Cardiology News / Recent Literature Review / Last Quarter 2021

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27th Annual International AF Symposium, 13-15/1/22, New York, NY, USA

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

Brugada Syndrome (BrS) is Associated With Increased Collagen Content Throughout Both Ventricles, With Maximal Collagen Proportions Observed Within BrS RVOT Epicardium

Evaluation of 28 whole hearts from consecutive sudden cardiac death cases attributed to BrS (75% men; median age of death 25 years, death occurred in sleep or at rest in 86%) and 29 hearts from a comparator group comprised of noncardiac deaths (control subjects), showed that the highest proportion of collagen was observed in the epicardial right ventricular outflow tract (RVOT) of the BrS group (23.7%). Ventricular myocardium from BrS decedents demonstrated a higher proportion of collagen compared with controls (ratio 1.45; *P*<0.001), with no significant interactions with respect to sampling location or tissue layer. There was insufficient evidence to support differences in collagen proportion in *SCN5A*-positive cases (n=5) vs control subjects (ratio 1.23; *P*=0.27) (Miles C et al, *J Am Coll Cardiol* 2021;78:1511–21).

XIENCE Short DAPT Program: Among High Bleeding Risk (HBR) Patients Undergoing PCI, 1 Month of DAPT, Compared With 3 Months of DAPT, Was Associated With Similar Ischemic Outcomes and Lower Bleeding Risk

Patients who received 1-month DAPT (XIENCE 28 USA and 28 Global; n=1392) were compared with those on 3-month DAPT (XIENCE 90; n= 1972) using propensity score stratification. The primary endpoint of all-cause mortality or myocardial infarction was similar between the 2 groups (7.3% vs 7.5%; *P*=0.41). The key secondary endpoint of BARC (Bleeding Academic Research Consortium) type 2-5 bleeding was lower with 1-month DAPT compared with 3-month DAPT (7.6% vs 10%; *P*=0.012). Major BARC type 3-5 bleeding did not differ at 12 months (3.6% vs 4.7%; *P*=0.082), but was lower with 1-month DAPT at 90 days (1.0% vs 2.1%; *P*=0.015) (Valgimigli M et al, *J Am Coll Cardiol* 2021;78:2060–2072).

A Booster (Third Dose) at Least 5 Months After a Second Dose of BNT162b2 Vaccine (Pfizer–BioNTech) Conferred 90% Lower Mortality Due to Covid-19 vs Those Who Did Not Receive a Booster

Among 843,208 participants 758,118 (90%) received the booster during the 54-day study period. Death due to Covid-19 occurred in 65 participants in the booster group (0.16 per 100,000 persons per day) and in 137 participants in the nonbooster group (2.98 per 100,000 persons per day). The adjusted hazard ratio–HR for death due to Covid-19 in the booster group, as compared with the nonbooster group, was 0.10 (P<0.001) (Arbel R et al, *N Engl J Med* 2021; 385:2413-2420).

GIPS-III: Circulating Ketone Bodies (KBs) are Increased in Patients with STEMI / Higher KBs at 24h are Associated With Functional Outcomes After STEMI, Which Suggests a Potential Role for Ketone Metabolism in Response to Myocardial Ischemia

Circulating ketone bodies (KBs) were high at presentation with STEMI (median total KBs: 520 μmol/L). At 24 h after reperfusion, KBs were still high compared with levels at 4-months (206 μmol/L vs 166 μmol/L, respectively; *P*<0.001). Increased KB concentrations at 24 hours were independently associated with larger myocardial infarct size (total KBs, per 100 μmol/L: β = 1.56; 95% CI: 0.29-2.83; *P*=0.016) and lower LVEF (β = −1.78; 95% CI: (−3.17 to −0.39; *P*=0.012) (de Koning M-S LY et al, *J Am Coll Cardiol* 2021;78:1421-32).

IMPROVE-IT: Adding Ezetimibe to Statin Consistently Reduced the Risk for Cardiovascular Events in Post-ACS Patients Irrespective of Baseline LDL-C Values, Supporting the Use of Intensive Lipid-Lowering Therapy With Ezetimibe Even in Patients With Baseline LDL-C <70 mg/dL

Absolute differences in median LDL-C achieved at 4 months between treatment arms were similar (17-20 mg/dL). The effect of ezetimibe/simvastatin vs placebo/simvastatin on primary endpoint was consistent regardless of baseline LDL-C of 50-<70 mg/dL (HR: 0.92), 70-<100 mg/dL (HR: 0.93), or 100-125 mg/dL (HR: 0.94; *P* interaction = 0.95). Normalized relative risk reductions per 1-mmol/L difference in achieved LDL-C at 4 months between treatment arms were 21% in patients with baseline LDL-C of 50-<70 mg/dL, 16% in those with 70-<100 mg/dL, and 13% in those with 100-125 mg/dL (*P* interaction = 0.91). No significant treatment interactions by baseline LDL-C were present for safety endpoints (Oyama K et al, *J Am Coll Cardiol* 2021; 78:1499–1507).

The Impact of Transcatheter Mitral Valve Replacement (TMVR) on Severity of MR, Reduction in HFH Rate, and Improvement in Symptoms Was Sustained Through 2 Years / All-Cause Mortality and the Need for HFH Was Highest in the First 3 Months

Among the first 100 symptomatic (66% NYHA class III or IV) patients (aged 74.7 ± 8.0 years, 69% male; grade 3+ or 4+ MR, secondary or mixed in 89%) undergoing transapical TMVR, prostheses were successfully implanted in 97 (97%) patients. At 2 years, all-cause mortality was 39%; 17 (43.6%) of 39 deaths occurred during the first 90 days. Heart failure hospitalization (HFH) fell from 1.30 events per year preprocedure to 0.51 per year in the 2 years post-TMVR (P<0.0001). At 2 years, 93.2% of surviving patients had no MR. No patient had >1+ MR. The improvement in symptoms at 1 year (88.5% NYHA functional class I or II) was sustained to 2 years (81.6% NYHA functional class I or II). Among survivors, the LVEF was 45.6 ± 9.4% at baseline and 39.8 ± 9.5% at 2 years (P = 0.0012). Estimated right ventricular systolic pressure decreased from 47.6 ± 8.6 mm Hg to 32.5 ± 10.4 mm Hg (P < 0.005) (Muller DWM et al, *J Am Coll Cardiol* 2021;78:1847-59).

Compared With ≤6-Month DAPT, a 1-Year Duration of DAPT Was Not Associated With Reduced Adverse Ischemic Events But Was Associated With Greater Bleeding in Patients at Increased Risk of Bleeding

Ischemic and bleeding risk scores were generated from ADAPT-DES, a multicenter, international, "all-comers" registry that enrolled 8,665 patients treated with DES. The risk-benefit profile of 1-year vs ≤6-month DAPT was then investigated across risk strata from an individual patient data pooled dataset of 7 RCTs that enrolled 15,083 patients treated with DES. In the derivation cohort, the ischemic score and the bleeding score had c-indexes of 0.76 and 0.66, respectively, and both were well calibrated. In the pooled dataset, no significant difference was apparent in any ischemic endpoint between 1-year and ≤6-month DAPT, regardless of the risk strata. In the overall dataset, there was no significant difference in the risk of clinically relevant bleeding between 1-year and ≤6-month DAPT; however, among 2,508 patients at increased risk of bleeding, 1-year compared with ≤6-month DAPT was associated with greater bleeding (HR: 2.80) without a reduced risk of ischemic events in any risk strata, including those with ACS. These results were consistent in a network meta-analysis (Palmerini T et al, *J Am Coll Cardiol* 2021;78:1968-86).

MASTER DAPT Trial: An Abbreviated (1 Month) Vs Standard DAPT (3-12 Months) and Stopping of Antiplatelet Therapy at 6 Months After Coronary Stenting in Patients With or Without an Oral Anticoagulation (OAC) Indication Showed That at 1 Year, Ischemic and Net Risk Did Not Differ, Although Fewer Clinically Relevant Bleeding Events Occurred in the Group Without an OAC Indication

Net adverse clinical outcomes or major adverse cardiac and cerebral events did not differ with abbreviated versus nonabbreviated APT regimens in patients with OAC indication (n=1666; HR 0.83; and HR 0.88, respectively) or without OAC indication (n=2913; HR 1.01; or HR, 1.06; $P_{interaction}$=0.35 and 0.45, respectively). BARC 2, 3, or 5 bleeding did not significantly differ in patients with OAC indication (HR 0.83) but was lower with abbreviated APT in patients without OAC indication (HR 0.55; $P_{interaction}$=0.057). The difference in bleeding in patients without OAC indication was driven mainly by a reduction in BARC 2 bleedings (HR 0.48; $P_{interaction}$=0.021) (Smits PC et al, *Circulation* 2021;144:1196–1211).

MASTER-DAPT: 1-Month of Dual Antiplatelet Therapy (DAPT) Was Noninferior to ≥3-Month DAPT With Regard to Net Adverse Clinical Events and Major Adverse Cardiac or Cerebral Events (MACCE); Abbreviated Therapy Also Decreased Major or Clinically Relevant Nonmajor Bleeding

Among the 4434 patients in the per-protocol population, net adverse clinical events occurred in 165 patients (7.5%) in the abbreviated-therapy group and in 172 (7.7%) in the standard-therapy group (P<0.001 for noninferiority). A total of 133 patients (6.1%) in the abbreviated-therapy group and 132 patients (5.9%) in the standard-therapy group had a MACCE (P=0.001 for noninferiority). Among the 4579 patients in the intention-to-treat population, major or clinically relevant nonmajor bleeding occurred in 148 patients (6.5%) vs 211 (9.4%) (P<0.001 for superiority) (Valgimigli M et al, *N Engl J Med* 2021; 385:1643-55).

Dilated Cardiomyopathy (DCM) Patients With Pathogenic or Likely Pathogenic Variants Had Worse Prognosis Than Genotype-Negative Individuals

A total of 372 (37%) patients among 1,005 genotyped DCM probands had pathogenic or likely pathogenic variants (genotype positive) and 633 (63%) were genotype negative. After a median follow-up of ~4 years, the primary endpoint (composite of major adverse CV events) had occurred in 118 (31.7%) patients in the genotype-positive group and in 125 (19.8%) patients in the genotype-negative group (hazard ratio-HR: 1.51; P=0.001). Secondary endpoints were end-stage heart failure (ESHF), malignant ventricular arrhythmia (MVA), and LV reverse

remodeling (LVRR). ESHF occurred in 60 (16.1%) genotype-positive patients and in 55 (8.7%) genotype-negative patients (HR: 1.67; *P*=0.006). MVA occurred in 73 (19.6%) genotype-positive patients and in 77 (12.2%) genotype-negative patients (HR: 1.50; *P*=0.013). LVRR occurred in 39.6% in the genotype-positive group and in 46.2% in the genotype-negative group (*P*=0.047). Among individuals with baseline LVEF≤35%, genotype-positive patients exhibited more MACE, ESHF, and MVA than their genotype-negative peers (all *P*<0.02). LVRR and clinical outcomes varied depending on the underlying affected gene (Escobar-Lopez L et al, *J Am Coll Cardiol* 2021;78:1682–1699).

FUTURE trial: No Evidence that an FFR-Guided Treatment Strategy in Patients with Multivessel CAD Reduced the Risk of Ischemic CV Events or Death at 1-Year Follow-Up

The trial which randomized (1:1) to treatment strategy based on functional flow reserve (FFR) in all stenotic (≥50%) coronary arteries or to a traditional strategy without FFR, was stopped prematurely after a safety analysis of 927 patients. At 1-year, by intention to treat, there were no significant differences in MACCE rates between groups (14.6% in the FFR group vs 14.4% in the control group; hazard ratio-HR: 0.97; *P*=0.85). The difference in all-cause mortality was nonsignificant, 3.7% vs 1.5% (HR 2.34; *P*=0.06), and this was confirmed with a 24 months' extended follow-up. FFR reduced the proportion of revascularized patients, with more patients referred to exclusively medical treatment (*P*=0.02) (Rioufol G et al, *J Am Coll Cardiol* 2021;78:1875-85).

A Total of 85% of Surgical AVR (SAVR) Patients Receiving Bioprostheses Have Low Surgical Risk / Estimated Survival is Substantial Following SAVR, Especially in Younger, Low-Risk Patients, Which Should be Considered in Heart Team Discussions

Patients ≥60 years with aortic stenosis who underwent isolated SAVR with a bioprosthesis (n = 8,353) were risk-stratified before surgery into low (n=7,123, 85.1%), intermediate (n=942, 11.3%), or high surgical risk (n=288, 3.5%) using the logistic EuroSCORE or EuroSCORE II. Median survival time was 10.9 years in low-risk, 7.3 years in intermediate-risk, and 5.8 years in high-risk patients. The 5-year cumulative mortality was 16.5%, 30.7%, and 43.0%, respectively. In low-risk patients, median survival time ranged from 16.2 years in patients aged 60 to 64 years to 6.1 years in patients aged ≥85 years. Age was associated with 5-year mortality only in low-risk patients (interaction *P*< 0.001) (Martinsson A et al, *J Am Coll Cardiol* 2021; 78:2147–57).

Exercise-Induced Ventricular Ectopy: High-Grade PVCs Occurring During Recovery vs During Exercise Were Associated With Long-Term Risk of CV Mortality in Asymptomatic Individuals

Among 5,486 asymptomatic individuals (aged 45.4 ± 10.8 years; 42% women), during a mean of 20.2±3.9 years, 840 deaths occurred, including 311 CV deaths. High-grade PVCs occurred during exercise in 1.8% of individuals, during recovery in 2.4%, and during both in 0.8%. After adjusting for several parameters, high-grade PVCs during recovery were associated with CV mortality (hazard ratio -HR: 1.82; *P*=0.006), which remained significant after further adjusting for exercise duration, heart rate recovery, achieving target heart rate, and ST-segment depression (HR: 1.68; *P*=0.020). Results were similar by clinical subgroups. High-grade PVCs occurring during the exercise phase were not associated with increased risk. Recovery PVCs did not improve 20-year CV mortality risk discrimination beyond clinical variables (Refaat MM et al, *J Am Coll Cardiol* 2021;78:2267–77).

TOMAHAWK Trial: Among Patients With Resuscitated Out-Of-Hospital Cardiac Arrest Without ST-Segment Elevation, Performing Immediate Angiography Provided No Benefit Over a Delayed or Selective Strategy Regarding 30-Day Mortality Risk

At 30 days, among 554 patients, 143 of 265 patients (54%) in the immediate-angiography group and 122 of 265 patients (46%) in the delayed-angiography group had died (hazard ratio-HR, 1.28; P=0.06). The composite of death or severe neurologic deficit occurred more frequently in the immediate-angiography group (in 164 of 255 patients [64.3%]) than in the delayed-angiography group (in 138 of 248 patients [55.6%]), for a relative risk of 1.16. Values for peak troponin release and for the incidence of moderate or severe bleeding, stroke, and renal-replacement therapy were similar in the two groups (Desch S et al, *N Engl J Med* 2021; 385:2544-53).

CLICK Trial: Among Patients With Advanced Chronic Kidney Disease (CKD) and Poorly Controlled Hypertension, Chlorthalidone vs Placebo Therapy Improved Blood-Pressure Control at 12 Weeks

A total of 160 patients (baseline eGFR 23.2±4.2 ml/min/1.73m^2, mean number of antihypertensive drugs 3.4±1.4; mean 24-hour ambulatory systolic BP 142.6±8.1 mmHg / diastolic BP 74.6±10.1 mmHg in the chlorthalidone group and 140.1±8.1 mm Hg & 72.8±9.3 mm Hg in the placebo group, respectively) were randomized to chlorthalidone vs placebo; 121 (76%) had diabetes mellitus and 96 (60%) were receiving loop diuretics. The adjusted change in 24-hour systolic BP from baseline to 12 weeks was −11.0 mm Hg vs −0.5 mm Hg (P<0.001). The percent change in the urinary albumin-to-

creatinine ratio from baseline to 12 weeks was lower in the chlorthalidone group than in the placebo group by 50 percentage points. Hypokalemia, reversible increases in serum creatinine level, hyperglycemia, dizziness, and hyperuricemia occurred more often in the chlorthalidone group (Agarwal R et al, *N Engl J Med* 2021; 385:2507-19).

EMPEROR Preserved Trial: In Patients With HFpEF, Empagliflozin Reduced the Risk and Severity of Several Inpatient and Outpatient Worsening Heart Failure (HF) Events

Among 5988 patients with class II-IV HF with an LVEF of >40%, empagliflozin reduced the combined risk of CV death, hospitalization for HF, or an emergency or urgent HF visit requiring IV treatment (432 vs 546 patients; hazard ratio-HR 0.77; *P*<0.0001). This benefit reached significance at 18 days after randomization. Empagliflozin reduced the number of HF hospitalizations that required intensive care (HR 0.71; *P*=0.028) and the number of all hospitalizations that required a vasopressor or positive inotropic drug (HR 0.73; *P*=0.033). Fewer patients in the empagliflozin group vs placebo reported outpatient intensification of diuretics (482 vs 610; HR 0.76; *P*<0.0001), and patients assigned to empagliflozin were 20-50% more likely to have a better NYHA class, with significant effects at 12 weeks that were maintained for at least 2 years. The benefit on total HF hospitalizations was similar in patients with an LVEF of >40% to <50% and 50% to <60%, but was attenuated at higher LVEFs (Packer M et al, *Circulation* 2021;144: 1284-94).

EMPEROR-Preserved: Empagliflozin Reduced the Risk of CV Death or Hospitalization for Heart Failure (HF) in Patients With HF and a Preserved Ejection Fraction (HFpEF), Regardless of Diabetes Presence

Among 5988 patients with class II–IV HF and an LVEF of >40% randomized to empagliflozin (10 mg qd) or placebo, in addition to usual therapy, over a median of 26.2 months, a primary outcome event (composite of CV or hospitalization for HF) occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (HR, 0.79; P<0.001). This effect was mainly related to a lower risk of hospitalization for HF in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for HF was lower in the empagliflozin than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin (Anker SD et al, *N Engl J Med* 2021; 385:1451-61).

TEMPO: Compared With Placebo, Metoprolol Reduced LVOT Obstruction at Rest and During Exercise, Provided Symptom Relief, and Improved Quality of Life (QOL) in Patients With Obstructive HCM With no Change in Maximum Exercise Capacity

Among 29 patients with obstructive HCM and NYHA class ≥II symptoms, compared with placebo, the LVOT gradient during metoprolol was lower at rest (25 mm Hg vs 72 mm Hg; *P*=0.007), at peak exercise (28 mm Hg vs 62 mm Hg; *P*<0.001), and postexercise (45 mm Hg vs 115 mm Hg; *P*<0.0001). During metoprolol treatment, 14% of patients were in NYHA class III or higher compared with 38% of patients receiving placebo (*P*<0.01). Similarly, no patients were in CCS class III or higher during metoprolol treatment compared with 10% during placebo treatment (*P*<0.01). These findings were confirmed by higher QOL during metoprolol treatment (76.2±16.2 vs 73.8±19.5; *P*=0.039). Measures of exercise capacity, peak oxygen consumption, and N-terminal pro–B-type natriuretic peptide did not differ between the study arms (Dybro AM et al, *J Am Coll Cardiol* 2021; 78:2505–2517).

Influenza Vaccination Early After an MI or in High-Risk Coronary Artery Disease Resulted in a Lower Risk of a Composite of All-Cause Death, MI, or Stent Thrombosis, and a Lower Risk of All-Cause Death and CV Death, at 1 Year Compared With Placebo

Among 2571 patients randomized to influenza vaccine (n=1290) or to placebo (n=1281), with 2532 of these receiving the study treatment (1272 influenza vaccine and 1260 placebo), over 1-year, the primary outcome (composite of all-cause death, MI, or stent thrombosis) occurred in 67 (5.3%) assigned influenza vaccine and 91 (7.2%) assigned placebo (HR, 0.72; *P*=0.040). Rates of all-cause death were 2.9% and 4.9% (HR 0.59; *P*=0.010), rates of CV death were 2.7% and 4.5%, (HR 0.59; *P*=0.014), and rates of MI were 2% and 2.4% (HR, 0.86; *P*=0.57) in the influenza vaccine and placebo groups, respectively (Frobert O et al, *Circulation* 2021;144:1476-84).

The Amulet Occluder Was Noninferior for Safety and Efficacy of Stroke Prevention for Nonvalvular Atrial Fibrillation (AF) vs the Watchman Device and Superior for LAA Occlusion / Procedure-Related Complications Were Higher With the Amulet Occluder and Decreased With Operator Experience

Among 1878 patients enrolled, the Amulet occluder was noninferior to the Watchman device for the primary safety end point (14.5% vs 14.7%; *P*<0.001 for noninferiority). Major bleeding and all-cause death were similar between groups (10.6% vs 10.0% & 3.9% vs 5.1%, respectively). Procedure-related complications were higher for the Amulet occluder (4.5% vs 2.5%), related to more frequent pericardial effusion and device embolization. The Amulet occluder was noninferior to the

Watchman device for the primary effectiveness end point (2.8% vs 2.8%; *P*<0.001 for noninferiority), and the composite of stroke, systemic embolism, or CV/ unexplained death (5.6% vs 7.7%; *P*<0.001 for noninferiority). The rate of major bleeding was similar between groups (11.6% vs 12.3%; *P*=0.32 for superiority). LAA occlusion was higher for the Amulet occluder than for the Watchman device (98.9% vs 96.8%; *P*<0.001 for noninferiority; *P*=0.003 for superiority) (Lakkireddy D et al, *Circulation* 2021;144:1543-52).

Antero–Lateral (AL) Electrode Positioning Was More Effective Than Antero–Posterior (AP) Electrode Positioning for Biphasic Cardioversion (CV) of Atrial Fibrillation (AF)

Among 468 patients randomized to AL (n=233) vs AP (n=234) positioning of the adhesive electrodes for AF conversion, the primary outcome (restored sinus rhythm-SR) occurred in 126 patients (54%) assigned to the AL electrode position and in 77 patients (33%) assigned to the AP electrode position (*P*<0.001). The number of patients in SR after the final CV shock was 216 (93%) assigned to AL electrode positioning and 200 (85%) assigned to AP electrode positioning. There were no significant differences between groups in any safety outcomes (Schmidt AS et al, *Circulation* 2021;144:1995-2003).

N.B.: the diagram of AP positioning of the adhesive electrode pads in this article shows part of the anterior pad over the sternum (instead of parasternal positioning) and part of the posterior pad over the scapula (instead of infrascapular positioning) which limit current conduction.

RE-SPECT ESUS Trial: Clinical Variables, e.g., Older Age, Higher BMI, Hypertension, and Absence of Diabetes, and, When Available, NT-ProBNP Levels, Could Help Identify a Population of Patients With Embolic Stroke of Undetermined Source Who are at Higher Risk of Developing Atrial Fibrillation (AF) and May Benefit From Prolonged Cardiac Monitoring

Of 5390 patients enrolled in an RCT assessing dabigatran vs aspirin for the prevention of recurrent stroke in patients with embolic stroke of undetermined source (ESUS) and followed for a median of 19 months, 403 (7.5%) were found to develop AF. In the multivariable model, older age (odds ratio-OR for 10-year increase, 1.99; *P*<0.001), hypertension (OR, 1.36; *P*=0.0304), diabetes (OR, 0.74; *P*=0.022), and BMI (OR for 5-U increase, 1.29; *P*<0.001) were independent predictors of AF during the study. In a sensitivity analysis restricted to 1117 patients with baseline NT-proBNP measurements, only older age and higher NT-proBNP were significant independent predictors of AF. Performance of several published predictive models was assessed, including HAVOC (AF risk score based on hypertension, age ≥75 years, valvular heart disease, peripheral vascular disease, obesity, heart failure, and CAD) and CHA_2DS_2-VASc scores, and higher scores were associated with higher rates of developing AF (Bahit MC et al, *Circulation* 2021;144:1738-46).

Meta-Analysis: Marine ω-3 Supplementation Was Associated With an Increased Risk of AF

Meta-analysis of 7 studies comprising 81,210 patients (mean age 65 years, 39% female) with 58,939 (72.6%) enrolled in trials testing ≤1 g/d and 22,271 (27.4%) in trials testing >1 g/d of ω-3 fatty acids, showed that over a mean of 4.9 years, the use of marine ω-3 fatty acid supplements was associated with an increased risk of AF (n=2905; HR, 1.25; *P*=0.013). In analyses stratified by dose, the HR was greater in the trials testing >1 g/d (HR, 1.49; *P*=0.042) compared with those testing ≤1 g/d (HR, 1.12; *P*=0.024; *P* for interaction <0.001). In meta-regression, the HR for AF increased per 1 g higher dosage of ω-3 fatty acids dosage (HR, 1.11; *P*=0.001) (Gencer B et al, *Circulation* 2021;144:1981-90).

Myocarditis Post-mRNA Vaccine Against Covid-19

Among patients in a large Israeli health care system who had received at least one dose of the BNT162b2 mRNA vaccine, the estimated incidence of myocarditis was 2.13 cases per 100,000 persons; the highest incidence was among male patients aged 16-29 years. Most cases of myocarditis were mild or moderate in severity (Witberg G et al, *N Engl J Med* 2021; 385:2132-2139).

The incidence of myocarditis, although low, increased after the BNT162b2 vaccine, particularly after the second dose among young males. The clinical presentation of myocarditis after vaccination was usually mild. Of 283 cases of myocarditis, 142 occurred after receipt of the BNT162b2 vaccine, with 136 diagnoses being definitive or probable. The clinical presentation was mild in 129 recipients (95%); one fulminant case was fatal. The overall risk difference between the first and second doses was 1.76 per 100,000 persons, with the largest difference among males between the ages of 16 and 19 years. As compared with the expected incidence based on historical data, the standardized incidence ratio was 5.34 and was highest after the second dose in males aged 16-19 years (13.60). The rate ratio 30 days after the second vaccine dose in fully vaccinated recipients, as compared with unvaccinated persons, was 2.35; the rate ratio was again highest in male recipients aged 16-19 years (8.96), with a ratio of 1 in 6637 (Mevorach D et al, *N Engl J Med* 2021; 385:2140-2149).

AXIOMATIC-TKR: Postoperative Factor XIa Inhibition With Oral Milvexian in Patients Undergoing Knee Arthroplasty Prevented Venous Thrombo-embolism (VTE) and Conferred a Low Risk of Bleeding

Among patients receiving milvexian bid, VTE developed in 27 of 129 (21%) taking 25 mg, in 14 of 124 (11%) taking 50 mg, in 12 of 134 (9%) taking 100 mg, and

in 10 of 131 (8%) taking 200 mg. Among those receiving milvexian qd, VTE developed in 7 of 28 (25%) taking 25 mg, in 30 of 127 (24%) taking 50 mg, and in 8 of 123 (7%) taking 200 mg, vs 54 of 252 patients (21%) on enoxaparin. The dose–response relationship with bid milvexian was significant (one-sided P<0.001), and the 12% incidence of VTE with bid milvexian was lower than the prespecified benchmark of 30% (one-sided P<0.001). Bleeding of any severity occurred in 4% taking milvexian and in 4% taking enoxaparin; major or clinically relevant nonmajor bleeding occurred in 1% and 2%, respectively; serious adverse events were reported in 2% and 4%, respectively (Weitz JI et al, *N Engl J Med* 2021; 385:2161-72).

***TALOS-AMI:* In Stabilized Patients With Acute MI After PCI, a Uniform Unguided De-Escalation Strategy Significantly Reduced the Risk of Net Clinical Events up to 1 Year, Mainly by Reducing Bleeding Events**

Of 2697 patients, 1349 were randomized to de-escalation and 1348 to active control groups. At 1 year, the primary endpoints (CV death, MI, stroke, or BARC bleeding type 2, 3, or 5) occurred in 59 (4.6%) in the de-escalation group and 104 (8.2%) patients in the active control group ($p_{non\text{-}inferiority}$<0·001; HR 0.55, $p_{superiority}$= 0.0001). There was no significant difference in composite of CV death, MI, or stroke between de-escalation (2.1%) and the active control group (3.1%; HR 0.69; p=0.15). Composite of BARC 2, 3, or 5 bleeding occurred less frequently in the de-escalation group (3% *vs* 5.6%, HR 0.52; p=0.0012) (Kim CJ et al, *Lancet* 2021;398:1305-16).

An Artificial Intelligence (AI)-Based Clustering Approach Detected Prognostic Response from β-Blockers (βBs) in Patients With Heart Failure and Reduced LVEF (HFrEF), Including Patients in Sinus Rhythm With Suboptimal Efficacy, and a Cluster of Younger AF Patients Where βBs Reduced Mortality

Among 15,659 patients with HFrEF (LVEF <50%, mean 27%; median age 65 years; 24% women) In sinus rhythm (n=12,822), AI clustering demonstrated a consistent overall mortality benefit from βBs, with odds ratios (ORs) ranging from 0.54 to 0.74. One cluster in sinus rhythm of older patients with less severe symptoms showed no significant efficacy (OR 0.86; p=0.22). In atrial fibrillation (n=2837), 4 of 5 clusters were consistent with the overall neutral effect of βBs vs placebo (OR 0·92; p=0.37). One cluster of younger AF patients at lower mortality risk but similar LVEF to average had a statistically significant reduction in mortality with βBs (OR 0.57; p=0.023). The robustness and consistency of clustering was confirmed for all models (p<0.0001 *vs* random), and cluster membership was externally validated across the 9 independent trials (Karwath A et al, *Lancet* 2021; 398: 1427-35).

STROKESTOP: Screening for Atrial Fibrillation (AF) Showed a Small Net Benefit Compared With Standard of Care, Indicating That Screening is Safe and Beneficial in Older Populations

Among 28,768 individuals randomly assigned to screening (n=13,979, with only 7165 or 51.3% finally participating) or the control group (n=13,996), over a median of 6.9 years, fewer primary endpoint events (stroke, systemic embolism, bleeding leading to hospitalization, and all-cause death) occurred in the intervention group (4456 or 31.9% of 13 979; 5.45 events per 100 years) than in the control group (4616 or 33% of 13 996; 5.68 events per 100 years; hazard ratio-HR 0·96; p=0·045) (Svennberg E et al, *Lancet* 2021;398:1498-1506).

LOOP Study: In Persons With Stroke Risk Factors, ILR Screening Revealed a 3-Fold Increase in AF Detection and Anticoagulation Initiation But No Reduction in Stroke Risk or Systemic Embolism, Implying That Not All AF is Worth Screening for, and Not All Screen-Detected AF Merits Anticoagulation

Among 6004 persons (age 74.7±4.1 years, 47.3% women, and 90.7% with hypertension) randomized, 1501 (25%) to implantable loop recorder (ILR) monitoring and 4503 (75%) to usual care, over a median of 64.5 months, AF was diagnosed in 1027 persons: 477 (31.8%) of 1501 in the ILR group vs 550 (12.2%) of 4503 in the control group (HR 3.17; p<0·0001). Oral anticoagulation was initiated in 1036 persons: 29.7% vs 13.1% respectively (HR 2.72; p<0.0001), and the primary outcome (time to first stroke or systemic embolism) occurred in 318 (315 stroke, 3 embolism): 4.5% in the ILR group vs 5.6% in the control group (HR 0.80; p=0.11). Major bleeding occurred in 221 participants: 4.3% vs 3.5% respectively (HR 1.26; p=NS) (Svendsen JH et al, *Lancet* 2021;398:1507-16).

Meta-Analysis: BP Lowering Prevents New-Onset Type 2 Diabetes (T2D) / Pharmacological Interventions Have Different Effects on T2D, With ACE Inhibitors and ARBs Having the Most Favorable Outcomes

Data from 19 RCTs with one-stage individual participant data meta-analysis or 22 trials with individual participant data network meta-analysis comprising patients with hypertension (N=145,939; 60.6% men) investigating the effect of blood pressure (BP) lowering per se on the risk of new-onset T2D, showed that over a median of 4.5 years, 9883 were diagnosed with new-onset T2D. Systolic blood pressure reduction by 5 mmHg reduced the risk of T2D across all trials by 11% (HR 0.89). Investigation of the effects of 5 major classes of antihypertensive drugs showed that compared to placebo, ACE inhibitors (RR 0.84) and ARBs (RR 0.84) reduced the risk of new-onset T2D; however, use of β blockers (RR 1.48) and thiazide diuretics (RR 1.20) increased this risk, and no material

effect was found for calcium channel blockers (RR 1.02) (Nazarzadeh M et al, *Lancet* 2021;398:1803-1810).

PALACs: Posterior Left Pericardiotomy is Effective in Reducing the Incidence of Atrial Fibrillation (AF) After Surgery on Coronary Arteries, Aortic Valve, or Ascending Aorta, or a Combination Without Additional Risk of Postoperative Complications

Among 420 patients (median age 61 years, 24% female, median CHA_2DS_2-VASc score of 2.0) randomized to the posterior left pericardiotomy group (n=212) or the no intervention group (n=208), intention-to-treat analysis showed that the incidence of postoperative AF was lower in the posterior left pericardiotomy group than in the no intervention group (17% *vs* 32%, p=0.0007; odds ratio adjusted for the stratification variable 0.44, p=0.0005). Two (1%) of 209 patients in the posterior left pericardiotomy group and one (<1%) of 211 in the no intervention group died within 30 days after discharge. The incidence of postoperative pericardial effusion was lower in the posterior left pericardiotomy group (12% *vs* 21%; relative risk 0.58). Postoperative major adverse events occurred in 3% vs 2% in the two groups. No posterior left pericardiotomy related complications were seen (Gaudino M et al, *Lancet* 2021;398:2075-83).

Smoking Cessation, But Not Reduction, Reduces Cardiovascular Disease (CVD) Risk

A total of 897 975 current smokers aged ≥40 years who had undergone two consecutive national health examinations were classified as quitters (20.6%), reducers I (≥50% reduction, 7.3%), reducers II (20–50% reduction, 11.6%), sustainers (45.7%), and increasers (≥20% increase, 14.5%). During follow-up, 17 748 stroke (3.2/1000 person years-PY) and 11 271 MI (2.0/1000 PY) events were identified. Quitters had decreased risk of stroke (adjusted hazard ratio - aHR 0.77) and MI (aHR 0.74) compared to sustainers after adjustment for demographic factors, comorbidities, and smoking status. The risk of stroke and MI incidence in reducers I (aHR 1.02 and aHR 0.99, respectively) and reducers II (aHR 1.00 and aHR 0.97, respectively) was not significantly different from the risk in sustainers. Further analysis with a subgroup who underwent a later examination showed that those who quit at the second examination but had starting smoking again by the third examination had 42–69% increased risk of CVD compared to sustained quitters (Jeong S-M et al, *Eur Heart J 2021;* 42:4141-53).

Meta-Analysis: Among Patients With Left Main Disease and, Mostly Low or Intermediate Coronary Anatomical Complexity, There Was No Difference in 5-Year All-Cause Death Between PCI and CABG

Meta-analysis of 4 RCTs (SYNTAX, PRECOMBAT, NOBLE, & EXCEL) comprising 4394 patients (median SYNTAX score of 25) randomized to PCI (n=2197) or CABG (n=2197), showed that the Kaplan-Meier estimate of 5-year all-cause death was 11.2% with PCI and 10.2% with CABG (HR 1.10; p=0.33). In Bayesian analyses, there was an 85.7% probability that death at 5 years was greater with PCI than with CABG; this difference was more likely than not less than 1% (<0.2% per year). The numerical difference in mortality was due more to non-CV than CV death. Spontaneous MI (6.2% *vs* 2.6%; HR 2·35; p<0.0001) and repeat revascularization (18.3% *vs* 10.7%; HR 1.78; p<0.0001) were more common with PCI. Differences in procedural MI between strategies depended on the definition used. Overall, there was no difference in the risk of stroke (2.7% vs 3.1%; HR 0.84; p=0.36), but the risk was lower with PCI in the first year (HR 0.37) (Sabatine MS et al, *Lancet* 2021;398:2247-57).

TWILIGHT-HBR: Among High Bleeding Risk (HBR) Patients Having PCI Completing 3-Month DAPT Without Major Adverse Events, Stopping Aspirin Followed by Ticagrelor Monotherapy Reduced Bleeding Without Increasing Ischemic Events

After 3 months of ticagrelor plus aspirin, event-free patients were randomized to 1 year of aspirin or placebo added to ticagrelor. A total of 1064 (17.2%) had HBR. Ticagrelor monotherapy reduced the incidence of the primary endpoint of BARC 2, 3, or 5 bleeding compared with ticagrelor plus aspirin in HBR (6.3% vs 11.4%; HR 0.53) and non-HBR patients (3.5% vs 5.9%; HR 0.59) with similar relative ($P_{interaction} = 0.67$) but a trend towards greater absolute risk reduction in the former (P=0.130). A similar pattern occurred for more severe BARC 3 or 5 bleeding with a larger absolute risk reduction in HBR patients (-3.5% vs -0.5%; P=0.008). There was no difference in the key secondary endpoint of death, MI, or stroke between treatment arms, irrespective of HBR status (Escaned J et al, *Eur Heart J* 2021;42: 4624-34).

APAF-CRT: Ablation + CRT Was Superior to Pharmacotherapy in Reducing Mortality in Patients With Permanent AF and Narrow QRS Who Were Hospitalized for HF, Irrespective of Their Baseline EF

A total of 133 patients (age 73 ± 10 years, 47% females) with symptomatic permanent AF >6 months, narrow QRS (≤110 ms) and at least one HF hospitalization in the previous year were randomized to Ablation + CRT or to rate control. The trial was stopped for efficacy at interim analysis after a median of 29 months of follow-up per patient. The primary endpoint occurred in 7 patients (11%) in the Ablation + CRT arm and in 20 patients (29%) in the Drug arm (HR 0.26, P = 0.004). The estimated death rates at 2 years were 5% and 21%, respectively; at 4 years, 14% and 41%. The benefit of Ablation + CRT of all-cause mortality was similar in patients with LVEF ≤35% and in those with >35%. The secondary endpoint combining all-

cause mortality or HF hospitalization was lower in the Ablation + CRT arm (29% vs. 51%; HR 0.40, $P = 0.002$) (Brignole M et al; *Eur Heart J* 2021;42:4731–4739).

Permanent Pacemaker (PPM) Implantation at Baseline and Within 30 Days Post-TAVI is Independently Associated With Higher Mortality and Heart Failure (HF) Hospitalization During Follow-Up

A retrospective study evaluated outcomes associated with PPM after TAVI among 49,201 patients. A total of 29,422 patients had follow-up ≥6 months (median 1.7 years), 22% already had PPM, and 22% underwent PPM within the first 30 days post-TAVI. Adjusted hazard ratios for the combined risk of all-cause death and hospitalization for HF, during the whole follow-up, were higher in both patients with a previous PPM and in those implanted within 30 days (hazard ratio 1.12 and 1.11, respectively) (Clementy N et al, *Heart Rhythm* 2021;18:2027-2032).

SAPIEN 3 (S3) Valve Recipients with New-Onset LBBB Have High Arrhythmic Burden/>1/3 Exhibit ≥1 Arrhythmic Episode Within 1 Year (10% AV Block) / ~1/2 of Bradyarrhythmic Events Occur within 1 Month

Among 104 TAVI patients with new-onset persistent LBBB following TAVI with the S3 valve, an implantable cardiac monitor revealed at least 1 significant arrhythmic event in 40 (38.5%), leading to a treatment change in 17 (42.5%). Bradyarrhythmias occurred in 20 of 104 patients (19.2%) (34 AV block, 252 severe bradycardia episodes), with 10 of 20 patients (50%) exhibiting at least 1 episode of high-degree/complete AVB with 60% occurring within 1 month. Permanent pacemaker was implanted in 9 (8.7%) over 1 year (6 AVB, 3 severe bradycardia) (Muntané-Caro G et al, *Heart Rhythm* 2021;18:1733-40).

Important Review and Other Articles

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

● **Bridging Antiplatelet Therapy After PCI** (Sullivan AE et al, *J Am Coll Cardiol* 2021;78:1550–63)

Lipid-Modulating Agents for Prevention or Treatment of COVID-19 (Talasaz AH et al, *JACC* 2021;78:1635-54)

● **New Therapies for Lowering Triglyceride-Rich Lipoproteins** (Rosenson RS et al, *JACC* 2021;78:1817-30)

● **Familial Hypercholesterolemia** (Brandts J & Ray KK, *J Am Coll Cardiol* 2021;78:1831-43)

● **AHA/ACC vs ESC Guidelines for Adults With Congenital Heart Disease** (Assenza GR et al, *JACC* 2021;78:1904-18)

● **In-Hospital Initiation of SGLT-2 Inhibitors for HFrEF** (Rao VN et al, *J Am Coll Cardiol* 2021;78:2004-12)

● **AHA Statement for Diagnosis and Management of Patients With Myocardial Injury After Noncardiac Surgery** (Ruetzler K et al, *Circulation* 2021;144:e287–e305)

● **Epicardial adipose tissue** accumulation is closely **associated with atrial and ventricular arrhythmias** and with ECG signs associated with arrhythmogenesis (Ernault MC et al, *J Am Coll Cardiol* 2021;78:1730–45)

● **Myocardial bridging** (Sternheim D et al**,** *J Am Coll Cardiol* 2021;78:2196–2212)

● **Antithrombotic Therapy in Patients Undergoing Transcatheter Interventions for Structural Heart Disease** (Calabro P et al, *Circulation* 2021;144:1323–43)

● **Inflammation & Immune Response in Arrhythmogenic Cardiomyopathy** (Asatryan B et al, *Circulation* 2021; 144:1646-55)

● **Exercise-Induced Cardiac Troponin Elevations** (Aengevaeren VL et al, *Circulation* 2021;144:1955-72)

● **2021 AHA Dietary Guidance to Improve CV Health** (Lichtenstein AH et al, *Circulation* 2021;144:e472–e487)

● **2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain** (Gulati M et al, *Circulation* 2021;144:e368–e454)

● **Heart failure** (Metra M & Teerlink JR, *Lancet* 2021;390:1981-95)

● **Hypertrophic cardiomyopathy** (Ommen SR et al, *Lancet* 2021;398:2102-2108)

● **Management of acute cardiovascular complications in pregnancy** (Assenza GE et al, *Eur Heart J* 2021;42:4224–40)

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

● **Pollution and the Heart** (Rajagopalan S et al, *N Engl J Med* 2021;385:1881-1892)

● **Salt handling and blood pressure** (Ellison DH & Welling P, *N Engl J Med* 2021; 385:1981-1993)

● **Pulmonary arterial hypertension** (Hassoun PM et al, *N Engl J Med* 2021; 385:2361-2376)

● **COVID-19 and cardiac injury & infarction** (Manolis AS et al, J *Cardiovasc Pharmacol Ther* 2021**;**26:399-414)

● **Update on Cilostazol's antithrombotic & CV actions and its clinical applications** (Manolis AA et al, *J Clin Pharmacol* 2021 Oct 20. doi: 10.1002/jcph.1988. Online ahead of print)

● **Lipoprotein(a) & CVD** (Melita H, *J Cardiovasc Pharmacol* 2021 Oct 20.doi:10.1097/FJC.0000000000001160.Online ahead of print)

● **Cardiovascular benefits of caffeinated beverages** (Manolis AA et al, *Curr Med Chem* 2021 Jul 7. doi: 10.2174/ 0929867328666210708091709

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

● **The Stanford experience of heart transplantation over 5 decades** (Zhu Y et al, *Eur Heart J* 2021;42:4934–4943)

● **CV immunotoxicities associated with immune checkpoint inhibitors** (Dolladille C et al, *Eur Heart J* 2021; 42:4964-77)