

Cardiology News / Recent Literature Review / Second Quarter 2022

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ESC Meeting, Barcelona, Spain, 26-29/8/2022

TCT 22, Boston, MA, USA, 16-20/9/22

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

Registry Study: In Patients With Multivessel Disease After Revascularization by PCI or CABG, Mildly Decreased Renal Function Did not Increase the Risk of the Primary Composite Outcome (Death, MI, or Stroke) and Mortality / Comparative Outcomes After PCI and CABG Were Similar in the Borderline-Risk Group

Among 10,354 eligible patients in a registry who underwent coronary revascularization, classified into 3 groups (stage I, n = 3,735, normal renal function; stage II, n = 5,122, mild dysfunction; and stage III, n = 1,497, moderate dysfunction), after propensity matching, the risk for primary composite outcome was not different between the stage I and the stage II group (HR: 1.12). However, the risk of the primary outcome was higher in the stage III group than in the stage I group (HR: 1.50). The relative effect of PCI vs CABG for the primary outcome was similar in the matched cohort of each renal function group of stages I, II, and III (Kim TO et al, *J Am Coll Cardiol* 2022;79:1270-84).

2-Cohort Studies: Long-Term Cumulative BP Was Associated With Subsequent Cognitive Decline, Dementia Risk, and All-Cause Mortality in Cognitively Healthy Adults Aged ≥ 50 Years / Efforts are Needed to Control Long-Term Systolic BP and Pulse Pressure and Maintain Adequate Diastolic BP

Data from the HRS (Health and Retirement Study, n=9,294, 45% men, median age 65 y) and ELSA (English Longitudinal Study of Ageing, n=7,566, 40% men, median age 62 y) indicated that over a median follow-up of 8 years

each, elevated cumulative systolic BP and pulse pressure were independently associated with accelerated cognitive decline ($P < 0.001$ for both), elevated dementia risk ($P < 0.001$ for both), and all-cause mortality ($P < 0.001$ for both), while a significant inverse association was observed for diastolic BP. Strong dose-response relationships were identified, with similar results for the 2 cohorts. (Li C et al, *J Am Coll Cardiol* 2022;79:1321–35).

The BIOSIGNAL Study: MR-proANP is a Valid Biomarker to Determine Risk of Newly Diagnosed Atrial Fibrillation (NDAF) and MACE in Patients With Acute Ischemic Stroke (AIS) and Can Be Used as a Decision Tool to Identify Patients for Prolonged Cardiac Monitoring

Among 1,759 patients Log₁₀MR-proANP levels were associated with cardioembolic (CE) stroke (OR: 7.96; risk ratio: 3.12), as well as NDAF (OR: 35.3; risk ratio: 11.47), and MACE (subdistributional HR: 2.02) during follow-up. The model to predict NDAF including only age and MR-proANP levels had a good discriminatory capacity with an area under the curve of 0.81, was well calibrated, and yielded higher net-benefit compared with validated scores to predict NDAF (AS5F score, CHA₂DS₂-VASc score) (Schweizer J et al, *J Am Coll Cardiol* 2022;79: 1369–81).

Among Medicare Beneficiaries With Obesity, Bariatric Surgery is Associated With Lower Risk of Mortality, New-Onset HF, and MI

The study cohort included 189,770 patients (94,885 matched patients in each group) with similar age (mean: 62.33 \pm 10.62 years), sex (70% female), and degree of obesity (mean body mass index: 44.7 \pm 7.3 kg/m²) and well balanced on all clinical variables. After a median of 4 years, bariatric surgery was associated with a lower risk of mortality (9.2 vs 14.7 per 1,000 person-years; HR: 0.63), new-onset HF (HR: 0.46), MI (HR: 0.63), and stroke (HR: 0.71) ($P < 0.001$). The benefit of bariatric surgery was evident in patients who were ≥ 65 years. Using instrumental variable analysis, bariatric surgery was associated with a lower risk of mortality, HF, and MI (Mentias A et al, *J Am Coll Cardiol* 2022;79:1429-37).

SURVIVE-VT: In ICD Patients With Ischemic Cardiomyopathy and Symptomatic VT, Catheter Ablation Reduced the Composite Endpoint of CV Death, Appropriate ICD Shock, Hospitalization Due to Heart Failure, or Severe Treatment-Related Complications vs Antiarrhythmic Drugs (AAD)

Among 144 patients (median age, 70 years; 96% men) randomized to catheter ablation (n=71) or AAD (n=73), after 24 months, the primary outcome (CV death, appropriate ICD shock, unplanned hospitalization for worsening heart failure-HF, or severe treatment-related complications) occurred in 28.2% of patients in the

ablation group and 46.6% of those in the AAD group (hazard ratio-HR: 0.52; $P=0.021$). This difference was driven by a significant reduction in severe treatment-related complications (9.9% vs 28.8%, HR: 0.30; $P=0.006$). Eight patients were hospitalized for HF in the ablation group and 13 in the AAD group (HR: 0.56; $P=0.198$). There was no difference in cardiac mortality (HR: 0.93) (Arenal A et al, *J Am Coll Cardiol* 2022;79:1441–53).

Lp(a) May be a Potential Causal Mediator in the Development of AF as the Effects of Lp(a) Extend Across Myocardial Tissues / Ongoing Clinical Trials for Lp(a)-Lowering Therapies Should Evaluate Effects on AF Prevention

Measured and genetically predicted Lp(a) levels were tested for association with 20,432 cases of incident AF in the UK Biobank (N=435,579). Mendelian randomization analyses were performed by using summary-level data for AF from publicly available genome-wide association studies (N=1,145,375). In the UK Biobank, each 50 nmol/L (23 mg/dL) increase in Lp(a) conferred an increased risk of incident AF using measured Lp(a) (HR: 1.03; $P=1.65 \times 10^{-8}$) and genetically predicted Lp(a) (OR: 1.03; $P=1.33 \times 10^{-5}$). Mendelian randomization analyses using independent data replicated the effect (OR: 1.04 per 50 nmol/L Lp(a) increase; $P=9.23 \times 10^{-10}$). There was no evidence of risk-conferring effect from low-density lipoprotein cholesterol or triglycerides, and only 39% of Lp(a) risk was mediated through ASCVD, suggesting that Lp(a) partly influences AF independent of its known effects on ASCVD (Mohammadi-Shemirani P, et al, *J Am Coll Cardiol* 2022;79:1579-90).

TEMPO Trial: In Patients With Obstructive Hypertrophic Cardiomyopathy (HCM), Exercise was Associated With an Abnormal Rise in Pulmonary Wedge Pressure (PWP), Which was Unaffected by Metoprolol / However, Metoprolol Increased Stroke Volume (SV) at Rest and Peak Exercise Following Changes in End-Diastolic Volume, LVOT Gradient, and Degree of Mitral Regurgitation

Among 28 patients with obstructive HCM and NYHA functional class \geq II, randomized to either metoprolol 150 mg or placebo for 2 consecutive 2-week periods, no treatment effect on PWP was observed between metoprolol and placebo treatment (21±9 mm Hg vs 23±9 mm Hg; $P=0.12$). At rest, metoprolol lowered heart rate ($P<0.0001$), left ventricular outflow tract (LVOT) gradient ($P=0.01$), and increased LV end-diastolic volume ($P=0.02$) and stroke volume (SV) (+6.4; $P=0.049$). During peak exercise, metoprolol was associated with a lower heart rate ($P<0.0001$), a lower LVOT gradient ($P=0.0005$), lesser degree of mitral regurgitation ($P=0.004$), and increased SV

(+9 mL; $P=0.008$) (Dybro AM et al, *J Am Coll Cardiol* 2022;79: 1565–75).

Hypertrophic Cardiomyopathy (HCM): Alcohol Septal Ablation (ASA) Increases Long-Term Mortality vs Surgical Septal Myectomy

Among 3,859 patients who underwent ASA or septal myectomy in 3 specialized HCM centers, 585 (15.2%) patients underwent ASA, and 3,274 (84.8%) underwent septal myectomy. Patients undergoing ASA were significantly older (median age: 63.0 years vs 53.7 years; $P<0.001$) and had smaller septal thickness (19 mm vs 20 mm; $P=0.007$). Patients undergoing ASA also had more comorbidities, including renal failure, diabetes, hypertension, and coronary artery disease. There were 4 (0.7%) early deaths in the ASA group and 9 (0.3%) in the myectomy group. Over a median follow-up of 6.4 years, the 10-year all-cause mortality rate was 26.1% in the ASA group and 8.2% in the myectomy group. After adjustment for age, sex, and comorbidities, the mortality remained greater in patients having septal reduction by ASA (HR: 1.68; $P<0.001$) (Cui H et al, *J Am Coll Cardiol* 2022;79:1647–55).

REDUCE-IT: Patients With a History of Prior MI Treated With Icosapent Ethyl Had Large and Significant Relative and Absolute Risk Reductions in Ischemic Events, Including CV Death

Icosapent ethyl (IPE) is an ethyl ester of the omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA) with pharmacological properties that reduce plaque volume, mitigate inflammation, promote nitric oxide release, and encourage membrane stabilization. Among 3,693 statin-treated patients with a history of MI, with controlled LDL cholesterol and moderately elevated triglycerides randomized to IPE or placebo, the primary endpoint (CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina) was reduced from 26.1% to 20.2% with IPE vs placebo; HR: 0.74 ($P=0.00001$). The key secondary endpoint (CV death, MI, or stroke) was reduced from 18% to 13.3%; HR: 0.71 ($P=0.00006$). There was also a significant 35% relative risk reduction in total ischemic events ($P=0.0000001$), a 34% reduction in MI ($P=0.00009$), a 30% reduction in CV death ($P=0.01$), and a 20% lower rate of all-cause mortality ($P=0.054$), although there was a slight increase in AF. Sudden cardiac death and cardiac arrest were also significantly reduced by 40% and 56%, respectively (Gaba P et al, *J Am Coll Cardiol* 2022;79: 1660–71).

Incidence of Sudden Cardiac Death (SCD) in the European Union

According to 4 large (ie, >2 million inhabitants) European population-based prospective registries collecting emergency medical services (EMS)-attended (ie, with attempted resuscitation) out-of-hospital cardiac arrest (OHCA) and SCD (OHCA without obvious extracardiac causes) for >5 consecutive years (2012-2017) in the Paris region (France), the North Holland region (the Netherlands), the Stockholm region (Sweden), and in all of Denmark, the average annual incidence of SCD ranged from 36.8 per 100,000 to 39.7 per 100,000. When extrapolating to each European country and accounting for age and sex, this yields to 249,538 SCD cases per year. The average annual incidence of OHCA in the 4 registries ranged from 47.8 per 100,000 to 57.9 per 100,000, corresponding to 343,496 OHCA cases per year in the European Union. Incidence rates of SCD and OHCA increased with age and were systematically higher in men compared with women (Empana J-P et al, *J Am Coll Cardiol* 2022;79:184=18–27).

Evaluation of Patients With Post-Acute Sequela of COVID-19 (PASC) with Head-Up Tilt Table (HUTT) Testing Revealed Orthostatic Intolerance Suggestive of Autonomic Dysfunction / Those With Provoked Orthostatic Intolerance (POI) May be Further Along the Path of Clinical Recovery Than Those Having Postural Orthostatic Tachycardia Syndrome (POTS)

Among 24 patients with PASC symptoms having HUTT a mean of 5.8 ± 3.5 months after symptom onset, 23 had orthostatic intolerance on HUTT, with 4 demonstrating POTS, 15 provoked orthostatic intolerance (POI) after nitroglycerin, 3 neurocardiogenic syncope, and 1 orthostatic hypotension. Compared with those with POTS, patients with POI described significantly earlier improvement of symptoms (Jamal SM et al, *J Am Coll Cardiol* 2022;79:2325–30).

Pre-Existing AF is Independently Associated With Postoperative Adverse Outcomes After Non-Cardiac Surgery (NCS)

Among 8,635,758 patients who underwent NCS (16.4% with AF), patients with AF were older, more likely to be men, and had higher prevalence of comorbidities. After propensity score matching, AF was associated with higher risk of mortality (OR: 1.31), heart failure (OR: 1.31), and stroke (OR: 1.40) and lower risk of MI (OR: 0.81). Results were consistent in subgroup analysis by sex, race, type of surgery, and all strata of CHA₂DS₂-VASc score (Prasada S et al, *J Am Coll Cardiol* 2022;79:2471–85).

Acute Myocarditis (AM) Occurrence is Estimated Between 2.4 and 4.1 out of 1000 Patients Hospitalized for COVID-19 / Majority Occurs in the Absence of Pneumonia, Often Complicated by Hemodynamic Instability

A total of 112 patients with suspected AM from 56 963 hospitalized patients with COVID-19 were evaluated. AM prevalence among hospitalized patients with COVID-19 was 2.4 per 1000 hospitalizations considering definite/probable and 4.1 per 1000 considering also possible AM. The median age of definite/probable cases was 38 years, and 38.9% were female. On admission, chest pain and dyspnea were the most frequent symptoms (55.5% and 53.7%, respectively). A total of 31 cases (57.4%) occurred in the absence of COVID-19-associated pneumonia. Twenty-one (38.9%) had a fulminant presentation requiring inotropic support or temporary mechanical circulatory support. The composite of in-hospital mortality or temporary mechanical circulatory support occurred in 20.4%. At 120 days, estimated mortality was 6.6%, 15.1% in patients with associated pneumonia versus 0% in patients without pneumonia ($P=0.044$). During hospitalization, LVEF improved from a median of 40% on admission to 55% at discharge ($n=47$; $P<0.0001$) similarly in patients with or without pneumonia. Corticosteroids were frequently administered (55.5%) (Ammirati E et al, *Circulation* 2022;145:1123–1139).

TRANSLATE-TIMI 70 : Vupanorsen at Monthly Equivalent Doses (80-320 mg) Significantly Reduced Non-HDL-Cholesterol and Additional Lipid Parameters / Injection Site Reactions and Liver Enzyme Elevations Were More Frequent at Higher Doses, and There Was a Dose-Dependent Increase in Hepatic Fat Fraction

Vupanorsen, a hepatically targeted antisense oligonucleotide that inhibits Angiopoietin-like 3 (ANGPTL3) protein synthesis, was given to adults with non-high-density lipoprotein cholesterol (non-HDL-C) ≥ 100 mg/dL and triglycerides 150 to 500 mg/dL on statin therapy who were randomized to placebo or 1 of 7 vupanorsen dose regimens (80, 120, or 160 mg SC every 4 weeks, or 60, 80, 120, or 160 mg SC every 2 weeks). A total of 286 persons were randomized: 44 to placebo and 242 to vupanorsen (median age 64 years, 44% female, median non-HDL-C 132.4 mg/dL, median triglycerides 216.2 mg/dL). Vupanorsen resulted in significant decreases from baseline over placebo in non-HDL-C ranging from 22% in the 60 mg every 2 weeks arm to 27.7% in the 80 mg every 2 weeks arm (all $P<0.001$ for all doses). There were dose-dependent reductions in

triglycerides that ranged from 41.3% to 56.8% (all $P<0.001$). The effects on LDL-C and ApoB were more modest (7.9%–16.0% and 6.0%–15.1%, respectively) and without a clear dose-response relationship, and only the higher reductions achieved statistical significance. ANGPTL3 levels were decreased in a dose-dependent manner by 69.9% to 95.2% (all $P<0.001$). There were no confirmed instances of significant decline in renal function or platelet count with vupanorsen. Injection site reactions and $>3\times$ elevations of liver enzymes were more common at higher total monthly doses (up to 33.3–44.4%), and there was a dose-dependent increase in hepatic fat fraction (up to 76%) (Bergmark BA et al, *Circulation* 2022;145:1377–1386).

Meta-Analysis: Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) Reduce the Risk of Serious Hyperkalemia in People With Type 2 Diabetes at High Cardiovascular Risk or With Chronic Kidney Disease Without Increasing the Risk of Hypokalemia

Among 49 875 patients in 6 trials assessing 4 SGLT2i, 1754 developed serious hyperkalemia, and an additional 1119 investigator-reported hyperkalemia events were recorded. SGLT2i reduced the risk of serious hyperkalemia (hazard ratio-HR 0.84), an effect consistent across studies ($P_{\text{heterogeneity}}=0.71$). The incidence of investigator-reported hyperkalemia was also lower with SGLT2i (HR, 0.80; $P_{\text{heterogeneity}}=0.21$). Reductions in serious hyperkalemia were observed across a range of subgroups, including baseline kidney function, history of heart failure, and use of renin-angiotensin-aldosterone system inhibitor, diuretic, and mineralocorticoid receptor antagonist. SGLT2i did not increase the risk of hypokalemia (HR, 1.04; $P_{\text{heterogeneity}}=0.42$) (Neunen BL et al, *Circulation* 2022;145:1460–70).

Greater Dietary Cholesterol And Egg Consumption Were Associated With Increased Risk Of Overall And CVD-Related Mortality.

In a prospective analysis of 27 78 men in the ATBC Study (Alpha-Tocopherol, Beta-Carotene Cancer Prevention) and a systematic review and meta-analysis of cohort studies, based on 482 316 person-years of follow-up, 22,035 deaths were identified, including 9110 deaths from cardiovascular disease (CVD). Greater dietary cholesterol and egg consumption were associated with increased risk of overall and CVD-related mortality. Hazard ratios for each additional 300 mg cholesterol intake per day were 1.10 and 1.13 for overall and CVD-related mortality, respectively; for each additional 50-g egg consumed daily, hazard ratios-HRs were 1.06 and 1.09, respectively, for overall and CVD-related mortality (all P values <0.0001). After multivariable adjustment, higher serum total cholesterol levels conferred an increased risk

of CVD-related mortality (HRs per 1 SD increment, 1.14; $P<0.0001$). The observed associations were generally similar across cohort subgroups. The updated meta-analysis of cohort studies on the basis of 49 risk estimates, 3 601 401 participants, and 255 479 events showed consumption of 1 additional 50-g egg daily was associated with significantly increased CVD risk (pooled relative risk, 1.04; $I^2=80.1\%$). In the subgroup analysis of geographic regions ($P_{\text{interaction}}=0.02$), an increase of 50-g egg consumed daily was associated with a higher risk of CVD in US cohorts (pooled relative risk, 1.08) and appeared related to a higher CVD risk in European cohorts with borderline significance (pooled relative risk, 1.05), but was not associated with CVD risk in Asian cohorts (Zhao B et al, *Circulation* 2022;145:1506–20).

RAFT-AF Trial: In Patients with High-Burden Atrial Fibrillation (AF) and Heart failure (HF), There was no Difference in All-Cause Mortality or HF Events With Ablation-Based Rhythm Control vs Rate Control / There Was a Nonsignificant Trend for Improved Outcomes With Ablation-Based Rhythm Control Over Rate Control

Among 411 patients randomly assigned to ablation-based rhythm control (n=214) or rate control (n=197), the primary outcome occurred in 50 (23.4%) patients in the ablation-based rhythm-control group and 64 (32.5%) patients in the rate-control group (hazard ratio-HR, 0.71; $P=0.066$). LVEF increased in the ablation-based group ($10.1\pm 1.2\%$ vs $3.8\pm 1.2\%$, $P=0.017$), 6-min walk distance improved (44.9 ± 9.1 m vs 27.5 ± 9.7 m, $P=0.025$), and NT-proBNP demonstrated a decrease (mean change -77.1% vs -39.2% , $P<0.0001$). Quality of life showed greater improvement in the ablation-based rhythm-control group (least-squares mean difference of -5.4 ; $P=0.0036$). Serious adverse events were observed in 50% of patients in both treatment groups (Parkash R et al, *Circulation* 2022;145:1693–1704).

A Single hs-cTnT Below the Limit of Quantitation of 6 ng/L is a Safe and Rapid Method to Identify a Substantial Number of Patients at Very Low Risk for Acute Myocardial Injury and Infarction

Among 85 610 patients evaluated in the CV Data Mart Biomarker cohort, 24 646 (29%) had a baseline hs-cTnT <6 ng/L. Women were more likely than men to have hs-cTnT <6 ng/L (38% vs 20%, $P<0.0001$). Among 11 962 patients with baseline hs-cTnT <6 ng/L and serial measurements, only 1.2% developed acute myocardial injury, resulting in a negative predictive value of 98.8% and sensitivity of 99.6%. In the adjudicated cohort, a nonischemic ECG with hs-

cTnT<6 ng/L identified 33% of patients (610/1849) as low risk and resulted in a negative predictive value and sensitivity of 100% and a 30-day rate of 0.2% for MI or death (Sandoval Y et al, *Circulation* 2022;145:1708–19).

Transient Exposure to Air Pollutants PM_{2.5}, NO₂, SO₂, or CO, but not PM_{2.5-10} or O₃, May Trigger the Onset of Acute Coronary Syndrome (ACS), Even at Concentrations Below the World Health Organization Air Quality Guidelines

A time-stratified case-crossover study among 1 292 880 Chinese patients with ACS from 2239 hospitals in 318 Chinese cities showed that acute exposures to PM_{2.5}, NO₂, SO₂, and CO were each associated with the onset of ACS and its subtypes. These associations were strongest in the concurrent hour of exposure and were attenuated thereafter, with the weakest effects observed after 15 to 29 hours. There were no apparent thresholds in the concentration–response curves. An interquartile range increase in concentrations of PM_{2.5} (36.0 µg/m³), NO₂ (29.0 µg/m³), SO₂ (9.0 µg/m³), and CO (0.6 mg/m³) over the 0-24 h before onset was significantly associated with 1.32%, 3.89%, 0.67%, and 1.55% higher risks of ACS onset, respectively. For a given pollutant, the associations were comparable in magnitude across different subtypes of ACS. NO₂ showed the strongest associations with all 3 subtypes, followed by PM_{2.5}, CO, and SO₂. Greater magnitude of associations was observed among patients >65 years and in the cold season. Null associations of exposure to either PM_{2.5-10} or O₃ with ACS onset were observed (Chen R et al, *Circulation* 2022;145:1749–60).

PARTITA Trial: Ventricular Tachycardia (VT) Ablation After First Appropriate Shock Reduced Risk of the Combined Death or Worsening Heart Failure Hospitalization End Point, & Lowered Mortality, and ICD Shocks, Providing Support for VT Ablation After the First ICD Shock

Of the 517 patients enrolled in phase A, 154 (30%) had VT, 56 (11%) received an appropriate shock over a median follow-up of 2.4 years, and 47 of 56 (84%) agreed to participate in phase B. After 24.2 months, the primary end point occurred in 1 of 23 (4%) patients in the ablation group and 10 of 24 (42%) patients in the control group (hazard ratio-HR, 0.11; $P=0.034$). The results met the prespecified termination criterion of >99% Bayesian posterior probability of superiority of treatment over standard therapy. No deaths were observed in the ablation group vs 8 deaths (33%) in the control group ($P=0.004$); there was 1 worsening heart failure

hospitalization in the ablation group (4%) vs 4 in the control group (17%; $P=0.159$). ICD shocks were less frequent in the ablation group (9%) than in the control group (42%; $P=0.039$) (Della Bella P et al, *Lancet* 2022;399:719-728).

PAUSE SCD Trial: Among Patients With Cardiomyopathies, Early Catheter Ablation Performed at the Time of ICD Implantation Significantly Reduced the Composite Primary Outcome of VT Recurrence, Cardiovascular Hospitalization, or Death, Driven by a Reduction in ICD Therapies

Among 180 patients with cardiomyopathy (CM) and monomorphic VT with an indication for ICD implantation, 121 patients were randomly assigned (1:1) to ablation plus an ICD vs conventional medical therapy plus an ICD. Patients who refused ICD ($n=47$) were followed in a prospective registry after stand-alone ablation treatment. Randomly assigned patients had a mean age of 55 years and LVEF of 40%; 81% were male. The underlying heart disease was ischemic CM in 35%, nonischemic CM in 30%, and arrhythmogenic CM in 35%. Ablation was performed a median of 2 days before ICD implantation. At 31 months, the primary outcome (VT recurrence, CV hospitalization, or death) occurred in 49.3% of the ablation group and 65.5% in the control group (hazard ratio-HR, 0.58; $P=0.04$). The observed difference was driven by a reduction in VT recurrence in the ablation arm (HR 0.51; $P=0.02$). A statistically significant reduction in both ICD shocks (10% vs 24.6%; $P=0.03$) and antitachycardia pacing (16.2% vs 32.8%; $P=0.04$) was observed in patients who underwent ablation compared with control. No differences in CV hospitalization (32% vs 33.7%; HR, 0.82; $P=0.55$) or mortality (8.9% vs 8.8%; HR, 1.40; $P=0.62$) were observed. Ablation-related complications occurred in 8.3% of patients (Tung R et al, *Circulation* 2022;145:1839–49).

DISCHARGE Trial: Among Patients Referred for Invasive Coronary Angiography (ICA) Because of Stable Chest Pain and Intermediate Pretest Probability of CAD, the Risk of Major Adverse Cardiovascular (CV) Events Was Similar in the CT Group and the ICA Group with Lower Frequency of Major Procedure-Related Complications With an Initial CT Strategy

Among 3561 patients (56.2% women) with stable chest pain and intermediate pretest probability of obstructive CAD referred for ICA, comparing CT with ICA as initial diagnostic imaging strategies, showed that major adverse CV events occurred in 38 of 1808 patients (2.1%) in the CT group and in 52 of 1753 (3.0%) in the ICA group (hazard ratio-HR, 0.70; $P=0.10$). Major

procedure-related complications occurred in 9 patients (0.5%) in the CT group and in 33 (1.9%) in the ICA group (HR 0.26). Angina during the final 4 weeks of follow-up was reported in 8.8% of the patients in the CT group and in 7.5% of those in the ICA group (odds ratio, 1.17) (DISCHARGE Trial Group, *N Engl J Med* 2022; 386:1591-1602).

Childhood Risk Factors and the Change in the Combined-Risk Z Score Between Childhood and Adulthood Were Associated With Cardiovascular Events in Midlife

A prospective cohort study evaluated whether childhood risk factors (at the ages of 3-19 years) were associated with cardiovascular (CV) events in adulthood after a mean follow-up of 35 years. In the analysis of 319 fatal CV events that occurred among 38,589 participants (49.7% male and 15.0% Black; mean age at childhood visits, 11.8±3.1 years), the hazard ratios (HRs) for a fatal CV event in adulthood ranged from 1.30 per unit increase in the z score for total cholesterol level to 1.61 for youth smoking (yes vs. no). The HR for a fatal CV event with respect to the combined-risk z score was 2.71 per unit increase. The HRs and their 95% confidence intervals in the analyses of fatal CV events were similar to those in the analyses of 779 fatal or nonfatal CV events that occurred among 20,656 participants who could be evaluated for this outcome. In the analysis of 115 fatal CV events that occurred in a subgroup of 13,401 participants (31.0±5.6 years of age at the adult measurement) who had data on adult risk factors, the adjusted HR with respect to the childhood combined-risk z score was 3.54 per unit increase, and the mutually adjusted HR with respect to the change in the combined-risk z score from childhood to adulthood was 2.88 per unit increase. The results were similar in the analysis of 524 fatal or nonfatal CV events (Jacobs DR et al, *N Engl J Med* 2022; 386:1877-88).

SUGAR Trial: In Patients With Diabetes, Cre8 EVO Stents are Non-Inferior to Resolute Onyx Stents in Target-Lesion Failure Composite Outcome

Among 1175 patients with diabetes undergoing PCI, randomly assigned (1:1) to receive Cre8 EVO (amphilimus-eluting) (n=586) or Resolute Onyx (zotarolimus-eluting) stents (n=589), there were 106 primary events (target-lesion failure, defined as a composite of cardiac death, target-vessel MI, and clinically indicated target-lesion revascularization at 1-year), 42 (7.2%) in the Cre8 EVO group and 64 (10.9%) in the Resolute Onyx group (HR 0.65; $P_{\text{non-inferiority}} < 0.001$; $P_{\text{superiority}} = 0.030$). Among the secondary endpoints, Cre8 EVO stents had significantly lower rate than Resolute Onyx stents of target-vessel failure (7.5% vs. 11.1%, HR: 0.67; $P =$

0.042). Probable or definite stent thrombosis and all-cause death were not significantly different between groups (Romaguera R et al, *Eur Heart J* 2022; 43: 1320–1330).

Multiple Arterial Grafting (MAG) is More Desirable for CABG to Achieve Lower All-Cause Mortality Than PCI in Patients With 3-Vessel Disease (3VD) and/or Left Main Coronary Artery Disease (LMCAD)

A *post hoc* analysis of the SYNTAX Extended Survival Study compared PCI with CABG in patients with 3VD and/or LMCAD and evaluated survival with ≥10 years of follow-up. Of the 1743 patients, 901 (51.7%) had PCI, 532 (30.5%) received single arterial grafting (SAG), and 310 (17.8%) had MAG. At maximum follow-up, all-cause death occurred in 305 (33.9%), 175 (32.9%), and 70 (22.6%) patients in the PCI, SAG, and MAG groups, respectively ($P < 0.001$). MAG (adjusted HR 0.66), but not SAG (adjusted HR 0.83) was associated with significantly lower all-cause mortality compared with PCI. In patients with 3VD, both MAG (adjusted HR 0.55) and SAG (adjusted HR 0.68) conferred significantly lower mortality than PCI, whereas in LMCAD patients, no significant differences between PCI and MAG (adjusted HR 0.90) or SAG (adjusted HR 1.11) were observed. In patients with revascularization of all 3 major myocardial territories, a positive correlation was observed between the number of myocardial territories receiving arterial grafts and survival ($P_{\text{trend}} = 0.003$) (Davierwala PM et al, *Eur Heart J* 2022; 43:1334–1344).

Seven Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and 4 Short QT Syndrome (SQTS) Genes Have Valid Evidence for Disease Causation and Should be Included in Genetic Testing Panels

According to a Channelopathy Expert Panel, 7 genes have definitive/moderate evidence for disease causation in CPVT, with either autosomal dominant (*RYR2*, *CALM1*, *CALM2*, *CALM3*) or autosomal recessive (*CASQ2*, *TRDN*, *TECRL*) inheritance. For SQTS, only 1 gene (*KCNH2*) was classified as definitive, with 3 others (*KCNQ1*, *KCNJ2*, *SLC4A3*) having strong/moderate evidence. The majority of genetic evidence for SQTS genes was derived from very few variants (5 in *KCNJ2*, 2 in *KCNH2*, 1 in *KCNQ1/SLC4A3*) (Walsh R et al, *Eur Heart J* 2022;43:1500–10)

Automated External Defibrillators (AEDs) Can be Carried by Drones to Real-Life Cases of Out-Of-Hospital Cardiac Arrest (OHCA) With a Successful AED Delivery Rate of 92%

In a prospective clinical trial, 3 AED-equipped drones were placed within controlled airspace in Sweden, covering ~80,000 inhabitants (125 km²). Totally, 14 cases

were eligible for dispatch during the study period in which AED drones took off in 12 alerts to suspected OHCA, with a median distance to location of 3.1 km. AED delivery was feasible within 9 m from the location and successful in 11 alerts (92%). AED drones arrived prior to ambulances in 64%, with a median time benefit of 01:52 min when drone arrived first. In an additional 61 test flights, the AED delivery success rate was 90% (55/61) (Schierbeck S et al, *Eur Heart J* 2022;43:1478-87).

5-Year Outcomes of EFFORTLESS Registry Patients With Early Generation Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) Devices

Among 984 of 994 enrolled patients with diverse diagnoses (28% female, 48 ± 17 years, body mass index 27 ± 6 kg/m², ejection fraction 43 ± 18%) who received an S-ICD, over a median of 5.1 years, all-cause mortality was 9.3%; 703 patients remained in follow-up on study completion, 171 withdrew including 87 (8.8%) with device explanted, and 65 (6.6%) lost to follow-up. Of the explants, only 20 (2.0%) patients needed a transvenous device for pacing indications. First and final shock efficacy for ventricular arrhythmias was consistent at 90% and 98%, respectively, with storm episode final shock efficacy at 95.2%. Time to therapy remained unaltered. Overall 1- and 5-year complication rates were 8.9% and 15.2%, respectively. Early complications did not predict later complications. There were no structural lead failures. Inappropriate shock (IAS) rates at 1 and 5 years were 8.7% and 16.9%, respectively. Self-terminating inappropriately sensed episodes predicted late IAS. Predictors of late appropriate shock (AS) included self-terminating appropriately sensed episodes and earlier AS (Lambiase PD et al, *Eur Heart J* 2022;43:2037-2050).

PACIFIC-AF: The FXIa Inhibitor Asundexian at Doses of 20 mg and 50 mg QD Resulted in Lower Rates of Bleeding Compared With Standard Dosing of Apixaban, With Near-Complete In-Vivo FXIa Inhibition in Patients With Atrial Fibrillation (AF)

Asundexian is a novel, oral small molecule activated coagulation factor XIa (FXIa) inhibitor. Of 753 AF patients being included in the analysis, 249 received asundexian 20 mg, 254 received asundexian 50 g, and 250 received apixaban. The mean age of participants was 73.7 ± 8.3 years, 309 (41%) were women, 216 (29%) had chronic kidney disease, and mean CHA₂DS₂-VASc score was 3.9 ± 1.3. Asundexian 20 mg resulted in 81% inhibition of FXIa activity at trough concentrations and 90% inhibition at peak concentrations; asundexian 50 mg resulted in 92% inhibition at trough concentrations and 94% inhibition at peak concentrations. Ratios of incidence proportions for the primary endpoint (composite of major or clinically relevant non-major bleeding) were 0.50 for asundexian 20 mg (3 events), 0.16 for asundexian 50 mg

(1 event), and 0.33 for pooled asundexian (4 events) vs apixaban (6 events). The rate of any adverse event occurring was similar in the 3 treatment groups: 118 (47%) with asundexian 20 mg, 120 (47%) with asundexian 50 mg, and 122 (49%) with apixaban (Piccini JP et al, *Lancet* 2022; 399:1383-90).

Increased, Albeit Rare, Risk of Myocarditis or Pericarditis Observed After COVID-19 mRNA Vaccination / Highest in Men Aged 18–25 Years After a Second Dose of the Vaccine

According to a US retrospective cohort study, examining the primary outcome of myocarditis or pericarditis, or both, occurring 1–7 days post-vaccination, evaluated in COVID-19 mRNA vaccinees aged 18–64 years, reported a total of 411 myocarditis or pericarditis, or both, events observed among 15 148 369 people aged 18–64 years who received 16 912 716 doses of BNT162b2 and 10 631 554 doses of mRNA-1273. Among men aged 18–25 years, the pooled incidence rate was highest after the second dose, at 1.71 per 100 000 person-days for BNT162b2 and 2.17 per 100 000 person-days for mRNA-1273. The pooled incidence rate ratio in the head-to-head comparison of the two mRNA vaccines was 1.43, with an excess risk of 27.80 per million doses in mRNA-1273 recipients compared with BNT162b2 (Wong H-L et al, *Lancet* 2022; 399: 2191-99).

CORDIOPREV Study: In Secondary Prevention, the Mediterranean Diet Was Superior to the Low-Fat Diet in Preventing Major Cardiovascular (CV) Events

Among 1002 patients enrolled, 500 (49.9%) in the low-fat diet group and 502 (50.1%) in the Mediterranean diet group (age 59.5 ± 8.7 years, 82.5% men), the primary endpoint (MI, revascularisation, ischemic stroke, peripheral artery disease, and CV death) occurred in 198 participants: 87 in the Mediterranean diet group and 111 in the low-fat group (crude rate per 1000 person-years: 28.1 in the Mediterranean diet group vs 37.7 in the low-fat group, log-rank p=0.039). Multivariable-adjusted hazard ratios (HRs) of the different models ranged from 0.719 to 0.753 in favour of the Mediterranean diet. These effects were more evident in men, with primary endpoints occurring in 67 (16.2%) of 414 men in the Mediterranean diet group vs 94 (22.8%) of 413 men in the low-fat diet group (multiadjusted HR 0.669, log-rank p=0.013), than in 175 women for whom no difference was found between groups (Delgado-Lista J et al, *Lancet* 2022;399: 1876-85).

SODIUM-HF: In Ambulatory Patients With Heart Failure, a Dietary Intervention to Reduce Sodium Intake Did Not Reduce Clinical Events

Among 806 patients (median age 67 years, 33% women) randomly assigned to a low sodium (<1500 mg/d) diet (n=397) or usual care (n=409), by 12 months, events

comprising the primary outcome (cardiovascular-related admission to hospital, CV-related emergency department visit, or all-cause death) had occurred in 60 (15%) of 397 patients in the low sodium diet group and 70 (17%) of 409 in the usual care group (HR 0.89; p=0.53). All-cause death occurred in 22 (6%) patients in the low sodium diet group and 17 (4%) in the usual care group (HR 1.38; p=0.32), CV-related hospitalisation occurred in 40 (10%) patients in the low sodium diet group and 51 (12%) patients in the usual care group (HR 0.82; p=0.36), and CV-related emergency department visits occurred in 17 (4%) patients in the low sodium diet group and 15 (4%) patients in the usual care group (HR 1.21; p=0.60). No safety events related to the study treatment were reported in either group (Ezekowitz JA et al, *Lancet* 2022; 399:1391-1400).

Important Review and Other Articles

Sex & Gender Differences in Cardiovascular Health (Mensah GA, Fuster V, *JACC* 2022;79:1385-1425).

- **Nutrition Assessment and Dietary Interventions in Heart Failure** (Driggin E et al, *J Am Coll Cardiol* 2022;79:1623–35)

- **2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults** (Gluckman TJ et al, *J Am Coll Cardiol* 2022;79:1717-56)

- **2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure** (Heidenreich PA et al, *JACC* 2022;79:1757-80 & e263–e421) (*Circulation* 2022;45:e876–e1032)

- **Guidelines for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes** (Kelsey MD, *J Am Coll Cardiol* 2022;79:1849-57)

- **The Increasing Role of Rhythm Control in Patients with AF** (Camm AJ et al, *JACC* 2022;79:1932-48)

- **Infective Endocarditis in Drug Addicts** (Yucel E et al, *J Am Coll Cardiol* 2022; 79:2037-57)

- **Sodium Glucose Cotransporter-2 Inhibition for Acute Myocardial Infarction** (Udell JL et al, *J Am Coll Cardiol* 2022;79:2058–68)

Sodium-Glucose Cotransporter type 2 Inhibitors and Cardiac Arrhythmias (Manolis AS et al, *Trends Cardiovasc Med* 2022 Apr 18;S1050-1738(22)00062-7. doi: 10.1016/j.tcm.2022.04.003)

- **Transcatheter Closure of Atrial and Ventricular Septal Defects** (Turner ME et al, *JACC* 2022;79:2247-58)

- **Inflammasome Signaling in AF** (Ajoalabady A et al, *J Am Coll Cardiol* 2022;79:2349–66)

- **Premature MI** (Rallidis LS et al, *JACC* 2022;79:2431–49)

- **Inappropriate Sinus Tachycardia** (Ahmed A et al, *J Am Coll Cardiol* 2022; 79:2450–62)

- **Cardio-Oncology Drug Interactions** (Beavers CJ et al, *Circulation* 2022;145:e811–e838)

- **AHA Scientific Statement on the Importance of the Lay Responder Experience in Out-of-Hospital Cardiac Arrest** (Dainty KN et al, *Circulation* 2021;144:e472–e487)

- **AHA Statement on SARS-CoV-2 Infection and Associated Cardiovascular Manifestations and Complications in Children and Young Adults** (Jones P-N et al, *Circulation* 2022;145:e1037–e1052)

- **Gut Microbiota and Cardiovascular Disease** (Manolis AA et al, *Curr Med Chem* 2022;29:4050-4077)

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

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

- **AF-Induced Tachycardiomyopathy and Heart Failure** (Manolis AS et al, *Heart Fail Rev* 2022 Mar 23. doi: 10.1007/s10741-022-10221-1).

- **COVID-19** (Manolis AS et al, *Obes Res Clin Pract* 2021;15:523-535)

Low serum albumin: A neglected predictor in patients with cardiovascular disease. *Eur J Intern Med* 2022 May 7;S0953-6205(22)00181-9. doi: 10.1016/j.ejim.2022.05.004.

- **Gliflozins in the Management of Cardiovascular Disease** (Braunwald E, *NEJM* 2022;386:2024-34).

- **Lipoprotein(a) & CVD** (Melita H et al, *J Cardiovasc Pharmacol* 2022;79:e18-e35)

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

- **Bariatric surgery and cardiovascular disease** (Van Veldhuisen SL et al, *Eur Heart J* 2021; 43:1955–1969)

- **COVID-19** (Manolis AS & Manolis TA, *Rhythmos* 2022;17:1-8)

- **The Proarrhythmic conundrum of alcohol** (Manolis TA, et al, *Trends Cardiovasc Med* 2022; 32(4):237-245.

- **Electrical management of heart failure** (Prinzen FW et al, *Eur Heart J* 2022;43:917–27)

- **Cardiac sympathetic denervation for genetically mediated life-threatening ventricular arrhythmias** (Schwartz PJ & Ackerman MJ, *Eur Heart J* 2022;43,:2096–2102)

- **Acute coronary syndromes** (Bergmark BA et al, *Lancet* 2022;399:1347-58)