Cardiology News / Recent Literature Review / First Quarter 2022

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ACC.22, Washington, DC, USA, 2-4/4/22

EHRA 22, Copenhagen, Denmark, 3-5/4/22

HRS 22, San Francisco, CA, USA, 29/4-1/5/22

EuroPCR, Paris, France, 17-20/5/22

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

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

PRAGUE-17: **Left Atrial Appendage Closure (LAAC) Remains Noninferior to DOACs for Preventing Major CV, Neurological, or Bleeding Events / Nonprocedural Bleeding Was Significantly Reduced With LAAC**

A total of 402 patients with AF (201 per group, age 73.3±7.0 years, 65.7% male, CHA_2DS_2-VASc 4.7±1.5, HASBLED 3.1±0.9) were randomized to percutaneous LAAC (Watchman or Amulet) with DOACs (95% apixaban). After a median of 3.5 years, LAAC was noninferior to DOACs for the primary endpoint (composite of cardioembolic events-i.e., stroke, TIA, or systemic embolism-, CV death, clinically relevant bleeding, or procedure-/device-related complications (LAAC group only)), by modified intention-to-treat (sub-distribution HR [sHR]: 0.81; *P* = 0.27; *P* for noninferiority = 0.006). For the components of the composite endpoint the corresponding sHRs were 0.68 (*P*= 0.19) for CV death, 1.14 (*P*=0.72) for all-stroke/TIA, 0.75 (*P*=0.28) for clinically relevant bleeding, and 0.55 (*P*=0.039) for nonprocedural clinically relevant bleeding. The primary endpoint outcomes were similar in the per-protocol (sHR: 0.80; *P*=0.25) and on-treatment (sHR: 0.82; *P*=0.30) analyses (Osmancik P et al, *J Am Coll Cardiol* 2022;79:1-14).

Higher Olive Oil Intake Conferred Lower Risk of Total and Cause-Specific Mortality / Replacing Margarine, Butter, Mayonnaise, and Dairy Fat with Olive Oil Lowered Mortality

Among 60,582 women (Nurses' Health Study, 1990-2018) and 31,801 men (Health Professionals Follow-up Study, 1990-2018) who were free of cardiovascular (CV) disease or cancer, over 28 years, 36,856 deaths occurred. The multivariable-adjusted pooled HR for all-cause mortality among persons who had the highest consumption of olive oil (>0.5 tablespoon/day or >7 g/d) was 0.81 compared with those who never or rarely consumed olive oil. Higher olive oil intake conferred a 19% lower risk of CV mortality (HR: 0.81), 17% lower risk of cancer mortality (HR: 0.83), 29% lower risk of neurodegenerative disease mortality (HR: 0.71), and 18% lower risk of respiratory disease mortality (HR: 0.82). In substitution analyses, replacing 10 g/d of margarine, butter, mayonnaise, and dairy fat with the equivalent amount of olive oil conferred 8%-34% lower risk of total and cause-specific mortality. No significant associations were observed when olive oil was compared with other vegetable oils combined (Guasch-Ferré M et al, *J Am Coll Cardiol* 2022;79:101–112).

Among Patients With Advanced Stable Coronary Artery Disease, Lp(a) is Associated With Accelerated Progression of Coronary Low-Attenuation Plaque (Necrotic Core) / This May Explain the Association Between Lp(a) and the High Residual Risk of Myocardial Infarction, Providing Support for Lp(a) as a Treatment Target in Atherosclerosis

Among 191 patients (65.9 ± 8.3 years of age; 80% male) with median Lp(a) values of 100 (82-115) mg/dL and 10 (5-24) mg/dL in the high and low Lp(a) groups, respectively, patients with high Lp(a) showed accelerated progression of low-attenuation plaque vs low Lp(a) patients (26.2 ± 88.4 mm^3 vs −0.7 ± 50.1 mm^3; *P*=0.020). Multivariable analysis confirmed the relation between Lp(a) and low-attenuation plaque volume progression (β = 10.5% increase for each 50 mg/dL Lp(a), 95% CI: 0.7%-20.3%). There was no difference in total, calcific, and noncalcific plaque volume progression (Kaiser Y et al, *J Am Coll Cardiol* 2022;79: 223–233).

Sports-Related Sudden Cardiac Arrest (SrSCD): Incidence Remained Stable Over Time, Indicating a Need for Improvement in Screening Strategies / But, Major Improvements in On-Field Resuscitation Led to a 3-Fold Increase in Survival, Emphasizing the Value of Public Education in Basic Life Support

Among the 377 SrSCA, 20 (5.3%) occurred in young competitive athletes, whereas 94.7% occurred in middle-aged recreational sports participants. Comparing the last 2-year to the first 2-year period, SrSCA incidence remained stable (6.24 vs 7.00 per million inhabitants/y; *P*=0.51), with no significant differences in patients' mean age (46.6 ± 13.8 years vs 51.0±16.4 years; *P*=0.42), sex (men 94.7% vs 95.2%; *P*=0.99), and history of heart disease (12.5% vs 15.9%; *P*=0.85). However, frequency of bystander CPR and public automated external defibrillator use increased significantly (34.9% vs 94.7%; *P*<0.001 & 1.6% vs 28.8%; *P*=0.006, respectively). Survival to hospital discharge improved steadily, reaching 66.7% in the last study period compared with 23.8% in the first (*P*<0.001) (Karam N et al, *J Am Coll Cardiol* 2022;79:238-246).

Irrespective of Heart Failure (HF) Phenotype, Low Serum Iron or Transferrin Saturation (TSAT) is Associated With Higher Mortality, While iron deficiency (ID), as Defined in Current HF Guidelines, is not / Serum Ferritin May Better Reflect Inflammation Than ID in Patients With HF

The WHO defines ID as a serum ferritin <15 ng/mL; most clinical laboratories as <30 ng/mL; but, international guidelines on HF define ID as a serum ferritin <100 ng/mL or, when ferritin is 100-299 ng/mL, a TSAT <20%

Of 4,422 patients with HF (median age 75 years, 60% men, 32% with reduced LVEF), 46% had TSAT <20%, 48% had serum iron ≤13 μmol/L, 57% had serum ferritin <100 ng/mL, and 68% fulfilled current guideline criteria for ID, of whom 35% had a TSAT >20%. Irrespective of definition, ID was more common in women and those with more severe symptoms, anemia, or preserved ejection fraction. TSAT <20% and serum iron ≤13 μmol/L, but not guideline criteria, were associated with higher 5-year mortality (HR: 1.27; *P*< 0.001; and HR: 1.37; *P*<0.001, respectively). Serum ferritin <100 ng/mL tended to be associated with lower mortality (HR: 0.91; *P*=0.09) (Masini G et al, *J Am Coll Cardiol* 2022; 79:341–351).

AUGUSTUS: Findings Support Use of Apixaban and a $P2Y_{12}$ Inhibitor Without Aspirin for Most Patients With AF and ACS and/or PCI, Irrespective of a Patient's Baseline Bleeding and Stroke Risk

Of 4,386 (95.1%) patients with calculable scores among those randomized to open-label apixaban or VKA and blinded aspirin or placebo., 66.8% had HAS-BLED ≥3 and 81.7% had CHA_2DS_2-VASc ≥3. Bleeding rates were lower with apixaban than VKA irrespective of baseline risk (HR: 0.57, [HAS-BLED ≤2]; HR: 0.72, [HAS-BLED ≥3]; interaction *P*=0.23). Aspirin increased bleeding irrespective of baseline risk (HR: 1.86, HAS-BLED ≤2; HR: 1.81, HAS-BLED ≥3; interaction *P*=0.88). Apixaban resulted in a lower risk of death or hospitalization than VKA without a significant interaction with baseline stroke risk (HR: 0.92, CHA_2DS_2-VASc ≤2; HR: 0.82, CHA_2DS_2-VASc ≥3; interaction *P*=0.53) (Harskamp RE et al, *J Am Coll Cardiol* 2022;79:417-427).

Myocardial Fibrosis Quantified via CMR Predicts Ventricular Arrhythmias and Sudden Death (SCD) After Cardiac Electronic Device Implantation

Among 700 patients (age 68±12 years), 27 (3.85%) experienced a SCD and 121 (17.3%) met the arrhythmic endpoint over median 6.93 years. Myocardial fibrosis on visual assessment (MF_{VA}) by CMR predicted SCD (HR: 26.3; negative predictive value: 100%). In competing risk analyses, MF_{VA} also predicted the arrhythmic endpoint (subdistribution HR: 19.9; negative predictive value: 98.6%). Compared with no MF_{VA}, a gray zone fibrosis (GZF) mass measured with the 5SD method (GZF_{5SD}) >17 g was associated with highest risk of SCD (HR: 44.6) and the arrhythmic endpoint (subdistribution HR: 30.3). Adding GZF_{5SD} mass to MF_{VA} led to reclassification of 39% for SCD and 50.2% for the arrhythmic endpoint. In contrast, LVEF did not predict either endpoint (Leyva F et al, *J Am Coll Cardiol* 2022;79:665–678).

MESA & DHS Trials: Lipoprotein(a)-Lp(a) and Coronary Artery Calcium-CAC are Independently Associated with Atherosclerotic CVD Risk and May be Useful Concurrently for Guiding Primary Prevention Therapy Decisions

Plasma Lp(a) and CAC were measured at enrollment among asymptomatic participants of the MESA (Multi-Ethnic Study of Atherosclerosis) (n=4,512) and DHS (Dallas Heart Study) (n=2,078) cohorts. Among MESA participants (61.9 years of age, 52.5% women), 476 incident CV events were observed during 13.2 years of follow-up. Elevated Lp(a) and CAC score (1-99 and ≥100) were independently associated with CV risk (HR: 1.29; HR: 1.68; and HR: 2.66, respectively), and Lp(a)-by-CAC interaction was not noted. Compared with participants with nonelevated Lp(a) and CAC = 0, those with elevated Lp(a) and CAC ≥100 were at the highest risk (HR: 4.71), and those with elevated Lp(a) and CAC = 0 were at a similar risk (HR: 1.31). Similar findings were observed when guideline-recommended Lp(a) and CAC thresholds were considered, and findings were replicated in the DHS (Mehta A et al, *J Am Coll Cardiol* 2022;79:757–768).

HATTUSHA Study: **Low-Dose and Slow/Ultraslow Infusion of t-PA Had Low Complications and Mortality and High Success Rates and Should be Considered as a Viable Treatment in Patients With Obstructive Prosthetic Valve Thrombosis (PVT)**

Among 158 patients with obstructive prosthetic valve thrombosis (PVT) (65% women; median age 49 years), thrombolytic therapy (TT) was performed using slow (6 h) and/or ultraslow (25 h) infusion of low-dose tissue plasminogen activator (t-PA) (25 mg) mostly in repeated sessions. The initial management strategy was TT in 83 (52.5%) patients and surgery in 75 (47.5%) cases. The success rate of TT was 90.4% with a median t-PA dose of 59 mg. Outcomes in surgery and TT groups were as follows: minor complications 39% and 8.4%, respectively; major complications 41% and 6%, respectively, and; the 3-month mortality rate 189% and 2.4%, respectively) (Ozkan M et al, *J Am Coll Cardiol* 2022;79:977-989).

EMPEROR-Preserved Trial: Empagliflozin Improved Health Status & Quality of Life in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)

The effect of empagliflozin on reducing the risk of time to CV death or heart failure (HF) hospitalization was

consistent (hazard ratio-HR, 0.83, 0.70, and 0.82 for QOL scores <62.5, 62.5–83.3, and ≥83.3, respectively; *P* trend=0.77). Similar results were seen for total HF hospitalizations. Patients treated with empagliflozin had significant improvement in QOL vs placebo (*P*<0.01). At 12 weeks, patients on empagliflozin had higher odds of improvement ≥5 points (odds ratio-OR, 1.23), ≥10 points (OR, 1.15), and ≥15 points (OR, 1.13) and lower odds of deterioration ≥5 points in QOL score (OR, 0.85). A similar pattern was seen at 32 and 52 weeks, and results were consistent for Total Symptom Score and Overall Summary Score (Butler J et al, *Circulation* 2022;145:184–193***).***

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT): Nadolol, or Propranolol if Nadolol is Unavailable, Should be the Preferred β-Blocker for Treating Symptomatic CPVT

In 2 international registries, among 329 patients with CPVT (*RYR2* variant–carrying symptomatic children, defined as syncope or sudden cardiac arrest before β-blocker initiation and age at start of β-blocker therapy <18 years; median age at diagnosis, 12 years, 35% females), treated with a β-blocker, 99 (30%) patients experienced the primary outcome (first occurrence of sudden cardiac death, sudden cardiac arrest, appropriate ICD shock, or syncope) and 74 (22.5%) experienced the secondary outcome (first occurrence of any of the primary outcomes except syncope) during a median follow-up of 6.7 years. A nonselective β-blocker (mainly nadolol, n=140 or propranolol, n=70) was used in 66% and 111 (33.7%) had a β1-selective β-blocker (mainly atenolol, n=51; metoprolol, n=33; or bisoprolol, n=19) as initial β-blocker. Baseline characteristics did not differ. The HRs for both the primary and secondary outcomes were higher for β1-selective compared with nonselective β-blockers (HR, 2.04; and HR, 1.99, respectively). When assessed separately, the HR for the primary outcome was higher for atenolol (HR, 2.68), bisoprolol (HR, 3.24), and metoprolol (HR, 2.18) compared with nadolol, but did not differ from propranolol. The HR of the secondary outcome was only higher in atenolol compared with nadolol (HR, 2.68). Thus, β1-selective β-blockers conferred a higher risk for arrhythmic events in symptomatic children with CPVT compared with nonselective β-blockers, specifically nadolol (Peltenburg PJ et al, *Circulation* 2021;145:333-44***)***

Most Cases of Suspected COVID-19 Vaccine Myocarditis in Persons <21 Years Have a Mild Clinical Course With Rapid Resolution of Symptoms / Abnormal Findings on Cardiac MRI are Frequent

Among 139 adolescents and young adults (91% male; median age 15.8 years) with 140 episodes of suspected myocarditis (49 confirmed, 91 probable) at 26 centers, suspected myocarditis occurred in 136 patients (97.8%) after the mRNA vaccine, with 131 (94.2%) after the Pfizer-BioNTech vaccine; 128 (91.4%) occurred after the second dose. Symptoms started at a median of 2 days after vaccination. The most common symptom was chest pain (99.3%). Patients were treated with nonsteroidal anti-inflammatory drugs (81.3%), intravenous immunoglobulin (21.6%), glucocorticoids (21.6%), colchicine (7.9%), or no anti-inflammatory therapies (8.6%). Twenty-six patients (18.7%) were in the intensive care unit, 2 were treated with inotropic/vasoactive support, and none required extracorporeal membrane oxygenation or died. Median hospital stay was 2 days. All patients had elevated troponin I (n=111, 8.12 ng/mL) or T (n=28, 0.61 ng/mL); 69.8% had abnormal ECGs and arrhythmias (7 with nonsustained ventricular tachycardia); and 18.7% had LVEF <55% on echocardiogram. Of 97 patients who underwent cardiac MRI at a median 5 days from symptom onset, 75 (77.3%) had abnormal findings: 74 (76.3%) had late gadolinium enhancement, 54 (55.7%) had myocardial edema, and 49 (50.5%) met Lake Louise criteria. Among 26 patients with LVEF <55%, all with follow-up had normalized function (n=25) (Truong DT et al, *Circulation* 2022;145:345–356**)**.

PATH-BP Trial: Regular Daily Intake of 4 g Acetaminophen Increases Systolic BP in Individuals With Hypertension by ≈5 Mm Hg vs Placebo

Among 103 patients randomized to receive 1 g acetaminophen 4× daily or matched placebo for 2 weeks followed by a 2-week washout period before crossing over to the alternate treatment, regular acetaminophen, compared with placebo, resulted in a significant increase in mean daytime systolic BP (132.8±10.5 to 136.5±10.1 mm Hg, acetaminophen vs 133.9±10.3 to 132.5±9.9 mm Hg, placebo; *P*<0.0001) with a placebo-corrected increase of 4.7 mm Hg and mean daytime diastolic BP (81.2±8.0 to 82.1±7.8 mm Hg, acetaminophen vs 81.7±7.9 to 80.9±7.8 mm Hg, placebo; *P*=0.005) with a placebo-corrected increase of 1.6 mm Hg. Similar findings were seen for 24-hour ambulatory and clinic BPs (MacIntyre IM et al, *Circulation.* 2022;145:416–423*).*

DANISH Trial: During Long-Term FU (Median 9.5 Years), ICD Implantation did not Provide Overall Survival Benefit in Patients With Nonischemic Systolic Heart Failure / In Patients ≤70 Years, ICD Lowered the Incidence of All-Cause Mortality, CV Death, and Sudden Cardiac Death

In DANISH, 556 patients with nonischemic systolic heart failure were randomized to receive an ICD and 560 to receive usual clinical care. In this long-term follow-up study of a median of 9.5 years, 208/556 patients (37%) in the ICD group and 226/560 patients (40%) in the control group died. Compared with the control group, the ICD did not significantly lower all-cause mortality (HR 0.89;

P=0.24). In patients ≤70 years (n=829), all-cause mortality was lower in the ICD group than the control group (30% vs 36%; HR, 0.78; *P*=0.04), whereas in patients >70 years (n=287), all-cause mortality was not significantly different between the ICD and control group (54% vs 57%; HR, 0.92; *P*=0.75). Cardiovascular death showed similar trends (overall, 26% vs 29%; HR, 0.87; *P* =0.20; ≤70 years, 22% vs 28%; HR, 0.75; *P*=0.04; >70 years, 36% vs 35%; HR, 0.97; *P*=0.91). The ICD group had a significantly lower incidence of sudden CV death in the overall population (6% vs 10%; HR, 0.60; *P*=0.02) and in patients ≤70 years (5% vs 11%; HR, 0.42; *P*=0.0008), but not in patients >70 years (10% vs 7%; HR, 1.34; *P*= 0.39) (Yafasova A et al, *Circulation* 2022;145:427–436***).***

AVATAR Trial: Early Surgical Aortic Valve Replacement (AVR) in Asymptomatic Patients With Severe Aortic Stenosis (AS) Reduced a Primary Composite of All-Cause Death, Acute Myocardial Infarction, Stroke, or Unplanned Hospitalization for Heart Failure Vs Conservative Treatment

A total of 157 asymptomatic patients with severe AS (mean age, 67 years; 57% men) were randomly assigned to early surgery (n=78) or conservative treatment (n=79). Over a median of 32 months, there was a total of 39 events, 13 in early surgery and 26 in the conservative treatment group. In the early surgery group, 72 patients (92.3%) underwent AVR with operative mortality of 1.4%. In an intention-to-treat analysis, patients randomized to early surgery had a significantly lower incidence of primary composite end point than those in the conservative arm (hazard ratio-HR, 0.46; *P*=0.02). There was no statistical difference in secondary end points, but trends were consistent with the primary outcome (Banovic M et al, *Circulation* 2022;145:648–658).

DREAM-ICD-II Study: Rate of Appropriate Therapies Resulting in Sudden Cardiac Incapacitation in Recipients of a Secondary Prevention ICD is Much Lower Than Previously Reported and Declines Significantly After the First 3 Months, Allowing for Lowering Driving Restrictions to 3 Months

A Canadian retrospective study of 721 patients with new secondary prevention ICD implants showed that, over a median of 2 years, the risk of recurrent ventricular arrhythmia was highest during the first 3 months after device insertion (34.4%) and decreased over time (10.6% between 3 and 6 months, 11.7% between 6 and 12 months). The corresponding incidence rate per 100 patient-days was 0.48 at 3 months, 0.28 at 6 months, and 0.21 between 6 and 12 months after ICD insertion (*P*<0.001). The cumulative incidence of arrhythmic syncope resulting in sudden cardiac incapacitation was 1.8% within the first 3 months and subsequently dropped to 0.4% between 3 and 6 months (*P*<0.001) after ICD insertion (Steinberg C et al, *Circulation* 2022;145:742–753***).***

FAME-3 Failed to Show Non-Inferiority of FFR-Guided PCI to CABG in Patients With 3-Vessel Coronary Disease, Regarding a Composite of Death, MI, Stroke, or Repeat Revascularization at 1 Year

Among 1500 patients randomized to PCI (3.7±1.9 stents) or CABG (3.4±1.0 distal anastomoses), the 1-year incidence of the composite primary end point was 10.6% among patients assigned to undergo FFR-guided PCI and 6.9% among those assigned to undergo CABG (hazard ratio-HR, 1.5), findings that were not consistent with noninferiority of FFR-guided PCI (P=0.35 for noninferiority). The incidence of death, MI, or stroke was 7.3% in the FFR-guided PCI group and 5.2% in the CABG group (HR, 1.4). The incidences of major bleeding, arrhythmia, and acute kidney injury were higher in the CABG group than in the FFR-guided PCI group (Fearon WF et al, *N Engl J Med* 2022; 386:128-137).

Among Children and Adolescents 5-17 Years Old With Latent Rheumatic Heart Disease, Secondary Antibiotic Prophylaxis Reduced the Risk of Disease Progression at 2 Years

Among 818 Ugandan children and adolescents 5-17 years of age with latent rheumatic heart disease determined by Echo, randomized to injections of penicillin G benzathine every 4 weeks for 2 years or no prophylaxis (799 or 97.7% completed the trial), a total of 3 participants (0.8%) in the prophylaxis group had echocardiographic progression at 2 years, as compared with 33 (8.2%) in the control group (risk difference, −7.5 percentage points; P<0.001). Two participants in the prophylaxis group had serious adverse events that were attributable to receipt of prophylaxis, including one episode of a mild anaphylactic reaction (representing <0.1% of all administered doses of prophylaxis) (Beton A et al, *N Engl J Med* 2022;386:230-240).

CTSN: Among Patients Undergoing Mitral-Valve Surgery, Those Who Also Received Concomitant Tricuspid Annuloplasty (TA) Had a Lower Incidence of a Primary-End-Point Event Than Those Who Underwent Mitral-Valve Surgery Alone at 2 Years, Albeit More Permanent Pacemaker Implantations

Among 401 patients undergoing mitral-valve surgery for degenerative mitral regurgitation who were randomized to receive concomitant tricuspid annuloplasty (TA), those who underwent mitral-valve surgery plus TA had fewer primary-end-point events (composite of reoperation for tricuspid regurgitation, progression of tricuspid regurgitation by two grades from baseline or the presence of severe tricuspid regurgitation, or death) than those who underwent mitral-valve surgery alone (3.9% vs.

10.2%) (relative risk-RR, 0.37; P=0.02). Two-year mortality was 3.2% vs 4.5% (RR, 0.69). The 2-year prevalence of progression of tricuspid regurgitation was lower in the surgery-plus-TA group than in the surgery-alone group (0.6% vs. 6.1%; RR, 0.09). The frequencies of major adverse cardiac and cerebrovascular events, functional status, and quality of life were similar in the two groups at 2 years, although the incidence of permanent pacemaker implantation was higher in the surgery-plus-TA group than in the surgery-alone group (14.1% vs. 2.5%; rate ratio, 5.75) (Gammie JS et al, *N Engl J Med* 2022; 386:327-339).

Worldwide, Patients With Homozygous Familial Hypercholesterolemia (HoFH) are Diagnosed Too Late, Undertreated, and at High Premature Atherosclerotic Cardiovascular Disease (CVD) Risk / Greater Use of Multi-Lipid Lowering Therapies (LLT) is Associated With Lower LDL Cholesterol Levels and Better Outcomes

Among 751 patients (median age of diagnosis at 12 years; 52% female) with HoFH, a rare inherited disorder resulting in extremely elevated low-density lipoprotein (LDL) cholesterol levels and premature atherosclerotic CVD, 565 (75%) had biallelic pathogenic variants. The major manifestations of CVD or aortic stenosis were already present in 65 (9%) of patients at diagnosis of HoFH. Globally, pretreatment median LDL cholesterol levels were 568.5 mg/dl. Among patients with detailed therapeutic information, 491 (92%) of 534 received statins, 342 (64%) of 534 received ezetimibe, and 243 (39%) of 621 received lipoprotein apheresis. On-treatment LDL cholesterol levels were lower in high-income countries (152 mg/dL) vs non-high-income countries (360 md/dL), with greater use of ≥3 lipid-lowering therapies (LLT; high-income 66% ***vs*** non-high-income 24%) and consequently more patients attaining guideline-recommended LDL cholesterol goals (high-income 21% ***vs*** non-high-income 3%). A first major adverse cardiovascular event occurred a decade earlier in non-high-income countries, at a median age of 24.5 years vs 37 years in high-income countries (adjusted hazard ratio 1.64) (Tromp TR et al, *Lancet* 2022;399:719-728).

AURORA: Evidence for Benefit of Endovascular Thrombectomy in Patients With Anterior Circulation Stroke With Evidence of Reversible Cerebral Ischemia Across the 6–24 h Time Window

Patient level data analysis from 6 RCTs on 505 individuals (n=266 intervention, n=239 control; age 68.6±13·7 years; 51% women) showed a benefit of thrombectomy with an unadjusted common odds ratio (OR) of 2.42 (P<0.0001) and an adjusted common OR (for age, gender, baseline stroke severity, extent of infarction on baseline head CT, and time from onset to random assignment) of 2.54 (P<0.0001). Thrombectomy was associated with higher rates of independence in activities of daily living (mRS 0–2) than best medical therapy alone (45.9% ***vs*** 19.3%; P<0.0001). No significant difference between intervention and control groups was found when analyzing either 90-day mortality (16.5% ***vs*** 19.3%) or symptomatic intracerebral hemorrhage (5.3% ***vs*** 3.3%). No heterogeneity of treatment effect was noted across subgroups; treatment effect was stronger in patients randomly assigned within 12–24 h (common OR 5.86) than those randomly assigned within 6–12 h (OR 1.76; $p_{interaction}$=0.0087) (Jovin TD et al, *Lancet* 2022;399:249-258).

MICHELLE: In Patients at High Risk Discharged After Hospitalization Due to COVID-19, Thromboprophylaxis With Rivaroxaban 10 mg/d for 35 Days Improved Clinical Outcomes Compared With No Extended Thromboprophylaxis

Among 320 patients randomized to rivaroxaban (n=160 [50%]) or no anticoagulation (n=160 [50%]), the primary efficacy outcome (symptomatic or fatal venous thromboembolism-VTE, asymptomatic VTE on bilateral lower-limb venous ultrasound and CT pulmonary angiogram, symptomatic arterial thromboembolism, and CV death at day 35) occurred in 5 (3%) of 159 patients assigned to rivaroxaban and 15 (9%) of 159 patients assigned to no anticoagulation (relative risk 0·33, P=0.0293). No major bleeding occurred in either study group. Allergic reactions occurred in 2 (1%) patients in the rivaroxaban group (Ramacciotti E et al, *Lancet* 2022;399:50-59).

Pelacarsen Significantly Lowers Direct Lp(a)-Cholesterol and Has Neutral/Mild Lowering of LDL-C_{corr} / In Patients With Elevated Lp(a), LDL-C_{corr} Provides More Accurate Reflection of Changes in LDL-Cholesterol

Among 286 patients with established CV disease and screening Lp(a) levels ≥60 mg/dL (≥150 nmol/L) (baseline median Lp(a)-C values 11.9 - 15.6 mg/dL), the effect of pelacarsen was assessed on directly measured Lp(a)-C and LDL-C corrected for its Lp(a)-C content (randomized to 5 groups of cumulative monthly doses of 20-80 mg pelacarsen vs placebo). Compared with placebo, pelacarsen resulted in dose-dependent decreases in Lp(a)-C (2% vs −29% to −67%; $P \leq 0.0001$). Baseline laboratory-reported mean LDL-C ranged from 68.5 to 89.5 mg/dL, whereas LDL-C_{corr} ranged from 55 to 74 mg/dL. Pelacarsen resulted in mean percent/absolute changes of −2% to −19%/−0.7 to −8.0 mg/dL (P=0.95-0.05) in LDL-C_{corr}, −7% to −26%/−5.4 to −9.4 mg/dL (P=0.44-<0.0001) in laboratory-reported LDL-C, and 3.1% to 28.3%/0.1 to 9.5 mg/dL (P=0.006-0.50) increases in LDL-$C_{corrDahlén}$. Total apoB declined by 3%-16% (P = 0.40-<0.0001), but

non-Lp(a) apoB was not significantly changed (Yeang C et al, *J Am Coll Cardiol* 2022;79: 1035-46).

Homologous Boosters (Same as the Primary Vaccine) and Heterologous Boosters (Different From the Primary Vaccine) are Equally Immunogenic in Fully Vaccinated Recipients

Among 458 participants, 154 received mRNA-1273 (Moderna), 150 received Ad26.COV2.S (J&J), and 153 received BNT162b2 (Pfizer) as booster vaccines. Reactogenicity was similar to that reported for the primary series. Over 50% reported having injection-site pain, malaise, headache, or myalgia. For all combinations, antibody neutralizing titers against a SARS-CoV-2 D614G pseudovirus increased by a factor of 4-73, and binding titers increased by 5-55. Homologous boosters increased neutralizing antibody titers by 4-20, whereas heterologous boosters increased titers by 6-73. Spike-specific T-cell responses increased in all but the homologous Ad26.COV2.S-boosted subgroup. CD8+ T-cell levels were more durable in the Ad26.COV2.S-primed recipients, and heterologous boosting with the Ad26.COV2.S vaccine considerably increased spike-specific CD8+ T cells in the mRNA vaccine recipients (Atmar RL et al, *N Engl J Med* 2022; 386:1046-57).

REDUCE LAP-HF II: Placement of an Atrial Shunt Device Did Not Reduce the Total Rate of Heart Failure (HF) Events or Improve Health Status in Patients With Heart Failure and Ejection Fraction of ≥40%

Patients were randomly assigned (1:1) to receive either a shunt device or sham procedure.

Among 1072 patients (≥40 years) with symptomatic HF, an ejection fraction of at least 40%, and pulmonary capillary wedge pressure during exercise of at least 25 mm Hg while exceeding right atrial pressure by at least 5 mm Hg, of whom 626 randomized to either the atrial shunt device (n=314) or sham procedure (n=312), there were no differences between groups in the primary composite endpoint (hierarchical composite of CV death or non-fatal ischemic stroke at 1 year, rate of HF events up to 2 years, and change in quality of life score at 1 year) (win ratio 1.0; p=0·85) or in the individual components of the primary endpoint. The prespecified subgroups demonstrating a differential effect of atrial shunt device treatment on HF events were pulmonary artery systolic pressure at 20W of exercise ($P_{interaction}$=0·002 [>70 mmHg conferred worse outcomes]), right atrial volume index ($P_{interaction}$=0·012 [≥29·7 mL/m^2, worse outcomes]), and sex ($P_{interaction}$=0·02 [men, worse outcomes]). There were no differences in the composite safety endpoint between the two groups (n=116 [38%] for shunt device ***vs*** n=97 [31%] for sham procedure; P=0·11) (Shah SJ et al, *Lancet* 2022;399:1130-1140)

New Users of Apixaban Had Lower Rates of Recurrent Venous Thromboembolism (VTE) and Bleeding Than New Users of Rivaroxaban

Among 18,618 new users of apixaban and 18,618 new users of rivaroxaban, after propensity score matching, over a median of ~3.5 months, apixaban (vs rivaroxaban) was associated with a lower rate for recurrent VTE (HR, 0.77) and bleeding (HR, 0.60). The absolute reduction in the probability of recurrent VTE with apixaban vs rivaroxaban was 0.006 within 2 months and 0.011 within 6 months of initiation. The absolute reduction in the probability of gastrointestinal and intracranial bleeding with apixaban vs rivaroxaban was 0.011 within 2 months and 0.015 within 6 months of initiation (Dawwas GK et al, *Ann Intern Med* 2022;175:20-28).

Case-Control study: Despite a Low Absolute Risk, There is an Increased Risk for Carditis Associated With BNT162b2 (Pfizer) Vaccination

Among160 patients (aged ≥12 years first diagnosed with carditis) and 1533 controls (hospitalized patients without carditis), incidence of carditis per 100,000 doses of CoronaVac and BNT162b2 administered was estimated to be 0.31 and 0.57, respectively. Multivariable analyses showed that recipients of the BNT162b2 vaccine had higher odds of carditis (adjusted odds ratio -OR, 3.57) than unvaccinated persons. Stratified by sex, the OR was 4.68 for males and 2.22 for females receiving the BNT162b2 vaccine. The ORs for adults and adolescents receiving the BNT162b2 vaccine were 2.41 and 13.79, respectively. Subanalysis showed an OR of 9.29 for myocarditis and 1.06 for pericarditis associated with BNT162b2. The risk was mainly seen after the second dose of BNT162b2 rather than the first. No association between CoronaVac and carditis with a magnitude similar to that for BNT162b2 was seen (Lai FTT et al, *Ann Intern Med* 2022;175:362-370**).**

Registry Study: Left Bundle Branch Area Pacing (LBBAP) Improved Clinical Outcomes Compared to Right Ventricular Pacing (RVP) / Higher Burden of Ventricular Pacing (>20%) Was the Primary Driver of These Outcome Differences

Among 703 paced patients (321 LBBAP and 382 RVP), QRS duration during LBBAP was similar to baseline (121 ± 23 ms vs 117 ± 30 ms; P=0.302) and narrower compared to RVP (121 ± 23 ms vs 156 ± 27 ms; P<0.001). The primary composite outcome (all-cause mortality, heart failure hospitalization - HFH, or upgrade to biventricular pacing) was significantly lower with LBBAP (10%) vs RVP (23.3%) (hazard ratio-HR 0.46; P<0.001). Among patients with ventricular pacing burden >20%, LBBAP was associated with significant reduction in the primary outcome compared to RVP (8.4% vs 26.1%;

HR 0.32; P<0.001). LBBAP was also associated with significant reduction in mortality (7.8% vs 15%; HR 0.59; P= 0.03) and HFH (3.7% vs 10.5%; HR 0.38; P=0.004) (Sharma PS et al, *Heart Rhythm* 2022;19:3-11).

Greater Alcohol Consumption Increased Ventricular Arrhythmias (VA), But a U-Shaped Association Was Present for Sudden Cardiac Death (SCD), With Lower Risk in Those Consuming <26 Drinks/w With the Nadir of Risk Seen at 7 Drinks/week (UK drink = 8 g alcohol)

Among 408,712 middle-aged individuals (52.1% female) over a median follow-up of 11.5 years, a total of 1733 incident VA events and 2044 SCDs occurred. For incident VA, no clear association was seen with total alcohol consumption, although consumption of greater amounts of spirits was associated with increased VA risk. For SCD, a U-shaped association was seen for total alcohol consumption, such that consumption of <26 drinks per week (1 standard UK drink was defined as 8 g of alcohol; N.B.: a US drink is 14 g of alcohol) was associated with lowest risk. Consumption of greater amounts of beer, cider, and spirits was associated with increasing SCD risk, whereas increasing red and white wine intake was associated with reduced risk (Tu SJ et al, *Heart Rhythm* 2022; 19:177-84).

Important Review and Other Articles

2021 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (Wyckoff MH et al, *Circulation* 2022;145:e645–e721

ECG in CRT Patients (Manolis AS et al, *J Cardiovasc Electrophysiol* 2021;32:3228-3244)

● **Coronary Atherosclerotic Plaque Regression** (Dawson LP et al, *J Am Coll Cardiol* 2022;79:66–82)

● **Staphylococcus Aureus Infective Endocarditis** (Grapsa J et al, *J Am Coll Cardiol* 2022;79:88-99)

● **2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization** (Lawton JS et al, *JACC* 2022;79:e21-e129 & *Circulation* 2022;145:e18–e114)

● **Management of Atrial Fibrillation in Patients ≥75 Years** (Volgman AS, *J Am Coll Cardiol* 2022;79:166-179)

● **Lead-Related Venous Obstruction in Patients With Implanted Cardiac Devices** (Zimetbaum P et al, *JACC* 2022;79:299-308)

● **Diagnosis, Evaluation & Management of Hypertrophic Cardiomyopathy** (Maron BJ et al, *J Am Coll Cardiol* 2022; 79:372-89 & 390-414)

● **Immune Checkpoint Therapies and Atherosclerosis** (Vuong JT et al, *J Am Coll Cardiol* 2022;79:577–593)

● **Autonomic Neuromodulation for AF Following Cardiac Surgery** (Zafeiropoulos S et al, *JACC* 2022;79:682-94)

● **SCAI SHOCK Stage Classification Expert Consensus Update** (Naidu SS et al**,** *J Am Coll Cardiol* 2022;79:933–946)

● **Anticoagulation in Patients With COVID-19** (Farkouh ME et al, *JACC* 2022;79:917–928)

● **LV Thrombus after acute MI** (Camaj A et al, *J Am Coll Cardiol* 2022; 79:1010–1022)

● **Familial Hypercholesterolemia** (Sniderman AD et al, *J Am Coll Cardiol* 2022;79:1023–1031)

● **E-Cigarettes and Cardiopulmonary Health** (Neczypor EW et al, *Circulation* 2021;144:e472–e487)

● **Atrial Fibrillation and Dementia** (Rivard L et al, *Circulation* 2022;145:392–409)

● **Heart Disease and Stroke Statistics—2022 Update** (Tsao CW et al, *Circulation* 2022;145:e153–e639)

● **Inherited Thrombophilias** are associated with a **Higher Risk of COVID-19–Associated Venous Thromboembolism** (Stevens H et al, *Circulation* 2022;145:940–942)

● **Takotsubo syndrome** (Singh T et al, *Circulation* 2022; 145:1002-1019)

● **Eisenmenger Syndrome** (Arvanitaki A et al, *J Am Coll Cardiol* 2022:79:1183-98)

● **Atrial Fibrillation Induced Cardiomyopathy** (Manolis AS et al, *Heart Fail Rev* 2022 Mar 23. doi: 10.1007/s10741-022-10221-1. Online ahead of print.

● **ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic** *(*ESC Task Force, *Eur Heart J* 2022; 43:1033-58 & 1059-1103*)*

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

● **Update on Cilostazol** (Manolis AA et al, *J Clin Pharmacol* 2022;62:320-358)

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

● **Gut Microbiota & Cardiovascular Disease** (Manolis AA et al, *Curr Med Chem* 2021 Dec 12. doi:10.2174/0929867328666211213112949. Online ahead of print.

● **Long COVID** (Raman B et al, *Eur Heart J* 2022;43:1157–1172.

● **Sports-related sudden cardiac death in women** (Rajan D et al, *Eur Heart J* 2021; 43:1198–1206)

● **COVID-19 Breakthrough Infections in Vaccinated Individuals** (Manolis AS & Manolis TA, *Rhythmos* 2022;17:1-8)

● The **Proarrhythmic Conundrum of Alcohol** intake (Manolis TA, et al, *Trends Cardiovasc Med* 2021 Mar 21:S1050-1738(21)00039-6. doi: 10.1016/j.tcm.2021.03.003. Online ahead of print.

● The **Cardiovascular Benefits of Caffeinated Beverages** (Manolis AA, et al. *Curr Med Chem*. 2021 Jul 7. doi: 10.2174/0929867328666210708091709. Online ahead of print.