patients with aortic stenosis undergoing TAVI comparing SEV (Evolut R) with BEV (Sapien 3), the primary efficacy endpoint of all-cause mortality, stroke, moderate/severe prosthetic valve regurgitation, and permanent pacemaker implantation at 30 days was powered for equivalence (28.4% vs 26.1%). Event rates for the individual components were as follows: all-cause mortality 3.2% vs 2.3% ($P_{equivalence} < 0.001$), stroke 0.5% vs 4.7% ($P_{equivalence} = 0.003$), moderate/severe paravalvular leak 3.4% vs 1.5% ($P_{equivalence} = 0.0001$), and permanent pacemaker implantation 23% vs 19.2% ($P_{equivalence} = 0.06$) (Thiele H et al, *Eur Heart J* 2020;41: 1890–1899).

Long-Term Effectiveness of Catheter Ablation (CA) in Patients With Atrial Fibrillation (AF) and Heart Failure (HF): Over 3 Years, Compared With Matched Non-CA Patients, CA Was Associated With a Long-Term Reduction in All-Cause Mortality and a Reduction in HF Rehospitalizations

Among 101,933 AF–HF patients, 451 underwent CA and were matched to 899 controls. Over a median of 3.8 years, CA was associated with a significant reduction in all-cause mortality (hazard ratio-HR 0.4), but no difference in stroke or major bleeding. The hazard of HF rehospitalization for CA patients, relative to non-CA patients, varied with time since CA ($P = 0.01$), with a with a reduction in HF rehospitalizations until ~3 years post-CA (Samuel M et al, *EP Europace* 2020;22: 739–747)

GOLD AF Registry: Phased RF Ablation for AF Had a 77.7% Freedom from AF Recurrence at 1 Year

Among 1054 patients (age 60.6, 67.6% male, 26.5% PersAF), freedom from AF recurrence was 77.7% at

12 months. Peri-procedural device or procedure-related complications were observed in 26 (2.5%) patients, with a low stroke rate of 0.3%. One-year post-ablation, symptoms decreased in 68% of patients. Quality of life score improved in 88-90% of patients (Boersma L et al, *EP Europace* 2020;22:888-96)

A Cardiac Magnetic Resonance (CMR) Scan is Pivotal in Risk-Stratifying Patients With Incidental LBBB (iLBBB): Outcomes in $iLBBB_{CMR+}$ Were Poor Whereas Survival in $iLBBB_{CMR-}$ Was Comparable With Controls / Myocardial Fibrosis and LVEF <50% Had an Additive Effect on the Risk of Clinical Outcomes

Amongst patients with iLBBB ($n = 193$, aged 62.7 ± 12.6 years), 110/193 (56.9%) had an abnormal CMR scan ($iLBBB_{CMR+}$) and 83/110 (43%) had a normal scan ($iLBBB_{CMR-}$). Over 3.75 years, $iLBBB_{CMR+}$ had a higher total mortality (adjusted hazard ratio-aHR 6.49, and total mortality or major adverse cardiac events (MACEs; aHR 9.15) than controls ($n = 107$). In contrast, $iLBBB_{CMR-}$ had a similar risk of total mortality compared with controls, but total mortality or MACEs was higher (aHR 4.24; $P = 0.028$). Amongst iLBBB patients, both myocardial fibrosis (aHR 5.15) and LVEF $\leq 50\%$ (aHR 3.88) predicted total mortality. Myocardial fibrosis plus LVEF $\leq 50\%$ was associated with the highest risk of total mortality (aHR: 9.87) and total mortality or MACEs (aHR 3.98) (Zegard A et al, *EP Europace* 2020;22: 956-63).

Important Review and Other Articles

● **AHA Statement** on Lifestyle and Risk Factor Modification for Reduction of **Atrial Fibrillation** *(*Chung MK, *Circulation* 2020;141:e750–e772)

● **Chinese Society of Cardiology Expert Consensus** on Clinical Management of Patients With Severe Emergent CV Diseases During the **COVID-19** Epidemic (Han Y et al, *Circulation* 2020;141:e810-e816)

● **AHA Statement** on Management of **Stable CAD** in **Diabetic** Patients (Arnold SV et al, *Circulation* 2020;141:e779-e806)

● **Guidance for Cardiac Electrophysiology** During the **COVID-19** Pandemic from Heart Rhythm and other Societies (Lakkireddy DR et al, *Circulation* 2020: 141:e823–e831)

● ***EHRA*** document on cardiac implantable electronic device infections (Blomström-Lundqvist C et al, *Eur Heart J* 2020;41:2012-32)

● **ICDs** in sudden death prevention (Goldenberg I et al, *Eur Heart J* 2020;41: 2003–2011)

● **Cardio-Obstetrics**/CV considerations in caring for pregnant women (Mehta LS et al, *Circulation* 2020;141:e884–e903)

● Cardiac **arrhythmias in pregnant women** (Manolis TA et al, *Curr Med Res Opin* 2020;36:1225-1243)

● Management of acute **ischemic stroke** due to large-vessel occlusion (Ospel JM et al, *J Am Coll Cardiol* 2020; 75:1832-43)

● Management of **intracerebral hemorrhage** (Schrag M & Kirshner H, *J Am Coll Cardiol* 2020; 75:1819-31)

● **Diabetic agents** (Wilcox T et al, *J Am Coll Cardiol* 2020; 75:1956-74)

● **Lipid** modifying agents (Preiss D et al, *J Am Coll Cardiol* 2020; 75: 1945-55)

● Catheterization laboratory considerations during the **COVID-19** Pandemic (Welt FGP et al, *J Am Coll Cardiol* 2020; 75: 2372-75)

● **Dyskalemia** in heart failure (Ferreira JP et al, *J Am Coll Cardiol* 2020;75:2836-50)

● Cardiac scintigraphy with technetium-labeled bone-tracers for suspected **amyloidosis** (Hanna M et al, *J Am Coll Cardiol* 2020;75:2851-62)

● **COVID-19** and thrombotic or thromboembolic disease (Bikdeli B, *J Am Coll Cardiol* 2020;75:2950-73)

● Implications of **SARS-CoV-2** interaction with renin angiotensin system (Brojakowska A et al, *J Am Coll Cardiol* 2020;75:3085-95)

● **Exercise** and coronary atherosclerosis (Aengevaeren VL et al, *Circulation* 2020;141:1338–1350)

● Evaluation and management of **PVCs** (Marcus GM et al, *Circulation* 2020;141:1404-18)

● Inherited **thoracic aortic disease** (Fletcher AJ et al, *Circulation* 2020;141:1570-87)

● **COVID-19** and CV disease (Clerkin KJ et al, *Circulation* 2020;141:1648–1655)

● CV complications of **COVID-19** (Manolis AS et al, *Rhythmos* 2020;15(2):23-28)

● Acute **COVID-19** cardiovascular syndrome (Hendren NS et al, *Circulation* 2020;141:1903-14)

● **COVID-19** and CV system (Xiong T-Y et al, *Eur Heart J* 2020;41: 1798-1800)

● **COVID-19** treatment effects on QTc (Roden DM et al, *Circulation* 2020;141:e906–e907)

● CV consequences of **acute kidney injury** (Legrand M et al, *N Engl J Med* 2020;382:2238-2247)

● **Depression** and coronary artery disease (Vaccarino V et al, *Eur Heart J* 2020;41:1687-96)

● **Autonomic nervous system** and arrhythmias (Manolis AA, et al, *Trends Cardiovasc Med* 2020 May 17:S1050-1738(20)30066-9. doi: 10.1016/j.tcm.2020.04.011.)

● **Atrial fibrillation** and cognitive impairment (Manolis TA et al, *Angiology* 2020;71:498-519)