Cardiology News / Recent Literature Review / First Quarter 2021

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EHRA online **Congress**, 23-25/4/2021

ACC Meeting: Atlanta, 15-17/5/2021

EuroPCR online, 18-20/5/201

ESC Digital **Congress** 27-30/8/2021

TCT Meeting, San Francisco, 22-26/10/2021

EARLY-AF: Cryoballoon Ablation Lowers Rate of Atrial Fibrillation (AF) Recurrence Among Patients Receiving Initial Treatment for Symptomatic, Paroxysmal AF, Compared With Antiarrhythmic Drug (AAD) Therapy, as Assessed by Continuous Cardiac Rhythm Monitoring

Among 303 patients with symptomatic, paroxysmal, untreated AF randomized to catheter ablation with a cryothermy balloon or antiarrhythmic drug (AAD) therapy for initial rhythm control, at 1 year, 66 of 154 patients (42.9%) assigned to ablation had AF recurrence vs 101 of 149 patients (67.8%) assigned to AAD (hazard ratio-HR, 0.48; P<0.001). Symptomatic AF recurred in 11% vs 26.2% (HR, 0.39). The median percentage of time in AF was 0% with ablation and 0.13% with AAD. Serious adverse events occurred in 5 (3.2%) vs 6 patients (4%) (Andrade JG et al, *N Engl J Med* 2021; 384:305-315).

STOP AF First: Cryoballoon Ablation as Initial Therapy was Superior to Drug Therapy for Prevention of Recurrence in Patients With Paroxysmal Atrial Fibrillation (AF) with Uncommon Serious Procedure-Related Adverse Events

According to a multicenter trial which randomized 203 patients 18-80 years of age with paroxysmal AF to antiarrhythmic drugs (class I or III agents) (n=99) or pulmonary vein isolation with a cryoballoon (n=104), with initial success of the ablation procedure achieved in 97%, the Kaplan–Meier estimate of treatment success at 1 year was 74.6% in the ablation group and 45% in the drug-therapy group (P<0.001 by log-rank test). Two primary safety end-point events occurred in the ablation group (Kaplan–Meier estimate of the percentage of patients with an event within 12 months, 1.9%) (Wazni OM et al, *N Engl J Med* 2021; 384:316-324).

GALACTIC-HF: Among Patients With Heart Failure and a Reduced Ejection, those on Omecamtiv Mecarbil Had a Lower Incidence of a Composite of a HF Event or Death from Cardiovascular Causes than on Placebo

Among 8256 patients (in- and out-patients) with symptomatic chronic HF and an ejection fraction of ≤35% assigned to omecamtiv mecarbil (25-50 mg bid) or placebo, in addition to standard HF therapy, over a median of 21.8 months, a primary-outcome event (composite of a first HF event, i.e. hospitalization or urgent visit for HF, or death from CV causes) occurred in 1523 of 4120 patients (37%) in the omecamtiv mecarbil group and in 1607 of 4112 patients (39.1%) in the placebo group (hazard ratio-HR, 0.92; P=0.03). A total of 808 patients (19.6%) and 798 patients (19.4%), respectively, died from CV causes (HR, 1.01). There was no significant difference between groups in the change from baseline on quality-of-life score. At week 24, the change from baseline for the median N-terminal pro–B-type natriuretic peptide level was 10% lower in the omecamtiv mecarbil group than in the placebo group; the median cardiac troponin I level was 4 ng/L higher. The frequency of cardiac ischemic and ventricular arrhythmia events was similar (Teerlink JR et al, *N Engl J Med* 2021; 384:105-116).

SOLOIST-WHF: In Patients With Diabetes and Recent Worsening Heart Failure (HF), Sotagliflozin Therapy, Initiated Before or Shortly After Discharge, Resulted in a Significantly Lower Total Number of Deaths from Cardiovascular (CV) Causes and Hospitalizations and Urgent Visits for HF

Among 1222 patients with type 2 diabetes (recently hospitalized for worsening HF) randomized to sotagliflozin (n=608) or placebo (n=614) and followed for a median of 9 months, 600 primary end-point events (total number of CV deaths and hospitalizations and urgent visits for HF) occurred (245 in the sotagliflozin group and 355 in the placebo group). The rate (the number of events per 100 patient-years) of primary end-point events was lower in the sotagliflozin group (51.0 vs. 76.3; hazard ratio-HR, 0.67; P<0.001). The rate of CV death was 10.6 vs 12.5 (HR, 0.84); the rate of death from any cause was 13.5 vs 16.3 (HR, 0.82). Diarrhea was more common with sotagliflozin (6.1% vs 3.4%), as was severe hypoglycemia (1.5% vs 0.3%). The percentage of patients with hypotension was similar (6% vs 4.6%), as was the percentage with acute kidney injury (4.1% vs 4.4%). The benefits of sotagliflozin were consistent in the prespecified subgroups of patients stratified according to the timing of the first dose (Bhatt DL et al, *N Engl J Med* 2021; 384:117-128)

RHAPSODY: Rilonacept vs Placebo Confers Rapid Resolution of Recurrent Pericarditis Episodes and Lower Risk of Pericarditis Recurrence

Among 86 patients with pericarditis pain and an elevated CRP, median time to resolution or near-resolution of pain was 5 days, and median time to normalization of the CRP was 7 days. A total of 61 patients were randomized. During the randomized-withdrawal period, there were very few recurrence events in the rilonacept group that did not allow for the median time to the first adjudicated recurrence to be calculated; the respective time in the placebo group was 8.6 weeks (hazard ratio-HR 0.04; P<0.00). During this period, pericarditis recurrence was noted in 7% in the rilonacept group vs 74% in the placebo group. In the run-in period, 4 patients had adverse events leading to the discontinuation of rilonacept therapy. The most common adverse events with rilonacept were injection-site reactions and upper respiratory tract infections (Klein AL et al, *N Engl J Med* 2021; 384:31-41).

PROSPECT II: Combined Near-Infrared Spectroscopy (NIRS) and Intravascular Ultrasound (IVUS) Detects Angiographically Non-Obstructive Lesions with a High Lipid Content and Large Plaque Burden that are at Increased Risk for Future Adverse Cardiac Outcomes

Among 898 patients with recent (4 weeks) myocardial infarction (MI) (83% men; median age 63 years), after treatment of all flow-limiting coronary lesions, 3-vessel imaging was done with a combined NIRS and IVUS catheter and 3629 non-culprit lesions were characterized. Over a median of 3.7 years, adverse events occurred in 112 (13.2%) patients, with 66 (8%) arising from 78 untreated non-culprit lesions (mean baseline angiographic diameter stenosis 46.9%). Highly lipidic lesions (24% of lesions, present in 59% of patients studied) were an independent predictor of patient-level non-culprit lesion-related MACEs (adjusted odds ratio-OR 2.27) and non-culprit lesion-specific MACEs (OR 7.83). Large plaque burden (22% of lesions/ 59% of patients) was also an independent predictor of non-culprit lesion-related MACEs. Lesions with both large plaque burden by IVUS and large lipid-rich cores by NIRS had a 4-year non-culprit lesion-related MACE rate of 7%. Patients in whom ≥1 such lesions were identified had a 4-year non-culprit lesion-related MACE rate of 13.2% (Erlinge D et al, *Lancet* 2021;397:985-95)

TAVI in Failed Transcatheter Aortic Valves (TAV-in-TAV) vs Surgical Aortic Valves (TAV-in-SAV): TAV-in-TAV Conferred Higher Procedural Success and Similar Procedural Safety or Mortality

Data on 434 TAV-in-TAV and 624 TAV-in-SAV consecutive procedures with 330 matched (165:165) patients analyzed. Indicated that for TAV-in-TAV vs TAV-in-SAV, procedural success was 72.7% vs 62.4% (P=0.045), driven by a numerically lower frequency of residual high valve gradient (P=0.095), ectopic valve deployment (P=0.081), coronary obstruction (P=0.091), and conversion to open heart surgery (P=0.082). Procedural safety was achieved in 70.3% vs 72.1% (P=NS). Mortality at 30 days was 3% vs 4.4% (P=NS). At 1 year, mortality was 11.9% vs 10.2% (P=NS). Aortic valve area was larger (1.55 ± 0.5 cm^2 vs 1.37 ± 0.5 cm^2; P=0.040), and the mean residual gradient was lower (12.6 ± 5.2 vs 14.9 ± 5.2 mm Hg; P=0.011) after TAV-in-TAV. The rate of moderate or greater residual aortic regurgitation was similar, but mild aortic regurgitation was more frequent after TAV-in-TAV (p = 0.003) (Landes U et al, *J Am Coll Cardiol* 2021;77: 1-14)

In Coronary Artery Disease (CAD) Patients, Myocardial Fibrosis on Visual Assessment (MF_{VA}) plus Quantified on Cardiac Magnetic Resonance (CMR) "Gray Zone" Myocardial Fibrosis (GZF_{3SD}) Mass was More Strongly Associated with Sudden Cardiac Death (SCD) and Ventricular Arrhythmias (VAs) than Left Ventricular Ejection Fraction (LVEF) / In Selecting Patients for ICDs, Assessment of MF_{VA} Followed by Quantification of GZF_{3SD} Mass May be Preferable to LVEF

Among 979 patients (mean age 65.8±12.3 years), 29 (2.96%) experienced SCD and 80 (8.17%) met the arrhythmic endpoint over median 5.82 years. In the whole cohort, MF_{VA} was strongly associated with SCD (hazard ratio-HR: 10.1) and the arrhythmic endpoint (HR: 28). In competing risks analyses, associations between LVEF <35% and SCD (subdistribution hazard ratio [sHR]: 2.99) and the arrhythmic endpoint (sHR: 4.71) were weaker. In competing risk analyses of the MF_{VA} subcohort (n=832), GZF using the 3SD method (GZF_{3SD}) >5 g was strongly associated with SCD (sHR: 10.8) and the arrhythmic endpoint (sHR: 7.40). Associations between LVEF <35% and SCD (sHR: 2.62) and the arrhythmic endpoint (sHR: 4.14) were weaker (Zegard A et al, *J Am Coll Cardiol* 2021;77: 29-41)

Proof-Of-Concept Study/Calcium-Induced Autonomic Denervation: Injection of $CaCl_2$ into the 4 Major Atrial Ganglionated Plexi (GPs) Reduced Post-Op AF Hazard by 63% /Inhibition of GP Function by Ca-Mediated Neurotoxicity May Underlie the Therapeutic Effect

Among 200 patients undergoing isolated, off-pump CABG, randomized to $CaCl_2$ (n=100) or NaCl (sham, n=100) injection into the 4 major atrial GPs, the post-op AF incidence was reduced from 36% to 15% (hazard ratio-

HR: 0.366; p=0.001). Length of hospitalization did not differ between the 2 groups. Post-op AF burden (first 7 post-op days), the use of amiodarone or esmolol, and the incidence of atrial couplets and nonsustained atrial tachyarrhythmias were significantly reduced in the $CaCl_2$ group. Heart rate variability data showed a decrease in both high-frequency and low-frequency power in the $CaCl_2$ group with a preserved low-frequency/high-frequency ratio, suggesting that the sympathetic/parasympathetic balance was not perturbed by $CaCl_2$ injection (Wang H et al, *J Am Coll Cardiol* 2021;77:57–67)

Concomitant Pathology of Aortic Stenosis-Cardiac Amyloidosis (AS-CA) is Common in Older Patients With Aortic Stenosis (AS) and can be Predicted Clinically / AS-CA Has Worse Clinical Presentation and a Trend Toward Worse Prognosis, Unless Treated / Thus, TAVI Should not be Withheld in AS-CA

Among 407 patients who were referred for TAVI (age 83.4±6.5 years; 49.8% men), bone scintigraphy was positive for cardiac amyloidosis (CA) in 48 patients (11.8%; grade 1: 3.9%; grade 2/3: 7.9%). Most patients had transthyretin CA; 1 patient had light chain CA. Patients with grade 2/3 had worse functional capacity, biomarkers (N-TproBNP and/or hs troponin T), and biventricular remodeling. A clinical score (RAISE) that used LV remodeling (hypertrophy/diastolic dysfunction), age, injury (hs troponin T), systemic involvement, and electrical abnormalities (RBBB/low voltages) was developed to predict the presence of AS-CA (area under the curve: 0.86; p<0.001). Decisions by the heart team (scintigraphy-blinded) resulted in TAVI (81.6%), surgical AVR (2.5%), or medical management (15.9%). After a median of 1.7 years, 23% of patients died. One-year mortality was worse in all patients with AS-CA (grade: 1 to 3) than those with lone AS (24.5% vs 13.9%; p=0.05). TAVI improved survival vs medical management; AS-CA survival post-TAVI did not differ from lone AS (p=0.36) (Nitsche C et al, *J Am Coll Cardiol* 2021;77:128–139)

The COVID-19 Pandemic May Have Had an Indirect Toll on Patients With Cardiovascular Disease / There was an Increase in Deaths Caused by Ischemic Heart Disease and Hypertensive Diseases in Some Regions of the US During the Initial Phase of the Pandemic

There were 397,042 cardiovascular deaths from January 1, 2020, to June 2, 2020. Deaths caused by ischemic heart disease (IHD) increased nationally after the onset of the pandemic in 2020, compared with changes over the same period in 2019 (ratio of the relative change in deaths per 100,000 in 2020 vs. 2019: 1.11). An increase was also observed for deaths caused by hypertensive disease (1.17), but not for other CV causes. New York City experienced a large relative increase in deaths caused by IHD (2.39) and hypertensive diseases (2.64) during the pandemic. More modest increases in deaths caused by these conditions occurred in the remainder of New York State, New Jersey, Michigan, and Illinois but not in Massachusetts or Louisiana (Wadhera RK et al, *J Am Coll Cardiol* 2021;77: 159–169).

World-Wide Survey: COVID-19 Conferred a Significant and Abrupt Reduction in Cardiovascular Diagnostic Testing Across the Globe, Especially Affecting the World's Economically Challenged

Surveys were submitted from 909 inpatient and outpatient centers performing cardiac diagnostic procedures, in 108 countries. Procedure volumes decreased 42% from March 2019 to March 2020, and 64% from March 2019 to April 2020. Transthoracic echocardiography decreased by 59%, transesophageal echocardiography 76%, and stress tests 78%, which varied between stress modalities. Coronary angiography (invasive or computed tomography) decreased 55% ($p < 0.001$ for each procedure). In multivariable regression, significantly greater reduction in procedures occurred for centers in countries with lower gross domestic product (an additional 22% reduction in cardiac procedures and less availability of personal protective equipment and telehealth) (Einstein AJ et al, *J Am Coll Cardiol* 2021;77:173–185).

EMPA-TROPISM: Empagliflozin in Nondiabetic HFrEF Patients Significantly Improves LV Volumes, LV Mass, LV Systolic Function, Functional Capacity, and Quality of Life When Compared With Placebo

Empagliflozin was associated with a significant reduction of LV end-diastolic volume (−25.1±26.0 ml vs. −1.5±25.4 ml for empagliflozin vs placebo, respectively; p<0.001) and LV end-systolic volume (−26.6±20.5 ml vs. −0.5±21.9 ml for empagliflozin vs placebo; p<0.001) in nondiabetic HFrEF patients (n=84) randomized to empagliflozin 10 mg qd or placebo for 6 months. Empagliflozin was associated with reductions in LV mass (−17.8±31.9 g vs 4.1±13.4 g, for empagliflozin vs placebo, respectively; p<0.001) and LV sphericity, and improvements in LVEF (6.0±4.2 vs −0.1±3.9; p<0.001). Patients who received empagliflozin had significant improvements in peak O_2 consumption (1.1±2.6 ml/min/kg vs. −0.5±1.9 ml/min/kg for empagliflozin vs placebo, respectively; p=0.017), oxygen uptake efficiency slope (111±267 vs −145±318; p<0.001), as well as in 6-min walk test (81±64 m vs −35±68 m; p<0.001) and quality of life

(p<0.001) (Santos-Gallego CG et al, *J Am Coll Cardiol* 2021;77:243-55).

INTCAR (International Cardiac Arrest Registry): Patients Successfully Resuscitated from Cardiac Arrest With 6 or More Unfavorable Features Have a Poor Long-Term Prognosis. Delaying or Even Forgoing Invasive Procedures in Such Patients is Reasonable

Seven unfavorable features (of 10 total) were captured in 2,508 patients successfully resuscitated after cardiac arrest. In total, 39% survived to hospital discharge. The odds ratio (OR) of survival to hospital discharge for each unfavorable feature was as follows: age >85 years OR: 0.30, time-to-ROSC >30 min OR: 0.30, nonshockable rhythm OR: 0.39, no bystander cardiopulmonary resuscitation OR: 0.49, lactate >7 mmol/l OR: 0.50, unwitnessed arrest OR: 0.58, pH <7.2 OR: 0.78, and chronic kidney disease OR: 0.96. The presence of any ≥3 unfavorable features predicted <40% survival. Presence of the 3 strongest risk factors (age >85 years, time-to-ROSC >30 min, and non-ventricular tachycardia/ventricular fibrillation) together or ≥6 unfavorable features predicted a ≤10% chance of survival to discharge (Harhash AA et al, *J Am Coll Cardiol* 2021;77: 360-71).

MATRIX: Among Patients with Acute Coronary Syndrome (ACS) Managed Invasively, In-Hospital Hemoglobin Drop ≥3 g/dl, Even in the Absence of Overt Bleeding, is Common and is Independently Associated With Increased Risk for 1-Year Mortality

Among 7,781 patients with ACS alive 24h after randomization with available hemoglobin data, 6,504 patients (83.6%) had hemoglobin drop, of whom 5,756 (88.5%) did not have overt bleeding and 748 (11.5%) had overt bleeding. Among patients without overt bleeding, minor (hazard ratio -HR: 2.37; p=0.004) and major (HR: 2.58; p=0.054) hemoglobin drop were independently associated with higher 1-year mortality. Among patients with overt bleeding, the association of minor and major hemoglobin drop with 1-year mortality was directionally similar (minor: HR: 3.53; major: HR: 13.32) (Leonardi S et al, *J Am Coll Cardiol* 2021;77:375-88).

SYNTAXES: At 10-Years, the Status of Total Occlusion (TO) Recanalization or Revascularization Did Not Affect Mortality, Irrespective of the Assigned Treatment and Location of TOs / The Present Study Might Support Practice of Recommending Recanalization Primarily for the Management of Angina Refractory to Medical Therapy When Myocardial Viability is Confirmed

Of 1,800 randomized patients to the PCI or CABG arm, 460 patients had at least 1 lesion of TO. In patients with TOs, the status of TO recanalization or revascularization was not associated with 10-year all-cause mortality, irrespective of the assigned treatment (PCI arm: 29.9% vs 29.4%; adjusted hazard ratio -HR: 0.992; p = 0.982; and CABG arm: 28.0% vs 21.4%; adjusted HR: 0.656; p=0.330). When TOs existed in left main and/or left anterior descending artery, the status of TO recanalization or revascularization did not have an impact on the mortality (34.5% vs 26.9%; adjusted HR: 0.896; p = 0.837) (Kawashima H et al, *J Am Coll Cardiol* 2021;77:529–540).

Pooled Analysis of Patient-Level Data Demonstrates that PFO Closure Was Safe and Significantly Reduced the Mean Number of Monthly Migraine Days and Monthly Migraine Attacks, and Resulted in a Greater Number of Subjects Who Experienced Complete Migraine Cessation

Data from 2 randomized migraine trials (the PRIMA and PREMIUM) indicated that among 337 subjects (176 randomized by blocks to device closure and 161 to medical treatment only), at 1 year, the analysis met 3 of the 4 efficacy endpoints: mean reduction of monthly migraine days (−3.1 days vs −1.9 days; p=0.02), mean reduction of monthly migraine attacks (−2.0 vs −1.4; p=0.01), and number of subjects who experienced complete cessation of migraine (9% vs 0.7%; p<0.001). For the safety analysis, 9 procedure-related and 4 device-related adverse events occurred in 245 subjects who eventually received devices. All events were transient and resolved (Mojadidi MK et al, *J Am Coll Cardiol* 2021;77:667-76).

Intracranial Atherosclerotic Plaque as a Potential Cause of Embolic Stroke of Undetermined Source

Among 243 patients with embolic stroke of undetermined source (ESUS), the prevalence of intracranial plaque was much higher in the ipsilateral than the contralateral side (63.8% vs 42.8%; odds ratio - OR: 5.25), a finding that was not evident in patients with small vessel disease (SVD) (35.6% vs 30.6%; OR: 2.14; p=0.134). Logistic analysis showed that remodeling index (RI) was independently associated with ESUS in model 1 (OR: 2.329; p<0.001) and model 2 (OR: 2.295; p<0.001). RI alone with an optimal cutoff of 1.162, corresponding to an area under the curve of 0.740, had good diagnostic efficiency for ESUS (Tao L et al, *J Am Coll Cardiol* 2021;77:680-91).

Ivabradine is Safe and Effective in Significantly Improving Heart Rate and Quality of Life (QOL) in Patients With Hyperadrenergic Postural Orthostatic Tachycardia Syndrome (POTS)

Among 22 patients with POTS, aged 33.9±11.7 years (21 women), who completed a randomized, double-

blinded, placebo-controlled, crossover trial with ivabradine, there was a significant reduction in heart rate between placebo and ivabradine ($p<0.001$). Patients reported significant improvements in QOL with RAND 36-Item Health Survey 1.0 for physical functioning ($p = 0.008$) and social functioning ($p=0.021$). There was a strong trend in reduction of norepinephrine levels upon standing with ivabradine ($p=0.056$). Patients did not experience any significant side-effects (bradycardia or hypotension) with ivabradine (Taub PR et al, *J Am Coll Cardiol* 2021;77:861-71).

TOPCAT-Americas: Among HFpEF Patients Spironolactone Increased Risk of Worsening Renal Function (WRF) Compared With Placebo / Rates of CV Death Were Lower With Spironolactone in Both Patients With and Without WRF

Among 1,767 patients randomized to spironolactone or placebo in the TOPCAT, WRF developed in 260 (14.7%) patients with higher rates in those assigned to spironolactone compared to placebo (17.8% vs 11.6%; odds ratio: 1.66; $p<0.001$). Regardless of treatment, incident WRF was associated with increased risk for the primary endpoint of CV death, HF hospitalization (HFH), or aborted cardiac arrest (hazard ratio: 2.04; $p<0.001$) after multivariable adjustment. Although there was no statistical interaction between treatment assignment and WRF regarding the primary endpoint (interaction $p=0.11$), spironolactone-associated WRF was associated with lower risk of CV death (interaction $p=0.003$) and all-cause mortality (interaction $p=0.001$) compared with placebo-associated WRF (Beldhuis IE et al, *J Am Coll Cardiol* 2021;77:1211-21).

EMPEROR-Reduced: Findings Do Not Support a Dominant Role of Diuresis in Mediating the Physiological Changes or Clinical Benefits of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors on the Course of Heart Failure (HF) in Patients With a Reduced Ejection Fraction

EMPEROR-Reduced compared the effects of empagliflozin and placebo in 3,730 patients with HFrEF, with or without diabetes; ~40% of the patients had volume overload in the 4 weeks before study enrollment. Patients with recent volume overload were more likely to have been hospitalized for HF and to have received an intravenous diuretic agent in an outpatient setting in the previous 1 year, and to experience a HF event following randomization, even though they were more likely to be treated with high doses of a loop diuretic agent as an outpatient (all $p<0.001$). When compared with placebo, empagliflozin reduced the composite risk of CV death or hospitalization for HF, decreased total hospitalizations for HF, and improved health status and functional class. Yet despite the predisposition of patients with recent volume overload to fluid retention, the magnitude of these benefits (even after 1 month of treatment) was not more marked in patients with recent volume overload (interaction p values >0.05). Changes in body weight, hematocrit, and natriuretic peptides (each potentially indicative of a diuretic action of SGLT2 inhibitors) did not track each other closely in their time course or in individual patients (Packer M et al, *J Am Coll Cardiol* 2021;77:1381-92).

Framingham Offspring Cohort: Higher Consumption of Ultra-Processed Foods is Associated With Increased Risk of CVD Incidence and Mortality

Among 3,003 adults free from cardiovascular (CV) disease (CVD) with valid dietary data at baseline, during follow-up (1991 to 2014/2017), the authors identified 251, 163, and 648 cases of incident hard CVD, hard CAD, and overall CVD, respectively. On average, participants consumed 7.5 servings per day of ultra-processed foods at baseline. Each additional daily serving of ultra-processed foods conferred a 7%, 9%, 5%, and 9% increase in the risk of hard CVD, hard CAD, overall CVD, and CVD mortality, respectively (Juul F et al, *J Am Coll Cardiol* 2021;77:1520-31).

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated With the Covid-19 Pandemic: Cardiac Involvement is Common MIS-C Leading to High Levels of NT-proBNP, Ferritin, D-Dimers, and Cardiac Troponin in Addition to High CRP and Procalcitonin Levels / In Comparison With Adults With COVID-19, Mortality in MIS-C is Uncommon Despite Multisystem Involvement, Very Elevated Inflammatory Markers, and Need for ICU Support

Among 286 children (median age 8.4 years; 67% boys), the most common CV complications were shock, cardiac arrhythmias, pericardial effusion, and coronary artery dilatation. Reduced LVEF was present in over half of the patients, and a vast majority of children had raised cardiac troponin when checked. The biochemical markers of inflammation were raised in most patients on admission: elevated CRP, serum ferritin, procalcitonin, NT-proBNP, interleukin-6 level, and D-dimers. There was a statistically significant correlation between degree of elevation in cardiac and biochemical parameters and the need for ICU support ($P<0.05$). PCR for SARS-CoV 2 was positive in 33.6%, whereas immunoglobulin M and immunoglobulin G antibodies were positive in 15.7% cases and immunoglobulin G in 43.6% cases, respectively, when

checked. One child in the study cohort died (Valverde I et al, *Circulation* 2021;143:21–32).

DAPA-HF: Baseline Kidney Function did not Modify the Benefits of Dapagliflozin on Morbidity & Mortality in HFrEF, and Dapagliflozin Slowed the Rate of Decline in eGFR, Including in Patients Without Diabetes

Of 4742 patients with HFrEF with or without type 2 diabetes with a baseline eGFR, 1926 (41%) had eGFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. The effect of dapagliflozin on the primary (CV death or worsening heart failure-HF) and secondary outcomes did not differ by eGFR category or examining eGFR as a continuous measurement. The hazard ratio for the primary end point in patients with chronic kidney disease was 0.71 vs 0.77 in those with an eGFR ≥60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ (interaction *P*=0.54). The composite renal outcome was not reduced by dapagliflozin (hazard ratio-HR 0.71; *P*=0.17) but the rate of decline in eGFR between day 14 and 720 was less with dapagliflozin, –1.09 vs placebo –2.85 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ per year (*P*<0.001). This was observed in those with and without type 2 diabetes (*P* for interaction=0.92) (Jhund PS et al, *Circulation* 2021;143:298–309).

Cardiac Injury in COVID-19/Pathological Study: The Most Common Pathological Cause of Myocyte Necrosis Was Microthrombi

Of the 40 hearts examined, 14 (35%) had evidence of myocyte necrosis, predominantly of the left ventricle. Compared with subjects without necrosis, subjects with necrosis tended to be female, have chronic kidney disease, and have shorter symptom onset to admission. The incidence of severe coronary artery disease (ie, >75% cross-sectional narrowing) was not significantly different between those with and without necrosis. Three of 14 (21.4%) subjects with myocyte necrosis showed evidence of acute MI, whereas 11 of 14 (78.6%) showed evidence of focal myocyte necrosis. Cardiac thrombi were present in 11 of 14 (78.6%) cases with necrosis, with 2 of 14 (14.2%) having epicardial coronary artery thrombi, whereas 9 of 14 (64.3%) had microthrombi in myocardial capillaries, arterioles, and small muscular arteries. Microthrombi had significantly greater fibrin and terminal complement C5b-9 immunostaining compared with intramyocardial thromboemboli from COVID-19–negative subjects and with aspirated thrombi. There were no significant differences between the constituents of thrombi aspirated from COVID-19–positive and –negative patients with STEMI (Pellegrini D et al, *Circulation* 2021;143:1031-1042)

Acute Cardiac Injury (ACI) in Severe COVID-19 is a Function of Baseline Comorbidities, Old Age, and Multisystem Organ Dysfunction, Similar to Traditional ARDS / The Adverse Prognosis of ACI in COVID-19 Relates Largely to Multisystem Organ Involvement and Critical Illness

Of 243 intubated patients with COVID-19, 51% had troponin (Tn) levels above the upper limit of normal (ULN). Chronic kidney disease, lactate, ferritin, and fibrinogen were associated with ACI. Mortality was 22.7% among patients with COVID-19 with Tn under the ULN and 61.5% for those with Tn levels >10 times the ULN (*P*<0.001). The association of ACI with mortality was not statistically significant after adjusting for age, sex, and multisystem organ dysfunction. Compared with patients with ARDS without COVID-19, patients with COVID-19 were older and had higher creatinine levels and less favorable vital signs. After adjustment, COVID-19–related ARDS was associated with lower odds of ACI compared with non–COVID-19–related ARDS (odds ratio, 0.55; *P*=0.005) (Metkus TS et al, *Circulation* 2021;143:553-65).

Artificial Intelligence-Enabled Assessment of the Heart Rate Corrected QT Interval (QTc) Using a Mobile ECG (mECG) Device Can Predict Accurately the QTc of a Standard ECG

Using >1.6 million ECGs from 538,200 patients, a deep neural network (DNN) was derived (patients for training, n=250,767; patients for testing, n=107,920) and validated (n=179,513 patients) to predict the QTc using cardiologist-overread QTc values as the "gold standard". The ability of this DNN to detect QTc prolongation was then tested prospectively on 686 patients with genetic heart disease (50% with long QT syndrome). In the validation sample, strong agreement was observed between human over-read and DNN-predicted QTc values (−1.76±23.14 ms). Similarly, within the prospective, genetic heart disease–enriched dataset, the difference between DNN-predicted QTc values derived from mECG tracings and those annotated from 12-lead ECGs by a QT expert (−0.45±24.73 ms) and a commercial core ECG laboratory (10.52±25.64 ms) was nominal. When applied to mECG tracings, the DNN's ability to detect a QTc ≥500 ms yielded an area under the curve, sensitivity, and specificity of 0.97, 80%, and 94.4%, respectively (Giudicessi JR et al, *Circulation* 2021;143: 1274-86).

Deep Neural Networks Can Predict New-Onset AF from the 12-Lead ECG and Help Identify Those at Risk of AF-Related Stroke

Using 1.6 M resting 12-lead digital ECG traces from 430,000 patients and deep neural networks trained to

predict new-onset AF (within 1 year) in patients without a history of AF, the area under the receiver operating characteristic curve and area under the precision-recall curve were 0.85 and 0.22, respectively, for predicting new-onset AF within 1 year of an ECG. The hazard ratio for the predicted high- versus low-risk groups over a 30-year span was 7.2. In a simulated deployment scenario, the model predicted new-onset AF at 1 year with a sensitivity of 69% and specificity of 81%. The number needed to screen to find 1 new case of AF was 9. This model predicted patients at high risk for new-onset AF in 62% of all patients who experienced an AF-related stroke within 3 years of the index ECG (Raghunath S et al, *Circulation* 2021;143: 1287-98).

The O And Rh− Blood Groups May be Associated With a Slightly Lower Risk for SARS-CoV-2 Infection and Severe COVID-19 Illness

Among 225,556 persons (mean age 54 years), the adjusted relative risks (aRR) of SARS-CoV-2 infection for O blood group vs A, AB, and B blood groups together was 0.88. Rhesus-negative (Rh−) blood type was protective against SARS-CoV-2 infection (aRR, 0.79), especially for those who were O-negative (O−) (aRR, 0.74). There was also a lower risk for severe COVID-19 illness or death associated with type O blood group vs all others (aRR, 0.87) and with Rh− vs Rh-positive (aRR, 0.82) (Ray JG et al, *Ann Intern Med* 2021;174:308-315)

Important Review and Other Articles

● **2020 Update** to the 2016 **ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter** (Heidenreich PA et al, *J Am Coll Cardiol* 2021;77: 326-41**)**

● **Heart Disease and Stroke Statistics-2021 Update** (Virani SS et al, *Circulation* 2021;143:e254–e743)

● Cardiovascular complications of **opioid use** (Krantz MJ et al, *J Am Coll Cardiol* 2021;77:205–223)

● **2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease** (Otto CM et al, *J Am Coll Cardiol* 2021;77:450–500 / *Circulation* 2021;143:e72–e227)

2020 ACC Expert Consensus Decision Pathway for **Anticoagulant and Antiplatelet Therapy in Patients with AF or Venous Thromboembolism Undergoing PCI** or with Atherosclerotic CV Disease (Kumbhani DJ et al, *J Am Coll Cardiol* 2021;77:629-58)

● **Antithrombotic Therapy in Patients with AF** treated with oral anticoagulation **Undergoing PCI / A North American Perspective**: 2021 Update (Angiolillo DJ et al**,** *Circulation* 2021;143:583–596)

● **Supplemental Vitamins and Minerals** for CV disease prevention and treatment (Jenkins DJA et al, *J Am Coll Cardiol* 2021;77:423-36)

● **Vitamin D, Calcium Supplements,** and implications for CV health (Michos ED et al, *J Am Coll Cardiol* 2021;77:437-49)

● **Management of Antithrombotic Therapy after ACS** (Rodriguez F & Harrington RA, *N Engl J Med* 2021;384:452-60)

● CV impact of nutritional supplementation with **Omega-3 Fatty Acids** (Weinberg RL et al, *J Am Coll Cardiol* 2021;77:593–608)

● **Vasculitis** (Saadoun D et al, *Circulation* 2021;143:267–282)

● **Coenzyme Q_{10}** for patients with CV disease (Raizner *AE &* Quiñones *MA, J Am Coll Cardiol* 2021;77:609-19)

● Pathophysiology of **Takotsubo** Syndrome (Lyon AR, *J Am Coll Cardiol* 2021;77:902–921)

● Cardiac Involvement in **Fabry** Disease (Pieroni M et al, *J Am Coll Cardiol* 2021;77:922–936)

● Management of **Giant Cell Myocarditis** (Bang V et al, *J Am Coll Cardiol* 2021;77:1122–1134)

● Cardiac involvement in **Multisystem Inflammatory Syndrome in Children** (Alsaied T et al, *Circulation* 2021;143: 78–88)

● **2021 ACC Expert Consensus** Decision Pathway **on Same-Day Discharge After PCI** (Rao SV et al, *J Am Coll Cardiol* 2021;77:811-25)

● 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for **Optimization of Heart Failure Treatment** (Maddox TM et al, *J Am Coll Cardiol* 2021;77:772-810)

● **Maternal stroke** (Elgendy IY et al, *Circulation* 2021;143: 727-38)

● **TAVI in bicuspid aortic valve stenosis** (Vincent F et al, *Circulation* 2021;143:1043–1061)

● **Mind-Heart-Body Connection /AHA Statement** (Levine GN, *Circulation* 2021;143:e763–e783)

● **Cardiovascular Disease in Chronic Kidney Disease** (Jankowski J, *Circulation* 2021;143:1157–1172)

● The **proarrhythmic conundrum of alcohol intake** (Manolis AS et al, *Trends Cardiovasc Med* 2021 Mar 21; doi: 10.1016/j.tcm.2021.03.003)

● Preventing arrhythmic death in patients With **Tetralogy of Fallot** (Cohen MI et al, *J Am Coll Cardiol* 2021:77:761-71)

● **Cardiovascular implications and complications of the COVID-19 pandemic** (Manolis AS et al, *Curr Opin Cardiol* 2021;36:241-251)

● Pathological evidence for **SARS-CoV-2** as a cause of **Myocarditis** (Kawakami R et al, *J Am Coll Cardiol* 2021; 77:314-25)