Cardiology News / Recent Literature Review / Third Quarter 2022

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HCS, 43rd International Congress of Cardiology, Athens, 20-22/10/22

NY Cardiovascular Symposium 2022, New York, NY, USA, 9-11/12/22

AF Symposium, Boston, MA, USA, 2-4/2/2023

ACC Annual Meeting, New Orleans, LA, USA, 4-6/3/23

EHRA Annual Meeting, Barcelona, Spain, 16-18/4/23

Euro PCR 2023, Paris, 16-19/5/2023

HRS Annual Meeting, New Orleans, LA, USA, 19-21/5/23

EMPEROR-Preserved: Empagliflozin Reduced Cardiovascular Disease (CVD) and Heart Failure (HF) Hospitalizations (HFH) and Improved Symptoms Across a Wide Age Range / High age was not Associated with Decreased Efficacy or Intolerability

The relationship of age and empagliflozin effects was evaluated in the EMPEROR-Preserved trial. Patients (N=5,988) were grouped according to their baseline age (<65 years, n = 1,199; 65-74 years, n = 2,214; 75-79 years, n = 1,276; ≥80 years, n = 1,299). The incidence of primary outcomes (CVD or HFH) (*P* trend = 0.02) and CVD (*P* trend = 0.003) increased with age. Empagliflozin reduced primary outcomes (*P* trend = 0.33), first HFH (*P* trend = 0.22), and first and recurrent HFH (*P* trend = 0.11) across all age groups with an effect being similar at ≥75 years or >80 years. Empagliflozin improved Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score at week 52 and attenuated the decline of estimated glomerular filtration rate without age interaction. There were no clinically relevant differences in adverse events between empagliflozin and placebo across the age groups. Thus, empagliflozin reduced primary outcomes and first and recurrent HFH and improved symptoms across a broad age spectrum. High age did not reduce efficacy or meaningful intolerability (Bohm M et al, *J Am Coll Cardiol* 2022;80:1-18).

ARIC Study: Adult Cancer Survivors Have Higher Risk of CVD, Especially HF, Independent of Traditional CV Risk Factors

A prospective community-based study including 12,414 ARIC (Atherosclerosis Risk In Communities) study participants (mean age 54 years, 55% female, 25% Black), of whom 3,250 (25%) had incident cancer over a median 13.6 years, indicated that age-adjusted incidence rates of CVD (per 1,000 person-years) were 23.1 (95% CI: 24.7-29.1) for cancer survivors and 12.0 (95% CI: 11.5-12.4) for subjects without cancer. After adjustment for CV risk factors, cancer survivors had significantly higher risks of CVD (HR: 1.37), HF (HR: 1.52), and stroke (HR: 1.22), but not CAD (HR: 1.11). Breast, lung, colorectal, and hematologic/lymphatic cancers, but not prostate cancer, were significantly associated with CVD risk (Florido R et al, *J Am Coll Cardiol* 2022;80:22–32).

VALOR-HCM Study: In Obstructive Hypertrophic Cardiomyopathy (OHCM) Patients With Intractable Symptoms, Mavacamten Reduced the Fraction of Patients Meeting Guideline Criteria for Septal Reduction Therapy (SRT) After 16 Weeks

Patients (N=112; age 60 ± 12 years, 51% men, 93% NYHA class III/IV) with left ventricular (LV) outflow tract (LVOT) gradient ≥50 mm Hg at rest/provocation who met guideline criteria for SRT were randomized, double blind, to mavacamten, 5 mg daily, or placebo, titrated up to 15 mg based on LVOT gradient and LV ejection fraction. After 16 weeks, 43 of 56 placebo patients (76.8%) and 10 of 56 mavacamten patients (17.9%) met guideline criteria or underwent SRT, difference (58.9%; *P* < 0.001). Hierarchical testing of secondary outcomes showed significant differences (*P* < 0.001) favoring mavacamten, mean differences in post-exercise peak LVOT gradient −37.2 mm Hg; ≥1 NYHA class improvement 41.1%; improvement in patient-reported outcome 9.4 points; and NT-proBNP and cardiac troponin I between-groups geometric mean ratio 0.33 and 0.53 (Desai MY et al, *J Am Coll Cardiol* 2022;80:95–108).

Early Myocardial Revascularization Significantly Reduced Mortality Among Both Patients With Normal LVEF and Severe Inducible Myocardial Ischemia and Patients With Low LVEF and Moderate r Severe Inducible Myocardial Ischemia

The study evaluated 43,443 patients undergoing stress-rest single-photon emission computed tomography myocardial perfusion imaging from 1998 to 2017. Median follow-up was 11.4 years. The frequency of myocardial ischemia varied markedly according to LVEF and angina, ranging from 6.7% among patients with LVEF ≥55% and no typical angina to 64% among patients with LVEF <45% and typical angina (*P* < 0.001). Among 39,883 patients with LVEF ≥45%, early revascularization conferred an increased mortality risk among patients without ischemia and lower mortality risk among patients with severe (≥15%) ischemia (HR: 0.70). Among 3,560 patients with LVEF <45%, revascularization did not confer mortality benefit among patients with no or mild ischemia, and decreased mortality among patients with moderate (10%-

14%) (HR: 0.67) and severe (≥15%) (HR: 0.55; 95%) ischemia (Rozanski A et al, *JACC* 2022;80: 202–215).

***EAST-AFNET 4*: Early Rhythm Control (ERC) Reduces the First Primary Composite Outcome in All AF Patterns / Patients With First Diagnosed AF are at High Risk for Hospitalization and Acute Coronary Syndrome, Particularly on ERC**

Clinical characteristics and outcomes were compared in patients presenting with different AF patterns on ERC vs usual care. First-diagnosed AF patients (n = 1,048, enrolled 7 days after diagnosing AF) were slightly older (71 years of age, 48% female) than patients with paroxAF (n = 994, 70 years of age, 50% female) and persAF (n = 743, 70 years of age, 38% female). ERC reduced the primary outcome (CV death, stroke, and hospitalization for heart failure and acute coronary syndrome) in all 3 AF patterns. Hospitalizations for acute coronary syndrome were highest in first diagnosed AF (incidence rate ratio - IRR: 1.50; *P* for interaction = 0.032) compared with paroxAF (IRR: 0.64) and persAF (IRR: 0.50). First diagnosed AF patients spent more nights in hospital (IRR: 1.38; *P* for interaction = 0.004) than paroxAF (IRR: 0.84), and persAF (IRR: 1.02) patients. ERC improved health-related quality of life in patients with paroxAF and persAF but not in patients with first diagnosed AF (*P* = 0.019) (Goette A et al, *J Am Coll Cardiol* 2022;80:283–295).

***PARTNER Trials:* In Patients Undergoing AVR, Extent of Extravalvular Cardiac Damage at Baseline and its Change at 1 Year Has Prognostic Implications / Earlier Detection of Aortic Stenosis and Intervention Before Development of Irreversible Cardiac Damage May Improve Global Cardiac Function and Prognosis**

Among 1,974 patients undergoing transcatheter or surgical AVR, classified by cardiac damage stage at baseline and 1 year (stage 0, no damage; stage 1, LV damage; stage 2, LA or mitral valve damage; stage 3, pulmonary vasculature or tricuspid valve damage; and stage 4, RV damage), 121 (6.1%) were stage 0, 287 (14.5%) stage 1, 1,014 (51.4%) stage 2, 412 (20.9%) stage 3, and 140 (7.1%) stage 4 pre-AVR. Two-year mortality was associated with extent of cardiac damage at baseline and 1 year. Compared with baseline, cardiac damage improved in ∼15%, remained unchanged in ∼60%, and worsened in ∼25% of patients at 1 year. The 1-year change in cardiac damage stage was independently associated with mortality (adjusted HR for improvement: 0.49; no change: 1.00; worsening: 1.95; *P* = 0.023) and composite of death or heart failure hospitalization (adjusted HR for improvement: 0.60; no change: 1.00; worsening: 2.25; *P* < 0.001) at 2 years. (Généreux P, et al, *J Am Coll Cardiol* 2022;80: 783–800).

Screening for Cardiac Amyloidosis (CA) in Patients With Prior Surgery for Bilateral Carpal Tunnel Syndrome (CTS) Detects ~5% With Early-Stage Transthyretin CA, with a Higher Yield (>1 In 5) When Focusing on Nonobese Men ≥70 Years, Indicating Potential for Systematic Screening

A total of 250 subjects aged 60-85 years (median age 70 years, 50% females) with prior CTS surgery, where the first procedure on the second wrist was performed 5-15 years earlier, were evaluated with echocardiography, ^{99m}technetium-pyrophosphate scintigraphy, and assessment of monoclonal proteins in serum and urine. CA was diagnosed in 12 patients (4.8%), and all cases were wild-type transthyretin amyloidosis (ATTRwt). The prevalence of ATTRwt in men was 8.8% (n = 11), and 21.2% in male subjects ≥70 years with a BMI <30 kg/m^2. All but 2 patients diagnosed with ATTRwt were in the lowest disease severity score (Mayo score) (Westin O et al, *J Am Coll Cardiol* 2022;80: 967−977).

There is a Significant Temporal Association Between Invasive Dental Procedures (IDPs) (Mainly Extractions and Oral-Surgical Procedures) and Subsequent Infective Endocarditis (IE) in High–IE-Risk Individuals, and a Significant Association Between Antibiotic Prophylaxis (AP) Use and Reduced Attendant IE Incidence/ Data Support the American Heart Association, and Other, Recommendations that Those at High IE Risk Should Receive AP Before IDP

A case-crossover analysis and cohort study of the association between IDPs and IE, and AP efficacy, in 7,951,972 U.S. subjects showed that IE was most likely to occur within 4 weeks of an IDP. For those at high IE risk, case-crossover analysis demonstrated a significant temporal association between IE and IDPs in the preceding 4 weeks (OR: 2.00; *P*=0.002). This relationship was strongest for dental extractions (OR: 11.08; *P*<0.0001) and oral-surgical procedures (OR: 50.77; *P* < 0.0001). AP was associated with a significant reduction in IE incidence following IDP (OR: 0.49; *P* = 0.01). The cohort study confirmed the associations between IE and extractions or oral surgical procedures in those at high IE risk and the effect of AP in reducing these associations (extractions: OR: 0.13; *P* < 0.0001; oral surgical procedures: OR: 0.09; *P* = 0.002) (Thornhill MH et al, *JACC* 2022;80:1029-41).

LBBP-RESYNC: Left Bundle Branch Pacing vs Biventricular Pacing for Cardiac Resynchronization Therapy (CRT) / Greater LVEF Improvement with LBBP-CRT than BiVP-CRT in Heart Failure Patients With Nonischemic Cardiomyopathy and LBBB

The efficacy of LBBP-CRT with BiVP-CRT was compared in 40 nonischemic cardiomyopathy patients

with heart failure and reduced left ventricular (LV) ejection fraction (LVEF) and LBBB (20 men, mean age 63.7 years, LVEF 29.7% ± 5.6%). Crossovers occurred in 10% of LBBP-CRT and 20% of BiVP-CRT. Intention-to-treat analysis showed significantly higher LVEF improvement at 6 months after LBBP-CRT than BiVP-CRT (mean difference: 5.6%; 95% CI: 0.3-10.9; P = 0.039). LBBP-CRT also appeared to have greater reductions in LV end-systolic volume (−24.97 mL; 95% CI: −49.58 to −0.36 mL) and NT-proBNP (−1,071.80 pg/mL; 95% CI: −2,099.40 to −44.20 pg/mL), and comparable changes in NYHA functional class, 6-min walk distance, QRS duration, and rates of CRT response Compared with BiVP-CRT (Wang Y et al, *J Am Coll Cardiol* 2022;80: 1205–1216).

MASTER DAPT Trial: Abbreviated Dual Antiplatelet Therapy (DAPT) After Coronary Stenting in Patients With Myocardial Infarction (MI) at High Bleeding Risk / A 1-Month DAPT Strategy Results in Similar Net Adverse Clinical Outcomes Events (NACE) and Major Adverse Cardiac and Cerebral Events (MACCE) Rates and Reduces Bleedings Compared With a Nonabbreviated DAPT Strategy

Among 4,579 patients at high bleeding risk (HBR) randomized after 1 month of dual antiplatelet therapy (APT) (DAPT) to abbreviated (DAPT stopped and 11 months single APT or 5 months in patients with oral anticoagulants) or nonabbreviated APT (DAPT for minimum 3 months) strategies, NACE and MACCE did not differ with abbreviated vs nonabbreviated APT regimens in patients with an acute or recent MI (n = 1,780; HR: 0.83 and 0.86, respectively) or without an acute or recent MI (n = 2,799; HR: 1.03 and 1.13; $P_{interaction}$ = 0.31 and 0.25, respectively). Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding was significantly reduced in patients with or without an acute or recent MI (HR: 0.65 and 0.71; $P_{interaction}$ = 0.72) with abbreviated APT (Smits PC et al, *J Am Coll Cardiol* 2022;80: 1220–1237)

Cost-Effectiveness of Catheter Ablation vs Antiarrhythmic Drug Therapy in Atrial Fibrillation: The CABANA Randomized Trial

In the CABANA trial, catheter ablation did not significantly reduce the primary end point of death, disabling stroke, serious bleeding, or cardiac arrest compared with drug therapy by intention-to-treat, but improved quality of life (QOL) and freedom from AF recurrence. In the heart failure subgroup, ablation improved both survival and QOL. A cost-effectiveness analysis using data from all CABANA patients (N=2204) showed that costs in the first 3 months averaged $20 794±1069 higher with ablation compared with drug therapy. The cumulative within-trial 5-year cost difference was $19 245 and the lifetime mean cost difference was $15 516 higher with ablation than with drug therapy. The drug therapy arm accrued an average of 12.5 life-years (LYs) and 10.7 quality-adjusted life-years (QALYs). For the ablation arm, the corresponding estimates were 12.6 LYs and 11.0 QALYs. The incremental cost-effectiveness ratio was $57 893 per QALY gained, with 75% of bootstrap replications yielding an incremental cost-effectiveness ratio <$100 000 per QALY gained. With no quality-of-life/utility adjustments, the incremental cost-effectiveness ratio was $183 318 per LY gained (Chew DS et al, *Circulation* 2022;146:535–547)

ODYSSEY OUTCOMES trial: Alirocumab Reduced MACE Across All Strata of Baseline Apolipoprotein B (ApoB), With Larger Absolute Reductions in Patients With Higher Baseline Levels

The proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab was compared with placebo in 18 924 patients with recent acute coronary syndrome and elevated atherogenic lipoproteins despite optimized statin therapy. Over a median of 2.8 years, MACE incidence increased across increasing baseline apoB strata (3.2, 4.0, and 5.5 events per 100 patient-years in strata <75, 75–<90, ≥90 mg/dL, respectively; P_{trend}<0.0001) and after adjustment for low-density lipoprotein cholesterol (P_{trend}=0.035). Higher baseline apoB stratum conferred greater relative (P_{trend}<0.0001) and absolute reduction in MACE with alirocumab vs placebo. In the alirocumab group, the incidence of MACE after month 4 decreased across decreasing achieved apoB strata (4.26, 3.09, and 2.41 events per 100 patient-years in strata ≥50, >35–<50, and ≤35 mg/dL, respectively). Compared with propensity score–matched patients from the placebo group, treatment hazard ratios for alirocumab also decreased across achieved apoB strata. Achieved apoB was predictive of MACE after adjustment for achieved LDL cholesterol or non–HDL cholesterol but not vice versa (Hangstrom E et al, *Circulation* 2022;146:657–672)
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The Risk of Acute Myocarditis is Greater After COVID-19 Infection than after COVID-19 Vaccination and Remains Modest After Sequential Doses Including a Booster Dose of BNT162b2 mRNA Vaccine / However, the Risk of Myocarditis After Vaccination is Higher in Younger Men, Particularly After a Second Dose of the mRNA-1273 Vaccine

In 42,842,345 people receiving at least 1 dose of vaccine, 21 242 629 received 3 doses, and 5,934,153 had SARS-CoV-2 infection before or after vaccination. Myocarditis occurred in 2861 (0.007%) people, with 617 events 1 to 28 days after vaccination. Risk of myocarditis was increased in the 1 to 28 days after a first dose of ChAdOx1 (incidence rate ratio, 1.33 [95% CI, 1.09–1.62]) and a first, second, and booster dose of BNT162b2 (1.52

[95% CI, 1.24–1.85]; 1.57 [95% CI, 1.28–1.92], and 1.72 [95% CI, 1.33–2.22], respectively) but was lower than the risks after a positive SARS-CoV-2 test before or after vaccination (11.14 [95% CI, 8.64–14.36] and 5.97 [95% CI, 4.54–7.87], respectively). The risk of myocarditis was higher 1 to 28 days after a second dose of mRNA-1273 (11.76 [95% CI, 7.25–19.08]) and persisted after a booster dose (2.64 [95% CI, 1.25–5.58]). Associations were stronger in men younger than 40 years for all vaccines. In men younger than 40 years old, the number of excess myocarditis events per million people was higher after a second dose of mRNA-1273 than after a positive SARS-CoV-2 test (97 [95% CI, 91–99] versus 16 [95% CI, 12–18]). In women younger than 40 years, the number of excess events per million was similar after a second dose of mRNA-1273 and a positive test (7 [95% CI, 1–9] versus 8 [95% CI, 6–8]) (Patone M et al, *Circulation* 2022;146:743–54).

CAPLA Study: Posterior Wall Isolation Does Not Improve Freedom from AF Recurrence, Compared to PVI Alone, in Patients with Persistent AF

At the 2022 European Society of Cardiology (ESC) Congress, Peter Kistler, MD, from the University of Melbourne, presented the results of the CAPLA study (**C**atheter **A**blation for persistent atrial fibrillation: A Multicentre randomised trial of **P**ulmonary vein antral isolation (PVAI) vs PVAI with posterior **L**eft **A**trial wall isolation), an international multicenter randomized controlled trial (RCT) that enrolled 338 patients with symptomatic persistent AF to pulmonary vein isolation (PVI) alone or PVI plus posterior wall isolation. The primary endpoint was freedom from AF (or atrial flutter) at 1 year. The results were disappointing. Freedom from AF in the two groups were almost identical (53.3% and 54.1%). Procedure times were longer in the PVI plus posterior wall group. Complications were low — 2.9% overall, not different between the two groups. The authors concluded that "these findings do not support the empiric inclusion of posterior wall isolation for persistent AF ablation." (Chieng D et al, *Am Heart J* 2022;243:210-220 / *Medscape*-Aug 26, 2022).

INVICTUS: Among Patients With Rheumatic Heart Disease–Associated Atrial Fibrillation (AF), Vitamin K Antagonist (VKA) Therapy Led to a Lower Rate of a Composite of Cardiovascular (CV) Events or Death than Rivaroxaban, Without a Higher Rate of Bleeding

Contrary to expectations, VKAs reduced the risk for ischemic stroke and death compared with the factor Xa inhibitor rivaroxaban in patients with rheumatic heart disease and AF. Patients receiving a VKA (N=446), typically warfarin, had a 25% lower risk for the primary outcome — a composite of stroke, systemic embolism, myocardial infarction, or death from vascular or unknown causes outcome — than receiving rivaroxaban (N=560) (hazard ratio-HR, 1.25; 95% CI, 1.10 - 1.41). This difference was driven primarily by a significant reduction in the risk for death in the VKA group, and without a significant increase in major bleeding. The authors concluded that "VKA should remain the standard of care for patients with rheumatic heart disease and AF" (Connolly SJ et al, *N Engl J Med* 2022; 387:978-988).

eBRAVE-AF: Smartphone Atrial Fibrillation (AF) Screening Doubles Detection

Digital smart devices have the capability of detecting AF, but the efficacy of this type of digital screening has not been directly compared to usual care for detection of treatment-relevant AF. In the eBRAVE-AF trial, 5,551 policyholders of a German health insurance company who were free of AF at baseline (age 65 years (median; interquartile range (11) years, 31% females) were randomly assigned to digital screening (n = 2,860) or usual care (n = 2,691). In this siteless trial, for digital screening, participants used a certified app on their own smartphones to screen for irregularities in their pulse waves. Abnormal findings were evaluated by 14-day external ECG loop recorders. After 6 months, participants were invited to cross-over for a second study phase with reverse assignment for secondary analyses. The primary endpoint of the trial (newly diagnosed AF within 6 months treated with oral anti-coagulation) was met, as digital screening more than doubled the detection rate of treatment-relevant AF in both phases of the trial, with odds ratios of 2.12 (P = 0.010) and 2.75 (P = 0.003) in the first and second phases, respectively. This digital screening technology provides substantial benefits in detecting AF compared to usual care and has the potential for broad applicability due to its wide availability on ordinary smartphones (Rizas KD et al, *Nat Med* 2022;28:1823-1830).

FLAVOUR Trial: In Patients With Intermediate Stenosis Who Were Being Evaluated for PCI, FFR Guidance Was Noninferior to IVUS Guidance With Respect to the Composite Primary Outcome of Death, MMI, or Revascularization at 2 Years

Among 1682 patients who were being evaluated for PCI for the treatment of intermediate stenosis (40-70% by visual estimation on coronary angiography) randomly assigned in a 1:1 ratio to undergo either an FFR-guided (if FFR≤0.80) or IVUS-guided procedure (with a minimal lumen area measuring either ≤3 mm^2 or measuring 3-4 mm^2 with a plaque burden of >70%), the frequency of PCI was 44.4% among patients in the FFR group and 65.3% among those in the IVUS group. At 2 years, a primary-outcome event (death, MI, or revascularization) had

occurred in 8.1% of the patients in the FFR group and in 8.5% of those in the IVUS group (absolute difference, −0.4 percentage points; upper boundary of the one-sided 97.5% confidence interval, 2.2 percentage points; P=0.01 for noninferiority). Patient-reported outcomes as reported on the Seattle Angina Questionnaire were similar in the two groups (Koo B-K et al, *N Engl J Med* 2022;387:779-789).

DELIVER Trial: Dapagliflozin Reduced the Combined Risk of Worsening Heart Failure or Cardiovascular Death Among Patients With Heart Failure and a Mildly Reduced or Preserved Ejection Fraction

Among 6263 patients with heart failure (HF) and a left ventricular ejection fraction (LVEF) of >40% randomly assigned to receive dapagliflozin (a10 mg qd) or matching placebo, in addition to usual therapy, the primary outcome (worsening HF or CV death) occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (hazard ratio-HR, 0.82; P<0.001) over a median of 2.3 years. Worsening HF occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (HR 0.79); CV death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (HR, 0.88). Total events and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a LVEF≥60% and those with a LVEF <60%, and results were similar in prespecified subgroups, including patients with or without diabetes. The incidence of adverse events was similar in the two groups (Solomon SD et al, *N Engl J Med* 2022; 387:1089-1098).

Meta-Analysis of 5 RCTs: SGLT2 Inhibitors Reduced the Risk of CV Death and Hospitalisations for Heart Failure (HF) in a Broad Range of Patients With HF, Supporting Their Role as a Foundational Therapy for HF, Irrespective of Ejection Fraction or Care Setting

A meta-analysis of DELIVER, EMPEROR-Preserved, DAPA-HF, EMPEROR-Reduced and SOLOIST-WHF indicated that among 12 251 participants from DELIVER and EMPEROR-Preserved, SGLT2 inhibitors reduced composite CV death or first hospitalisation for HF (HR 0.80) with consistent reductions in both components: CV death (HR 0.88) and first hospitalisation for HF (HR 0.74). In the broader context of the 5 trials of 21 947 participants, SGLT2 inhibitors reduced the risk of composite CV death or hospitalisation for HF (HR 0.77), CV death (HR 0.87), first hospitalisation for HF (HR 0.72), and all-cause mortality (HR 0.92). These treatment effects for each of the studied endpoints were consistently observed in both the trials of HF with mildly reduced or preserved ejection fraction and across all 5 trials. Treatment effects on the primary endpoint were generally consistent across the 14 subgroups examined, including ejection fraction (Vaduganathan M et al, *Lancet* 2022;400:757-767).

ADVOR Trial: Acetazolamide Added to Loop Diuretic Therapy in Patients With Acute Decompensated Heart Failure Resulted in More Successful Decongestion

Among 519 patients with acute decompensated heart failure (HF), clinical signs of volume overload (i.e., edema, pleural effusion, or ascites), and an N-terminal pro–B-type natriuretic peptide (NTproBNP) level of >1000 pg/ml or a BNP level of >250 pg/ml randomized to acetazolamide (500 mg qd) or placebo, added to standardized intravenous loop diuretics (at a dose equivalent to twice the oral maintenance dose), successful decongestion within 3 days occurred in 108 of 256 patients (42.2%) in the acetazolamide group and in 79 of 259 (30.5%) in the placebo group (risk ratio, 1.46; 95% confidence interval [CI], 1.17 to 1.82; P<0.001). Death from any cause or rehospitalization for HF within3 months occurred in 76 of 256 patients (29.7%) in the acetazolamide group and in 72 of 259 patients (27.8%) in the placebo group (HR, 1.07; 95% CI, 0.78 to 1.48). Acetazolamide treatment was associated with higher cumulative urine output and natriuresis, findings consistent with better diuretic efficiency. The incidence of worsening kidney function, hypokalemia, hypotension, and adverse events was similar in the two groups (Mullens W et al, *N Engl J Med* 2022;387:1185-1195).

RACING Trial: Among Patients With Atherosclerotic Cardiovascular Disease (CVD), Moderate-Intensity Statin With Ezetimibe Combination Therapy was Non-Inferior to High-Intensity Statin Monotherapy for the 3-Year Composite Outcomes With a Higher Proportion of Patients With LDL Cholesterol Concentrations of <70 mg/dl and Lower Intolerance-Related Drug Discontinuation or Dose Reduction

Among 3780 CVD patients enrolled, 1894 patients to the combination therapy group and 1886 to the high-intensity statin monotherapy group. The primary endpoint (3-year composite of CV death, major CV events, or non-fatal stroke) occurred in 172 patients (9.1%) in the combination (rosuvastatin 10 mg with ezetimibe 10 mg) therapy group and 186 patients (9.9%) in the high-intensity statin (rosuvastatin 20 mg) monotherapy group (absolute difference −0.78%; 90% CI −2.39 to 0.83). LDL cholesterol concentrations of less than 70 mg/dL at 1, 2, and 3 years were observed in 73%, 75%, and 72% of patients in the combination therapy group, and 55%, 60%, and 58% of patients in the high-intensity statin monotherapy group (all P<0.0001). Discontinuation or dose reduction of the study drug by intolerance was observed in 88 patients (4.8%) and 150 patients (8.2%),

respectively (p<0.0001) (Kim B-K et al, *Lancet* 2022;400:380-390).

Meta-Analysis: In Patients with Marfan Syndrome and no Prior Aortic Surgery, ARBs Reduced the Rate of Increase of the Aortic Root Z Score by ~Half, Including Among Those Taking a β-Blocker / The Effects of β-Blockers Were Similar τo Those of APBs / Combining Both ARBs and β-Blockers Upon Diagnosis Would Provide Even Greater Reductions in the Rate of Aortic Enlargement Than Either Treatment Alone, Which, if Maintained Over a Number of Years, Might Lead to a Delay in the Need for Aortic Surgery

Meta-analysis was conducted of 7 trials comprising 1442 patients; 4 trials involving 676 eligible participants compared ARB with control & 3 trials involving 766 eligible participants compared ARBs with β blockers. In the first group, over a median of 3 years, allocation to ARB almost halved the annual rate of change in the aortic root Z score (mean annual increase 0.07±0.02 ARB *vs* 0.13±0.02 control; absolute difference –0.07; p=0.012). Prespecified secondary subgroup analyses showed that the effects of ARB were particularly large in those with pathogenic variants in fibrillin-1, compared with those without such variants (heterogeneity p=0·0050), and there was no evidence to suggest that the effect of ARB varied with β-blocker use (heterogeneity p=0.54). In the second group, over a median of 3 years, the annual change in the aortic root Z score was similar in the two groups (annual increase –0.08±0.03 in ARB groups *vs* –0.11±0.02 in β-blocker groups; absolute difference 0.03; p=0.48). Thus, indirectly, the difference in the annual change in the aortic root Z score between β blockers and control was –0.09 (p=0·042) (Pitcher A et al, *Lancet* 2022;400:822-831).

Meta-Analysis: Both β-Blockers (BBs) and ACE Inhibitors/Angiotensin Receptor Blocker (ACEI/ARB) Therapies Were Beneficial, Associated With Preservation of LVEF During Trastuzumab and Anthracycline-Containing Regimens Compared With Placebo

A meta-analysis of 9 RCTs (N=1362, all women) examining the effect of b-blockers (BBs) and ACE inhibitors/angiotensin receptor blockers (ACEI/ARBs) on LVEF in patients treated with either trastuzumab or anthracyclines indicated that BBs and ACEI/ARBs were shown to attenuate the decline in LVEF during trastuzumab and anthracycline treatments [MD: 2.4; 95% confidence interval (CI): 0.3–4.2 and MD: 1.5; 95% CI: –0.6 to 3.7]. Compared with placebo, LVEF was higher in patients assigned to BB or ACEI/ARB on trastuzumab (MD: 2.3; 95% CI: 0.0–4.6) but not on anthracyclines (MD: 1.9; 95% CI: –0.5 to 4.2) (Lewinter C et al; *Eur Heart J* 2022*;*43:2562–2569).

ATLANTIS Trial: After TAVI, Apixaban Was Not Superior to the Standard of Care, Irrespective of an Indication for Oral Anticoagulation

After successful TAVI, 1500 patients were randomized (1:1) to receive apixaban 5 mg bid (2.5 mg bid if impaired renal function or concomitant antiplatelet therapy) ($n = 749$) twice daily, or standard of care ($n = 751$) (i.e. vitamin K antagonist - VKA /Stratum 1 or antiplatelet therapy /Stratum 2 if there was an indication for anticoagulation or not, respectively). The primary outcome (composite of death, MI, stroke or TIA, systemic embolism, intracardiac or bioprosthesis thrombosis, deep vein thrombosis or pulmonary embolism, and life-threatening, disabling, or major bleeding over 1-year follow-up) occurred in 138 (18.4%) and 151 (20.1%) patients receiving apixaban or standard of care, respectively (HR 0.92) and there was no evidence of interaction between treatment and stratum ($P_{\text{interaction}} = 0.57$). The primary safety endpoint (major, disabling, or life-threatening bleeding) was similar in both groups (HR 1.02). In Stratum 1 ($n = 451$), an exploratory analysis showed no difference for all endpoints between apixaban and VKA. In Stratum 2 ($n = 1049$), the primary outcome and primary safety endpoint did not differ, but obstructive valve thrombosis was reduced with apixaban vs antiplatelet therapy (HR 0.19), while a signal of higher non-cardiovascular mortality was observed with apixaban (Collet JP et al, *Eur Heart J* 2022;43,:2783–97).

EMPEROR-Pooled: Empagliflozin Reduced the Incidence of Hyperkalaemia Without Significant Increase in Hypokalaemia

EMPEROR-Pooled (i.e. EMPEROR-Reduced and EMPEROR-Preserved combined) included 9583 patients with available serum potassium levels at baseline (98.6% of the total EMPEROR-Pooled population, $n = 9718$). Patients with high potassium at baseline were more frequently diagnosed with diabetes and ischemic HF etiology and had lower LVEF and estimated glomerular filtration rate (GFR) but were more frequently treated with sacubitril/valsartan or mineralocorticoid receptor antagonists. Empagliflozin (compared with placebo) reduced the composite of investigator-reported hyperkalaemia or initiation of potassium binders (6.5% vs. 7.7%, HR 0.82, $P = 0.01$]. Empagliflozin reduced hyperkalaemia rates regardless of the definition used (serum potassium >5.5 mmol/l: 8.6% vs. 9.9%, HR 0.85, $P = 0.017$; serum potassium >6.0 mmol/l: 1.9% vs. 2.9%, HR 0.62, $P < 0.001$). The incidence of hypokalaemia (investigator-reported or serum potassium <3.0 mmol/l) was not significantly increased with empagliflozin (Ferreira JP et al; *Eur Heart J* 2022; 43:2984–2993).

Meta-Analysis: In All-Comers With Non-ST Elevation Acute Coronary Syndrome (NSTE-ACS), an Early Invasive Strategy (IS) Does Not Reduce All-Cause Mortality, MI, Admission for HF, Repeat Re-Vascularization, or Increase Major Bleeding or Stroke When Compared With a Delayed IS / Risk 0f Recurrent Ischemia and Length of Stay are Significantly Reduced With an Early IS

A systematic review of 17 RCTs (N=10,209) that compared an early IS vs delayed IS for NSTE-ACS showed no significant differences in risk for all-cause mortality (RR: 0.90), MI (RR: 0.86), admission for HF (RR: 0.66), repeat re-vascularization (RR: 1.04), major bleeding (RR: 0.86), or stroke (RR: 0.95). Recurrent ischaemia (RR: 0.57) and length of stay (median difference: −22 h) were reduced with an early IS. N.B.: The pooled medians timings to angiography across the included trials were 3.43 h (1.47–5.40 h) in the early IS group and 41.3 h (29.3–53.2 h) in the delayed IS group (Kite TA et al, *Eur Heart J* 2022; 43:3148–3161).

Meta-Analysis of >4 Million Patients: The Prevalence of Statin Intolerance (SI) is at ~9% When Diagnosed According to International Definitions /The Prevalence of Complete SI Might Often be Overestimated /There is Need for Careful Assessment of Patients With Potential Symptoms Related to SI

A meta-analysis of 176 studies (112 RCTs, 64 cohort studies; N=4,143,517) reported an overall prevalence of statin intolerance (SI) of 9.1%. The prevalence was similar when defined using several criteria (5.9%-7%). The prevalence of SI in RCTs was lower compared with cohort studies (4.9% vs. 17%). The prevalence of SI in studies including both primary and secondary prevention patients was much higher than when primary or secondary prevention patients were analysed separately (18%, 8.2%, 9.1%, respectively). Statin lipid solubility did not affect the prevalence of SI (4% vs. 5%). Age (odds ratio - OR 1.33, $P = 0.04$), female gender (OR 1.47, $P = 0.007$), Asian and Black race ($P < 0.05$ for both), obesity (OR 1.30, $P = 0.02$), diabetes mellitus (OR 1.26, $P = 0.02$), hypothyroidism (OR 1.37, $P = 0.01$), chronic liver, and renal failure ($P < 0.05$ for both) were significantly associated with SI in the meta-regression model. Antiarrhythmic agents, calcium channel blockers, alcohol use, and increased statin dose were also associated with a higher risk of SI (Bytyci I et al, *Eur Heart* J 2022; 43:3213–3223).

Empagliflozin Induced a Rapid and Sustained Reduction of Serum Uric Acid (SUA) Levels and of Clinical Events Related to Hyperuricemia

The association between SUA and the composite primary outcome of CV death or hospitalization for worsening HF, its components, and all-cause mortality was investigated in 3676 patients of the EMPEROR-Reduced trial (98.6% of the study cohort). The treatment effect of empagliflozin was studied in relation to SUA as continuous variable, to clinical hyperuricaemia (SUA >5.7 mg/dL for women, >7.0 mg/dL for men) and in subgroups of patients of tertiles of SUA.

Hyperuricaemia was prevalent in 53% of patients with no sex differences. Elevated SUA (highest tertile, mean SUA 9.38 ± 1.49 mg/dL) was associated with advanced severity of HF and with worst outcome (HR 1.64); CV mortality, HR 1.98; all-cause mortality, HR 1.8, all $P < 0.001$] in multivariate adjusted analyses, as compared with the lowest tertile. SUA was reduced following treatment with empagliflozin at 4 weeks (vs. placebo: -1.12 ± 0.04 mg/dL, $P < 0.0001$) and remained lower throughout follow-up, with a similar reduction in all prespecified subgroups. Empagliflozin reduced events of clinically relevant hyperuricaemia (acute gout, gouty arthritis or initiation of anti-gout therapy) by 32% (HR 0.68, $P = 0.004$). The beneficial effect of empagliflozin on the primary endpoint was independent of baseline SUA (HR 0.76, $P < 0.001$) and of the change in SUA at 4 weeks (HR 0.81, $P = 0.012$]. The authors concluded that hyperuricemia is common in HF and is an independent predictor of advanced disease severity and increased mortality. Empagliflozin induced a rapid and sustained reduction of SUA levels and of clinical events related to hyperuricaemia. The benefit of empagliflozin on the primary outcome was observed independently of SUA (Doehner W et al, *Eur Heart J* 2022; 43:3435–46).

ILLUMINATE-CS registry: **Although Mortality is Relatively Low in Cardiac Sarcoidosis (CS), Adverse Events are Common, Mainly Due to Fatal Ventricular Arrhythmia Events (FVAE) /Patients With Low LVEF, High BNP Levels, VT/VF History, or Requiring Ablation to Treat VT are at High Risk**

A retrospective multicenter registry study evaluated the prognosis and prognostic factors of 512 patients with cardiac sarcoidosis (CS), among whom 148 combined events (56 HF hospitalizations, 99 documented FVAE, and 49 all-cause deaths) were observed during a median follow-up of 1042 (interquartile range: 518–1917) days. The 10-year estimated event rates for the primary endpoint (composite of all-cause death, HF hospitalization, and documented fatal VAs, all-cause death, HF hospitalizations, and FVAE were 48.1, 18.0, 21.1, and 31.9%, respectively. On multivariable Cox regression, a history of VT or VF (HR 2.53, $P < 0.001$], log-transformed brain natriuretic peptide (BNP) levels (HR 1.28, $P = 0.008$), LVEF (HR 0.94 per 5% increase, $P = 0.046$), and post-diagnosis RF ablation for VT (HR 2.65,

$P = 0.045$) independently predicted the primary endpoint (Nabeta T, et al; *Eur Heart J* 2022;43:3450–3459).

Moderate Consumption of Unsweetened and Sugar-Sweetened Coffee Was Associated With Lower Risk for Death

A prospective cohort study extracted data from the UK Biobank on 171,616 participants (age, 55.6±7.9 years) without CV disease or cancer at baseline; dietary consumption of sugar-sweetened, artificially sweetened, and unsweetened coffee was self-reported. During a median of 7 years, 3177 deaths were recorded (including 1725 cancer deaths and 628 CVD deaths). Cox models with penalized splines showed U-shaped associations of unsweetened coffee, sugar-sweetened coffee, and artificially sweetened coffee with mortality. Compared with nonconsumers, consumers of various amounts of unsweetened coffee (>0 to 1.5, >1.5 to 2.5, >2.5 to 3.5, >3.5 to 4.5, and >4.5 drinks/d) had lower risks for all-cause mortality after adjustment for lifestyle, sociodemographic, and clinical factors, with respective HRs of 0.79, 0.84, 0.71, 0.71, and 0.77; the respective estimates for consumption of sugar-sweetened coffee were 0.91, 0.69, 0.72, 0.79, and 1.05. The association between artificially sweetened coffee and mortality was less consistent. The association of coffee drinking with mortality from cancer and CVD was largely consistent with that with all-cause mortality. U-shaped associations were also observed for instant, ground, and decaffeinated coffee. However, exposure assessed at baseline might not capture changes in intake over time (Liu D et al, *Ann Intern Med* 2022;175: 909-917).

Patients Receiving SGLT-2 Inhibitors as First-Line T2D Treatment Had a Similar Risk for MI/ Stroke/ Mortality, Lower Risk for HF Hospitalization (HHF)/ Mortality and HHF, and Similar Safety Profile Except for an Increased Risk for Genital Infections Compared With Those Receiving Metformin

A population-based cohort study assessed CV outcomes among adults with type 2 diabetes (T2D) who initiated first-line treatment with SGLT-2i (canagliflozin, empagliflozin, or dapagliflozin; n=8613) vs metformin (n=17,226). SGLT-2i initiators had a similar risk for MI/ stroke/mortality (HR 0.96) and a lower risk for HHF/ mortality (HR 0.80) during a mean of 1 year. Initiators receiving SGLT-2i showed a lower risk for HHF (HR, 0.78), a numerically lower risk for MI (HR, 0.70), and similar risk for stroke, mortality, and MI/stroke/ HHF/ mortality compared with metformin. Initiators receiving SGLT-2i had a higher risk for genital infections (HR, 2.19) and otherwise similar safety as those receiving metformin (Shin H et al, *Ann Intern Med* 2022;175:927-37).

Postacute Sequelae of SARS-Cov-2 Infection (PASC): A High Burden of Persistent Symptoms Was Observed in Persons After COVID-19 / Extensive Diagnostic Evaluation Revealed No Specific Cause of Reported Symptoms in Most Cases / Antibody Levels Were Highly Variable After COVID-19

A cohort study assessed medical sequelae and persistent symptoms after recovery from COVID-19 in 189 persons with laboratory-documented COVID-19 (12% of whom were hospitalized during acute illness) and 120 antibody-negative control participants. At enrollment, symptoms consistent with PASC were reported by 55% of the COVID-19 cohort and 13% of control participants. Increased risk for PASC was noted in women and those with a history of anxiety disorder. Persons with findings meeting the definition of PASC reported lower quality of life on standardized testing. Abnormal findings on physical examination and diagnostic testing were uncommon. Neutralizing antibody levels to spike protein were negative in 27% of the unvaccinated COVID-19 cohort and none of the vaccinated COVID-19 persons. Exploratory studies found no evidence of persistent viral infection, autoimmunity, or abnormal immune activation in participants with PASC. Most participants with COVID-19 had mild to moderate acute illness that did not require hospitalization. The prevalence of reported PASC was likely overestimated in this cohort (Sneller MC et al; *Ann Intern Med* 2022;175(7):969-979).

Postoperative AF After Noncardiac Surgery Confers Similar Risk for Thromboembolism Compared With Nonoperative AF

A cohort study compared the risks for ischemic stroke or TIA and other outcomes in patients with postoperative AF (within 30 d) vs those with incident AF not associated with surgery. Of 4231 predominantly white patients with incident AF, 550 (13%) had postoperative AF as their first-ever documented AF presentation. Over a mean of 6.3 years, 486 patients had an ischemic stroke or TIA and 2462 had subsequent AF; a total of 2565 deaths occurred. The risk for stroke or TIA was similar between those with postoperative AF and nonoperative AF (absolute risk difference-ARD at 5 years, 0.1%; HR 1.01). A lower risk for subsequent AF was seen for patients with postoperative AF (ARD at 5 years, −13.4%; HR, 0.68). Finally, no difference was seen for CV death or all-cause death between patients with postoperative AF and nonoperative AF (Siontis KC et al, *Ann Intern Med* 2022;175:1065-72).

SARS-Cov-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents: Both First and Second Doses of mRNA Vaccines Increased Risk of Myocarditis and Pericarditis

Among 23,122,522 Nordic residents (81% vaccinated by study end; 50% female), 1077 incident myocarditis

events and 1149 incident pericarditis events were identified. Within the 28-day period, for males and females ≥12 years old combined who received a homologous schedule, the second dose conferred higher risk of myocarditis, with adjusted IRRs of 1.75 for BNT162b2 and 6.57 for mRNA-1273. Among males 16-24 years of age, adjusted IRRs were 5.31 for a second dose of BNT162b2 and 13.83 for a second dose of mRNA-1273, and numbers of excess events were 5.55 events per 100,000 vaccinees after the second dose of BNT162b2 and 18.39 events per 100 000 vaccinees after the second dose of mRNA-1273. Estimates for pericarditis were similar (Karlstad O et al; *JAMA Cardiol* 2022 Jun 1;7:600-612).

Higher Tea Intake Lowers Mortality Risk Among Those Drinking ≥2 Cups/d, Regardless of Genetic Variation in Caffeine Metabolism, Suggest That Tea, Even at Higher Levels of Intake, Can Be Part of a Healthy Diet

A prospective cohort study comprising 498,043 men and women aged 40-69 years indicated that during a median of 11.2 years, higher tea intake was modestly associated with lower all-cause mortality risk among those who drank ≥2 cups per day. Relative to no tea drinking, the HRs (95% CIs) for participants drinking ≤1, 2-3, 4-5, 6-7, 8-9, and ≥10 cups per day were 0.95, 0.87, 0.88, 0.88, 0.91, and 0.89, respectively. Inverse associations were seen for mortality from all CVD, ischemic heart disease, and stroke. Findings were similar regardless of whether participants also drank coffee or not or of genetic score for caffeine metabolism (Inoue-Choi M et al; *Ann Intern Med* 2022;175:1201-1211).

Higher Maternal RBC Folate is Associated With Reduced Offspring Risk of Congenital Heart Disease (CHD) / For Primary CHD Prevention, Higher Target RBC Folate Levels Than Currently Recommended for Neural Tube Defect Prevention May Be Needed

According to a prospective, nested, case–control study and 1-sample Mendelian randomization among 197 mothers of offspring with CHD and 788 individually matched mothers of unaffected offspring having RBC folate measured before or at early pregnancy, case patients had lower median maternal RBC folate concentrations than control participants (714 nmol/L [interquartile range, 482 to 1008 nmol/L] vs. 788 nmol/L [557 to 1094 nmol/L]). Maternal RBC folate levels were inversely associated with offspring CHD (adjusted OR per 100 nmol/L, 0.93). The adjusted OR for mothers with periconception RBC folate of 906 nmol/L or more (vs. <906 nmol/L) was 0.61. Mendelian randomization showed that each 100-nmol increase in maternal RBC folate concentrations was significantly associated with reduced offspring CHD risk (OR, 0.75) (Chen H et al, *Ann Intern Med* 2022;175:1212-1220).

Left Atrial Appendage Occlusion *(LAAO) v*s Oral Anticoagulation in AF*:* Although LAAO Could be an Alternative to Anticoagulants for Those with High Bleeding Risk, Overall Benefit from LAAO Depends on the Combined Stroke and Bleeding Risks in Individual Patients / These Results Suggest the Need for a Sufficiently Low Stroke Risk for LAAO to be Beneficial

A decision analysis with a Markov model indicated that the baseline risks for stroke and bleeding determined whether LAAO was preferred over anticoagulants in patients with AF. The combined risks favored LAAO for higher bleeding risk, but that benefit became less certain at higher stroke risks, e.g. at a HAS-BLED score of 5, LAAO was favored in >80% of model simulations for CHA_2DS_2-VASc scores between 2 and 5. The probability of LAAO benefit in QALYs (>80%) at lower bleeding risks (HAS-BLED score of 0-1) was limited to patients with lower stroke risks (CHA_2DS_2-VASc score: 2). Because DOACs carry lower bleeding risks than warfarin, the net benefit of LAAO is less certain than that of DOACs (Chew DS et al; *Ann Intern Med* 2022;175:1230-1239).

In Persons Aged 18-74 Years, Adenoviral-Based Vaccines May Be Associated With Increased Incidence of MI and Pulmonary Embolism (PE) / No Association Between mRNA-Based Vaccines and CV Events

A study assessed short-term risk for severe CV events (excluding myocarditis and pericarditis) after COVID-19 vaccination in France's 46.5 million adults <75 years. The relative incidence (RI) of each CV event was estimated in the 3 weeks after vaccination vs other periods, with adjustment for temporality (7-day periods). No association was found between the Pfizer–BioNTech or Moderna vaccine and severe CV events. The first dose of the Oxford-AstraZeneca vaccine was associated with acute MI and PE in the 2nd week after vaccination (RI 1.29 and 1.41, respectively). An association with MI in the 2nd week after a single dose of the Janssen vaccine could not be ruled out (RI 1.75). It was not possible to ascertain the relative timing of injection & CV events on the day of vaccination. Outpatient deaths related to CV events were not included (Botton J et al, *Ann Intern Med* 2022;175:1250-57).

Leadless LV Endocardial Pacing for CRT May Be a Second-Line Therapy in Patients in Whom Standard CRT is Not Possible or is Ineffective

Per a meta-analysis of 5 studies (N=181), procedural success rate was 90.6%. Clinical response was 63%, with mean improvement in NYHA class of 0.43 (MD 0.43; P=0.01), with high heterogeneity (P<0.001; I^2=81%). There was a mean increase in LVEF of 6.3% (MD 6.3; P<0.001), with low heterogeneity (P=0.84; I^2 <0.001%). The echocardiographic response rate was 54%. Procedure-related complication and mortality rates were 23.8% &

2.8%, respectively (Wijesuriya N et al; *Heart Rhythm* 2022; 9:1176-83).

Important Review and Other Articles

● **Bioprosthetic Aortic Valve Hemodynamics** (Herrmann HC, *J Am Coll Cardiol* 2022;80: 527–544)

● **Carotid artery stenting** (White CJ et al, *J Am Coll Cardiol* 2022;80:155–170)

● **Coronary In-Stent Restenosis** (Giustino G et al, *J Am Coll Cardiol* 2022;80:348–72)

● **Severe Mitral Annular Calcification** (Chehab O et al, *J Am Coll Cardiol* 2022;80:722–738)

● **Ischemic heart disease in young women** (Minissian MB et al, *JACC* 2022;80:1014-22)

● **Exercise, CV Disease, and the Athlete's Heart** (Covacic JC & Fuster V et al, *JACC* 2022;80:1088-90)

● **Exercise for Primary & Secondary Prevention of CV Disease** (Tucker WJ et al, *JACC* 2022; 80:1091–1106)

● **Management of AF in Heart failure** (Reddy YNV et al, *Circulation* 2022; 146:339-357)

● **AHA Statement on Sleep-Disordered Breathing & Cardiac Arrhythmias** (Mehra R et al, *Circulation* 2022;146:e119–e136)

Targeted Lipid-Lowering Therapies (Tokgozoglu L et al, *Eur Heart J* 2022*;*34:3198–3208)

● **Hypertension in children and adolescents*:* A consensus document from ESC** (De Simone G et al, *Eur Heart J* 2022;43:3290-3301)

● **Inflammasome** (Ajoolabady A et al**,** *J Am Coll Cardiol* 2022;79:2349–66)

● **Cardiovascular Benefits of Caffeinated Beverages: Real or Surreal?** *(*Manolis AA et al, *Curr Med Chem* 2022;29:2235-60).

● **ACP Position Paper** on **Strengthening Food and Nutrition Security to Promote Public Health** *(*Serchen J et al, *Ann Intern Med* 2022;175(8):1170-1171)

● **PCSK9 inhibitors & ezetimibe for fewer CV events: A clinical practice guideline** (Hao Q et al, *BMJ* 2022;377: e069066)

● **Takotsubo Syndrome and Sudden Cardiac Death** (Manolis AA, et al**.** (Angiology 2022 Jun 6:33197221105757. doi: 10.1177/00033197221105757. Online ahead of print.)

● **AF-Induced Tachycardiomyopathy & Heart Failure** (Manolis AS et al, *Heart Fail Rev* 2022;27(6):2119-2135.

● **Gliflozins** (Braunwald E**,** *NEJM* 2022**;**386:2024-34)

● **Long COVID** (Raman B et al, *Eur Heart J* 2022;43:1157-72)

● **Life's Essential 8** (Lloyd-Jones DM et al, *Circulation* 2022;146:e18–e43)

● **Left Ventricular Remodelling post-MI** (Frantz S et al, *Eur Heart J,* 2022;27:2549–2561)

Escalating/De-escalating **Temporary Mechanical Circulatory Support in Cardiogenic Shock:** A Scientific Statement From the AHA (Geller BJ et al, *Circulation* 2022;146:e50–e68)

● **The High Risk in Patients with Polyvascular Disease** *(*Manolis AA et al, *Curr Vasc Pharmacol* 2022 Sep 12. doi: 10.2174/1570161120666220912103321. Online ahead of print)

● **Thrombus Aspiration in Acute MI (**Manolis AS et al, *Angiology* 2022 Aug 13:33197221121003. doi: 10.1177/00033197221121003. Online ahead of print

● **High C-Reactive Protein/Low Serum Albumin in CV Disease (**Manolis AS et al, *Angiology*. 2022;73(9):797-799)

● **Diet and Sudden Death (Manolis AS**, et al, *Curr Vasc Pharmacol* 2022 Jun 21. doi: 10.2174/ 1570161120666220621090343. Online ahead of print.

● **Low serum albumin: A neglected predictor in patients with cardiovascular disease (**Manolis AA et al, *Eur J Intern M*ed. 2022 Aug;102:24-39)

● **Gut Microbiota & CV Disease: Symbiosis vs Dysbiosis** (Manolis AA et al, Curr Med Chem. 2022;29(23):4050-4077)

● **Lipoprotein(a) and Cardiovascular Disease** (Melita H et al, *J Cardiovasc Pharmacol*. 2022 Jan 1;79(1):e18-e35).

● **Lipoprotein(a) and its Significance in Cardiovascular Disease** (Lau FD et al, JAMA Cardiol. 2022;7:760-769)

● **Athletic Activity for Patients With Hypertrophic Cardiomyopathy & Other Inherited CV Diseases (**Semsarian C et al, *J Am Coll Cardiol* 2022;80:1268-83)

● ***Severe Mental Illness and Cardiovascular Disease*** (Goldfarb M et al, *J Am Coll Cardiol*. 2022 Aug, 80 (9) 918–933).

● ***Inflammatory Diseases of the Aorta*** (Kadian-Dodov D et al, *J Am Coll Cardiol* 2022;80: 832–844)

● **Definitions and Standardized Endpoints for Treatment of Coronary Bifurcations** (Lunardi M et al, *J Am Coll Cardiol* 2022;80: 63–88)

● **Management of Atrial Fibrillation in Heart Failure Patients** (Reddy YNV et al, *Circulatio*n 2022;146:339–357)

● **Myocarditis** (Muller M et al, *Heart* 2022; 108:1486-1497)

● **Tetralogy of Fallot** (Zaidi AN, *Heart* 2022; 108:1408-1414)

● **Heart failure with preserved ejection fraction** (Gevaert AB et al, *Heart* 2022;108:1342-1350)

● **Hyponatremia in heart failure** (Kapłon-Cieślicka A et al, *Heart* 2022;108:1179-1185)

● **Adult congenital heart disease: left-sided obstructive lesions** (Haeffele C et al, *Heart* 2022;108:1148-1156)

● **Coronary artery anomalies** (Dolgner S et al; *Heart* 2022;108:1063-1070)

● **Recurrent pericarditis** (Kumar S et al, *JAMA Cardiol.* 2022;7:975-985)

● **Subclinical Leaflet Thrombosis and Anticoagulation After TAVI** (Cahill TJ et al, *JAMA Cardiol*. 2022;7:866-872)