Cardiology News / Recent Literature Review / Third Quarter 2021

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

42nd **Panhellenic Congress of Cardiology**, Athens, 21-23/10/21

AHA Sessions 2021, Boston, MA, USA, 13-15/10/21

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

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

Subanalysis of SYNTAXES: In Patients With 3-Vessel and/or Left Main Disease Having PCI or CABG, Those on Optimal Medical Therapy (OMT) at 5 Years Had a Survival Benefit at 10 Years

Among 1472 patients, patients on OMT at 5 years had a significantly lower mortality at 10 years compared with those on ≤2 types of medications (13.1% vs 19.9%; adjusted HR: 0.470; *P*=0.002) but had a mortality similar to those on 3 types of medications. Patients having CABG with antiplatelet drug and statin at 5 years had lower 10-year mortality than those without (Kawashima H et al, *J Am Coll Cardiol* 2021;78:27-38).

GALACTIC-HF: In Heart Failure (HF) Patients With Reduced Ejection Fraction (EF), Omecamtiv Mecarbil Conferred Greater Benefit as Baseline EF Decreased

The risk of the primary composite endpoint (PCE) of time-to-first HF event or CV death in the placebo group was ~1.8-fold greater in the lowest EF (≤22%) vs the highest EF (≥33%) quartile. Amongst the pre-specified subgroups, EF was the strongest modifier of the treatment effect of omecamtiv mecarbil on the PCE (P=0.004). Patients receiving omecamtiv mecarbil had a progressively greater relative and absolute treatment effect as baseline EF decreased, with a 17% relative risk reduction for the PCE in patients with baseline EF≤22% (n=2,246; HR 0.83) vs patients with EF ≥33% (n=1,750; HR 0.99; P=0.013). The absolute reduction in the PCE increased with decreasing EF (EF≤22%; risk reduction, 7.4 events per 100 patient-years; number needed to treat for 3 years = 11.8), compared with no reduction in the highest EF quartile (Teerlink JR et al, *J Am Coll Cardiol* 2021;78:97-108).

Repurposing Metoprolol for COVID-19–Associated ARDS Appears a Safe and Inexpensive Strategy That Can Alleviate the Burden of the COVID-19 Pandemic

Among 20 COVID-19 patients with ARDS on invasive mechanical ventilation randomized to metoprolol (n=12, 15 mg daily for 3 days) or control (n=8, no treatment), patients randomized to metoprolol had significantly fewer neutrophils in bronchoalveolar lavage (BAL) on day 4 (*P*=0.016). Metoprolol also reduced neutrophil extracellular traps content and other markers of lung inflammation. Oxygenation (PaO_2:FiO_2) significantly improved after 3 days of metoprolol treatment (*P*=0.003), whereas it remained unchanged in control subjects. Metoprolol-treated patients spent fewer days on invasive mechanical ventilation than those in the control group (15.5±7.6 vs 21.9±12.6 days; *P*=0.17) (Clemente-Moragon A et al, *J Am Coll Cardiol* 2021;78:1001-11)

ODYSSEY Outcomes Trial: In Patients With Recent ACS and LDL-C ~70 mg/dl on Optimized Statin Therapy, PCSK9 Inhibition Provides Incremental Benefit Only When Lipoprotein(a) is Mildly Elevated

ODYSSEY Outcomes compared alirocumab with placebo in 18,924 patients with recent ACS receiving optimized statin treatment. In 4,351 patients (23%), screening or randomization LDL-C was <70 mg/dL (median 69.4 mg/dL); in 14,573 patients (77%), both determinations were ≥70 mg/dL (median 94 mg/dL). In the lower LDL-C subgroup, MACE rates were 4.2 and 3.1 per 100 patient-years among placebo-treated patients with baseline Lp(a) greater than or less than or equal to the median (13.7 mg/dL). Corresponding adjusted treatment hazard ratios-HRs were 0.68 and 1.11, with treatment-Lp(a) interaction on MACE ($P_{interaction}$=0.017). In the higher LDL-C subgroup, MACE rates were 4.7 and 3.8 per 100 patient-years among placebo-treated patients with Lp(a) >13.7 mg/dL or ≤13.7 mg/dL; corresponding adjusted treatment HRs 0.82 and 0.89, with $P_{interaction}$= 0.43 (Schwartz GG et al, *J Am Coll Cardiol* 2021;78:421-33).

Shared Decision Making (SDM) for the Athlete With Sudden Cardiac Death–Predisposing Genetic Heart Diseases (GHDs), such as Long QT Syndrome (LQTS), and the Possibility for That Athlete's Return to Play

A total of 672 athletes with GHD including 494 athletes with LQTS (47% females; mean age at diagnosis 14.8 ± 10.5 years; mean follow-up 4.2 ± 4.8 years) were given return-to-play approval. Overall, 79 of 494 athletes with LQTS (16%) were symptomatic before diagnosis, and 58 (11.7%) had an ICD. In 2,056 combined years of follow-up, there was no GHD–sports associated mortality; 29 patients (5.9%) had ≥1 nonlethal, LQTS-associated breakthrough cardiac event. Of those, 15 (3%) were athletes at the time of the breakthrough cardiac event, with 3 (0.6%) experiencing a sports-related breakthrough cardiac event, and 12 (2.4%) a non–sports-related event. Overall, the event rate was 1.16 nonlethal events per 100

athlete-years of follow-up. This 20-year single center experience challenges the status quo of disqualification for all athletes with LQTS and provides additional observational evidence, in support of the more contemporary SDM approaches to this complex issue (Tobert KE et al, *J Am Coll Cardiol* 2021;78:594-604).

Markers of Myocardial Damage Predict Mortality in Patients With Aortic Stenosis (AS): Myocardial Fibrosis and Biventricular Remodeling Markers are the Top Predictors of Survival in AS

Among patients with severe AS undergoing aortic valve replacement (AVR) (n=440, derivation; n=359, validation cohort), over a median of 3.8 years, having CMR shortly before surgical or transcatheter AVR, there were 52 deaths in the derivation cohort and 51 deaths in the validation cohort. The 4 most predictive CMR markers were extracellular volume fraction, late gadolinium enhancement (LGE), indexed LV end-diastolic volume (LVEDVi), and RV ejection fraction. Across the whole cohort and in asymptomatic patients, risk-adjusted predicted mortality increased strongly once extracellular volume fraction was >27%, while LGE >2% showed persistent high risk. Increased mortality was also observed with both large (LVEDVi >80 mL/m^2) and small (LVEDVi ≤55 mL/m^2) ventricles, and with high (>80%) and low (≤50%) RV ejection fraction. The predictability was improved when these 4 markers were added to clinical factors. The prognostic thresholds and risk stratification by CMR variables were reproduced in the validation cohort (Kwak S et al, *J Am Coll Cardiol* 2021;78: 545-58).

Compared With Other Established Uses of DAPT, De-Escalation Was the Most Effective Strategy for ACS Treatment, Resulting in Fewer Bleeding Events Without Increasing Ischemic Events

Meta-analysis of 15 eligible RCTs, including 55,798 patients with ACS showed that de-escalation therapy was associated with reduced risk of primary bleeding outcomes (HR: 0.48 vs clopidogrel; HR: 0.32 vs ticagrelor; HR: 0.36 vs standard-dose prasugrel; and HR: 0.40 vs low-dose prasugrel) without negatively affecting primary efficacy outcomes. There were no significant differences in ischemic or bleeding outcomes between de-escalation to clopidogrel or low-dose prasugrel (Shoji S et al, *J Am Coll Cardiol* 2021;78:763-77).

DANCAVAS I+II: The Most Dominant Predictor for Having a Dilation at Any Aortic Segment is the Presence of an Aortic Dilation Elsewhere

Among 14,989 participants (14,235 men, 754 women) aged 60-74 years (mean age 68±4 years), the highest adjusted odd ratios for having any aortic dilation were observed when coexisting aortic dilations were present. Other predictors included coexisting iliac dilations, hypertension, increasing body surface area, male sex, familial disposition, and atrial fibrillation, which were present in various combinations for the different aortic parts. Smoking and acute myocardial infarction were inversely associated with ascending and abdominal dilations. Diabetes was a shared protective factor. (Obel LM et al, *J Am Coll Cardiol* 2021;78:201–211).

Predictors of Device-Related Thrombus (DRT) After Left Atrial Appendage Occlusion (LAAO)

Among 711 patients (237 with and 474 without DRT), over a median 1.6-1.8 years, DRTs were detected between days 0-45, 45-180, 180-365, and >365 in 24.9%, 38.8%, 16.0%, and 20.3% of patients. DRT presence was associated with a higher risk of the composite endpoint of death, ischemic stroke, or systemic embolization (HR: 2.37; *P*<0.001) driven by ischemic stroke (HR: 3.49; *P*=0.01). At last known follow-up, 25.3% of patients had DRT. Discharge medications after LAAO did not have an impact. Multivariable analysis identified 5 DRT risk factors: hypercoagulability disorder (odds ratio-OR 17.50), pericardial effusion (OR 13.45), renal insufficiency (OR 4.02), implantation depth >10 mm from the pulmonary vein limbus (OR: 2.41), and non-paroxysmal atrial fibrillation (OR: 1.90). Patients with ≥2 risk points for DRT had a 2.1-fold increased risk of DRT compared with those without any risk factors (Simard T et al, *J Am Coll Cardiol* 2021; 78: 297–313).

Increased Long-Term Intake of Lignans Confers Significantly Lower Risk of Total Coronary Heart Disease (CHD) in Both Men and Women

Lignans (matairesinol, secoisolariciresinol, pinoresinol, and lariciresinol) are polyphenolic substances found in plant-based foods (seeds, whole grains, fruits, vegetables, wine, tea, and coffee), efficiently processed by human gut microbiota to produce enterolignans, which are subsequently absorbed into human body. Among 214,108 men and women who did not have CHD or cancer at baseline, 10,244 CHD cases were documented, including 6,283 nonfatal MI and 3,961 fatal CHD cases. In multivariable-adjusted analyses, comparing extreme quintiles, the pooled HRs of CHD were 0.85 for total lignans, 0.76 for matairesinol, 0.87 for secoisolariciresinol, 0.89 for pinoresinol, and 0.89 for lariciresinol (all *P* values for trend ≤0.003). Nonlinear relationships were found for total lignan, matairesinol, and secoisolariciresinol: the risk reduction plateaued at intakes above ~300 μg/d, 10 μg/d, and 100 μg/d, respectively (*P*<0.01 for all nonlinearity). The inverse associations for total lignan intake were more

apparent among persons with higher total fiber intake (P=0.04 for interaction). In addition, lignan intake was more strongly associated with plasma concentrations of enterolactone when fiber intake was higher (Hu Y et al, *J Am Coll Cardiol* 2021;78:666-78)

A Healthy Sleep Pattern is Associated With Lower Risks of AF and Bradyarrhythmia, Independent of Traditional Risk Factors / the Association With AF is Modified by Genetic Susceptibility

Among 403,187 participants from UK Biobank, a healthy sleep pattern was associated with lower risks of AF (HR comparing extreme categories: 0.71) and bradyarrhythmia (HR: 0.65), but not ventricular arrhythmias, after adjustment for demographic, lifestyle, and genetic risk factors. Compared with individuals with a healthy sleep score of 0-1 (poor sleep group), those with a healthy sleep score of 5 had a 29% and 35% lower risk of developing AF and bradyarrhythmia, respectively. Additionally, the genetic predisposition to AF modified the association of the healthy sleep pattern with the risk of AF (P interaction=0.017). The inverse association of the healthy sleep pattern with the risk of AF was stronger among those with a lower genetic risk of AF (Li X et al, *J Am Coll Cardiol* 2021; 78:1197–1207).

FAST-MI: Coronary Revascularization of Latecomer STEMI Patients is Associated With Better Short and Long-Term Clinical Outcomes

Among 6,273 STEMI patients, 1,169 (18.6%) were latecomers. After exclusion of patients having fibrinolysis and patients deceased within 2 days after admission, 1,077 patients were analyzed, of whom 729 (67.7%) were revascularized within 48h after hospital admission. At 30 days, all-cause death rate was lower among revascularized latecomers (2.1% vs 7.2%; P<0.001). After a median of 58 months, all-cause death rate was 30.4 per 1,000 patient-years in the revascularized latecomers vs 78.7 per 1,000 patient-years in the nonrevascularized latecomers (P<0.001). In multivariate analysis, revascularization of latecomer STEMI patients was independently associated with a significant reduction of mortality occurrence during follow-up (HR: 0.65; P=0.001) (Bouisset F et al, *J Am Coll Cardiol* 2021; 78:1291–1305).

SYNTAX Extended Survival: Incomplete Revascularization (IR) is Common After PCI/Degree of Incompleteness was Associated With 10-Year Mortality / If Complete (or Nearly Complete) Revascularization (CR) Cannot be Achieved With PCI in Patients With 3-Vessel Disease, CABG Should be Considered

IR was more frequently observed in patients with PCI versus CABG (56.6% vs 36.8%) and more common in those with 3-vessel disease than left main CAD in both the PCI arm (58.5% vs 53.8%) and the CABG arm (42.8% vs 27.5%). Patients undergoing PCI with CR had no significant difference in 10-year all-cause death vs those undergoing CABG (22.2% for PCI with CR versus 24.3% for CABG with IR vs 23.8% for CABG with CR). In contrast, those with PCI and IR had a significantly higher risk of all-cause death at 10 years compared with CABG and CR (33.5% vs 23.7%; adjusted hazard ratio-HR, 1.48) (Takahashi K et al, *Circulation* 2021;144:96–109).

COAPT Trial: Reduced Mitral Regurgitation (MR) at 30 Days Conferred Greater Freedom From Death or Heart Failure Hospitalizations and Improved Quality of Life Through 2-Year Follow-Up Whether the MR Reduction was Achieved by TMVr or Medical Therapy

Transcatheter mitral valve repair (TMVr)-treated patients had less severe residual MR at 30d than medical therapy-treated patients (0/1+, 2+, & 3+/4+: 72.9%, 19.9%, & 7.2% vs 8.2%, 26.1%, & 65.8%, respectively, P<0.0001). The rate of composite death or heart failure hospitalizations between 30d and 2y was lower in patients with 30d residual MR of 0/1+ and 2+ compared with patients with 30d residual MR of 3+/4+ (37.7% vs 49.5% vs 72.2%, respectively, P<0.0001). This relationship was consistent in the TMVr and medical therapy arms ($P_{interaction}$=0.92). The improvement in quality of life from baseline to 30d was maintained between 30d and 2y in patients with 30d MR≤2+ but deteriorated in those with 30d MR 3+/4+ (–0.3±1.7 vs –9.4±4.6, P=0.0008) consistently in both groups ($P_{interaction}$=0.95) (Kar S et al, *Circulation* 2021;144:426–437).

EAST-AFNET4 Trial: Early Rhythm Control (ERC) Therapy Conveys Clinical Benefit When Initiated Within 1 Year of Diagnosing AF in Patients With Signs or Symptoms of Heart Failure (HF)

Analysis of 798 patients (38% female, median age 71.0 years, 785 with known LVEF) with the majority of patients having HF and preserved LVEF (n=442, LVEF≥50%, mean LVEF 61±6.3%; n=211; LVEF 40%–49%, mean LVEF 44 ± 2.9%; n=132; LVEF<40%, mean LVEF 31±5.5%), showed that over the 5.1-year median follow-up, the composite primary outcome of CV death, stroke, or hospitalization for worsening of HF or for ACS occurred less often in patients randomly assigned to ERC (94/396; 5.7 per 100 patient-years) compared with patients randomly assigned to usual care (130/402; 7.9 per 100 patient-years; hazard ratio-HR, 0.74; P=0.03), not altered by HF status (interaction P value=0.63). The primary safety outcome (death, stroke, or serious adverse events related to rhythm control therapy) occurred in 71 of 396

(17.9%) patients with HF assigned to ERC and in 87 of 402 (21.6%) patients with HF assigned to usual care (HR, 0.85; *P*=0.33). LVEF improved in both groups (LVEF change at 2 years: ERC 5.3±11.6%, usual care 4.9±11.6%, *P*=0.43). ERC also improved the composite outcome of death or hospitalization for worsening HF (Rillig A et al, *Circulation* 2021;144:845-58).

For Older Adults With AF, Apixaban Was Associated With Lower Rates of Adverse Events Across All Frailty Levels / Dabigatran and Rivaroxaban Were Associated With Lower Event Rates Only in Non-frail Patients

The role of differing levels of frailty in the choice of oral anticoagulants for older adults with atrial fibrillation (AF) was examined in 3 groups. In the dabigatran–warfarin cohort (*n*=158,730; median follow-up, 72 days), the event rate per 1000 person-years was 63.5 for dabigatran initiators and 65.6 for warfarin initiators (HR 0.98). For nonfrail, prefrail, and frail persons, HRs were 0.81, 0.98, and 1.09, respectively. In the rivaroxaban–warfarin cohort (*n*= 275,944; median follow-up, 82 days), the event rate per 1000 person-years was 77.8 for rivaroxaban initiators and 83.7 for warfarin initiators (HR, 0.98; rate difference-RD, −5.9). For nonfrail, prefrail, and frail persons, HRs were 0.88, 1.04, and 0.96, respectively. In the apixaban–warfarin cohort (*n*=218,738; median follow-up, 84 days), the event rate per 1000 person-years was 60.1 for apixaban initiators and 92.3 for warfarin initiators (HR 0.68; RD, −32.2). For nonfrail, prefrail, and frail persons, HRs were 0.61, 0.66, and 0.73, respectively. (Kim DH et al, *Ann Intern Med* 2021;174:1214-23).

COVID-19 is a Risk Factor for Acute Myocardial Infarction (MI) and Ischemic Stroke

Among 86,742 patients with COVID-19 and 348,481 matched control individuals, the incidence rate ratio (IRR) for acute MI was 2.89 for the first week, 2.53 for the second week, and 1.60 in weeks 3 and 4 following COVID-19. When day of exposure was included in the risk period, IRR was 8.44 for the first week, 2.56 for the second week, and 1.62 for weeks 3 and 4 following COVID-19. The corresponding IRRs for ischemic stroke when day of exposure was excluded from the risk period were 2.97 in the first week, 2.80 in the second week, and 2.10 in weeks 3 and 4 following COVID-19; when day of exposure was included in the risk period, the IRRs were 6.18 for the first week, 2.85 for the second week, and 2.14 for weeks 3 and 4 following COVID-19. In the matched cohort analysis excluding day 0, the odds ratio (OR) for acute MI was 3.41 and for stroke was 3.63 in the 2 weeks following COVID-19. When day 0 was included in the matched cohort study, the OR for acute MI was 6.61 and for ischemic stroke was 6·74 in the 2 weeks following COVID-19 (Katsularis I et al, *Lancet* 2021;398:599-607).

Guide-HF Trial: Hemodynamic-Guided Management of Heart Failure (HF) Using an Implantable Pulmonary Artery Pressure Monitor Did Not Reduce Mortality and Total HF Events Compared With The Control Group / A Pre-COVID-19 Impact Analysis Indicated a Possible Benefit Primarily Driven by a Lower HF Hospitalization vs the Control Group

Among 1000 patients implanted successfully, there were 253 primary endpoint events (0.563 per patient-year) among 497 patients in the hemodynamic-guided management group (treatment group) and 289 (0.640 per patient-year) in 503 patients in the control group (HR 0.88; p=0.16). A prespecified COVID-19 sensitivity analysis using a time-dependent variable to compare events before COVID-19 and during the pandemic suggested a treatment interaction ($p_{interaction}$=0.11). In the pre-COVID-19 impact analysis, there were 177 primary events (0.553 per patient-year) in the intervention group and 224 events (0.682 per patient-year) in the control group (HR 0.81; p=0.049). This difference in primary events almost disappeared during COVID-19, with a 21% decrease in the control group (0.536 per patient-year) relative to pre-COVID-19, virtually no change in the treatment group (0.597 per patient-year), and no difference between groups (HR 1.11; p=0.53). The cumulative incidence of HF events was not reduced by hemodynamic-guided management (0.85; p=0.096) in the overall study analysis but was significantly decreased in the pre-COVID-19 impact analysis (0.76; p=0.014). 1014 (99%) of 1022 patients had freedom from device or system-related complications (Lindenfeld J et al, *Lancet* 2021; 398:991-1001).

QUARTET: A Strategy With Early Treatment of a Fixed-Dose Quadruple Quarter-Dose Combination Achieved and Maintained Greater Blood Pressure (BP) Lowering Compared With the Common Strategy of Starting Monotherapy

Among 591 patients (aged 59±12 years, 60% male, 82% white; baseline mean unattended office BP 141±10/85±10 mmHg) randomly assigned to either treatment, that started with the quadpill (containing irbesartan at 37.5 mg, amlodipine at 1.25 mg, indapamide at 0.625 mg, and bisoprolol at 2.5 mg) (n=300) or an indistinguishable monotherapy control (irbesartan 150 mg) (n=291), by 12 weeks, 44 (15%) of 300 participants had additional BP medications in the intervention group compared with 115 (40%) of 291 participants in the control group. Systolic BP was lower by 6.9 mm Hg (p<0.0001) and BP control rates were higher in the intervention group

(76%) vs control group (58%; relative risk-RR 1.30; p<0.0001). There was no difference in adverse event-related treatment withdrawals at 12 weeks (4% *vs* 2.4%; p=0.27). Among the 417 patients who continued, uptitration occurred more frequently among control participants than intervention participants (p<0.0001). However, at 52 weeks mean unattended systolic BP remained lower by 7.7 mm Hg and BP control rates higher in the intervention group (81%) vs control group (62%; RR 1.32). In all randomly assigned participants up to 12 weeks, there were 7 (3%) serious adverse events in the intervention group and 3 (1%) serious adverse events in the control group (Whitlock RP et al, *Lancet* 2021; 398:1043-52).

Meta-Analysis: Pharmacological Blood Pressure (BP) Reduction is Effective Into Old Age, With no Evidence That Relative Risk Reductions for Prevention of MACE Vary by Systolic or Diastolic BP Levels at Randomization, Down to <120/70 mmHg

Among 358,707 participants from 51 RCTs (age ranging from 21 years to 105 years (median 65 years), with 42,960 (12%) participants <55 years, 128 437 (35.8%) aged 55–64 years, 128,506 (35.8%) 65–74 years, 54,016 (15.1%) 75–84 years, and 4788 (1.3%) ≥85 years, the hazard ratios-HRs for the risk of major cardiovascular events (MACE) per 5 mm Hg reduction in systolic BP for each age group were 0.82 in individuals <55 years, 0.91 in those aged 55–64 years, 0.91 in those aged 65–74 years, 0.91 in those aged 75–84 years, and 0.99 in those aged ≥85 years (adjusted $p_{interaction}$=0·050). Similar patterns of proportional risk reductions were observed for a 3-mmHg reduction in diastolic BP. Absolute risk reductions for MACE varied by age and were larger in older groups (adjusted $p_{interaction}$=0.024). There was no evidence for any clinically meaningful heterogeneity of relative treatment effects across different baseline BP categories in any age group. (BP Lowering Treatment Trialists' Collaboration et al, *Lancet* 2021; 398:19053-64).

Fixed-Dose Combination Treatment Strategies Substantially Reduce CV Disease, MI, Stroke, Revascularization, and CV Death in Primary CV Disease Prevention.

Using fixed-dose combination strategy of at least two BP lowering agents plus a statin (with or without aspirin), compared with a control strategy (either placebo or usual care) in 3 large RCTs (TIPS-3, HOPE-3, and PolyIran), with 18,162 participants (age 63±7.1 years, 50% female), estimated 10-year CV disease risk for the population was 17.7±8.7%. During a median of 5 years, the primary outcome (time to first occurrence of a composite of CV death, MI, stroke, or arterial revascularization) occurred in 276 (3%) participants in the fixed-dose combination strategy group compared with 445 (4.9%) in the control group (hazard ratio 0.62, p<0.0001). Reductions were also observed for the separate components of the primary outcome: MI (HR 0.52), revascularization (HR 0.54), stroke (HR 0.59), and CV death (HR 0.65). Significant reductions in the primary outcome and its components were observed in the analyses of fixed-dose combination strategies with and without aspirin, with greater reductions for strategies including aspirin. Treatment effects were similar at different lipid and blood pressure levels, and in the presence or absence of diabetes, smoking, or obesity. Gastrointestinal bleeding was uncommon but slightly more frequent in the fixed-dose combination strategy with aspirin group vs control (0.4% *vs* 0.2%, p=0.15). The frequencies of hemorrhagic stroke (0.2% *vs* 0.3%), fatal bleeding (<0.1% *vs* 0.1%), and peptic ulcer disease (0.7% *vs* 0.8%) were low and did not differ significantly between groups. Dizziness was more common with fixed-dose combination treatment (11.7% *vs* 9.2%, p<0.0001) (Joseph P et al, *Lancet* 2021; 398:1133-46).

Meta-Analysis: At a Mean of 2.5 years, Ultrathin-Strut Drug-Eluting Stents (DES) Reduced the Risk of Target Lesion Failure (TLF), Driven by Less Clinically Driven Target Lesion Revascularization (TLR) vs Conventional 2nd-Generation Thin-Strut DES, With Similar Risks of MI, Stent Thrombosis (ST), Cardiac Death, and All-Cause Mortality

Meta-analysis of 16 RCTs (N=20,701) comparing ultrathin-strut DES to conventional 2nd-generation thin-strut DES showed that over a mean of 2.5 years, ultrathin-strut DES were associated with a 15% reduction in long-term TLF compared with conventional 2nd-generation thin-strut DES (relative risk-RR 0.85, *P* = 0.008) driven by a 25% reduction in clinically driven TLR (RR 0.75, *P* = 0.005). There were no significant differences between stent types in the risks of MI, ST, cardiac death, or all-cause mortality (Madhavan MV et al, *Eur Heart J* 2021;42:2643–54).

CASPER Registry: Short-Coupled (Idiopathic) Ventricular Fibrillation (SCVF) is a Distinct Primary Arrhythmia Syndrome Accounting for at Least 6.6% of Unexplained Cardiac Arrest (UCA) / Quinidine is Effective in SCVF and Should be Considered as First-Line Treatment for Patients With Recurrent Episodes

The short-coupled ventricular fibrillation (SCVF), initiated by a trigger PVC with a coupling interval of <350 ms, was diagnosed in 24 of 364 (6.6%) UCA survivors with the he diagnosis of SCVF obtained in 19/24

(79%) individuals by documented VF during follow-up. Ventricular arrhythmia was initiated by a mean PVC coupling interval of 274 ± 32 ms. Electrical storm occurred in 21% of SCVF probands but not in any UCA proband ($P < 0.001$). The median time to recurrent ventricular arrhythmia in SCVF was 31 months. Half (12/24) of patients with recurrent VF received quinidine with excellent arrhythmia control (Steinberg C et al, *Eur Heart J* 2021; 42:2827–238).

Meta-Analysis: High Adiposity is Associated With Increased CVD Risk Despite Divergent Evidence Gradients / Adiposity Was a Causal Risk Factor for CVD Except All-Cause Mortality and Stroke

Twelve systematic reviews with 53 meta-analyses results (including over 501 cohort studies) and 12 Mendelian randomization (MR) studies indicated that a body mass index (BMI) increase was associated with higher risks of coronary heart disease, heart failure, atrial fibrillation, all-cause stroke, hemorrhagic stroke, ischemic stroke, hypertension, aortic valve stenosis, pulmonary embolism, and venous thrombo-embolism. The MR study results demonstrated a causal effect of obesity on all indices but stroke. The CVD risk increase for every 5 kg/m^2 increase in BMI varied from 10% (RR 1.10; certainty of evidence, low) for hemorrhagic stroke to 49% (RR 1.49; certainty of evidence, high) for hypertension. The all-cause and CVD-specific mortality risks increased with adiposity in cohorts, but the MR studies demonstrated no causal effect of adiposity on all-cause mortality (Kim MS et al, *Eur Heart J* 2021;42:3388–3403)

DAPA-HF: Dapagliflozin Reduced the Risk of Any Serious Ventricular Arrhythmia, Cardiac Arrest, or Sudden Death When Added to Conventional Therapy in Patients With HFrEF

A *post hoc* analysis of DAPA-HF, where a serious ventricular arrhythmia was reported in 115 (2.4%) of the 4744 patients (VF in 15 patients, VT in 86, 'other' ventricular arrhythmia (VA) in 12, and torsade de pointes in 2 patients) and 206 (41%) of the 500 CV deaths occurred suddenly (8 patients survived resuscitation from cardiac arrest), indicated that independent predictors of the composite outcome (first occurrence of any serious VA, resuscitated cardiac arrest or sudden death), ranked by chi-square value, were log-transformed N-terminal pro-B-type natriuretic peptide, history of VA, LVEF, systolic blood pressure, history of MI, male sex, BMI, serum sodium concentration, non-white race, treatment with dapagliflozin, and cardiac resynchronization therapy. Of participants assigned to dapagliflozin, 140/2373 patients (5.9%) experienced the composite outcome compared with 175/2371 patients (7.4%) in the placebo group (HR 0.79; $P = 0.037$), and the effect was consistent across each of the components of the composite outcome (Curtain JP et al, *Eur Heart J* 2021;42:3727–3738)

Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2is) are Associated With Significantly Reduced Risks of Incident Atrial Arrhythmias and Sudden Cardiac Death (SCD) in Patients With Type 2 Diabetes (T2D)

Meta-analysis of 34 randomized (25 placebo-controlled and 9 active-controlled) trials with 63,166 patients (35,883 SGLT2is vs 27,273 control: mean age 53–67 years; 63% male). indicated that over a mean of 24 weeks to 5.7 years, SGLT2i therapy was associated with a significant reduction in the risk of incident atrial arrhythmias (odds ratio 0.81; P=0.008) and the "SCD" component of the SCD outcome (odds ratio 0.72; P=0.03) compared with control. There was no significant difference in incident VA or the "cardiac arrest" SCD component between groups (Fernandes GC et al, *Heart Rhythm* 2021;18:1098-1105).

MAUDE Database (2016-2020): Micra Leadless Pacemaker Implantation May be Complicated by Myocardial and Vascular Perforations and Tears That Result in Cardiac Tamponade And Death / Estimated Incidence Is Low (<1%) / Rescue Surgery To Repair Perforations May Be Lifesaving / MACE are Significantly Less for Capsurefix Transvenous Ventricular Pacing Leads

Search identified 363 MACE for Micra and 960 MACE for CapSureFix leads, including 96 Micra deaths (26.4%) vs 23 CapSureFix deaths (2.4%) (P<0.001); 287 Micra tamponades (79.1%) vs 225 for CapSureFix (23.4%) (P<0.001); and 99 rescue thoracotomies for Micra (27.3%) vs 50 for CapSureFix (5.2%) (P<0.001). More Micra patients required cardiopulmonary resuscitation (21.8% vs 1.1%) and suffered hypotension or shock (22.0% vs 5.8%) than CapSureFix recipients (P<0.001). Micra patients were more likely to survive a myocardial perforation or tear if they had surgical repair (P=0.014) (Hauser RG et al, *Heart Rhythm* 2021;18:1132-39)

Important Review and Other Articles

● **ACC/AHA/ESC Eradicating Tobacco** (Willett J et al, *J Am Coll Cardiol* 2021;78: 77-81**)**

2020 ESC Guidelines for the management of **acute coronary syndromes** in patients presenting without persistent ST-segment elevation (Collet J-P et al, *Eur Heart J* 2021;42: 1289–1367)

● **2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy** (Glikson M et al, *Eur Heart J* 2021;42:3427–3520)

● **2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure** (McDonagh TA et al, *Eur Heart J* 2021;42: 3599–3726)

● Pathophysiology of the **lymphatic system** in patients with **heart failure** (Itkin M et al, *J Am Coll Cardiol* 2021;78:278-90)

● **Management of obesity** (Despres JP et al, *J Am Coll Cardiol* 2021;78:513-31)

● **Sleep disordered breathing and cardiovascular disease** (Cowie MR et al, *J Am Coll Cardiol* 2021;78:608-24)

● **Obstructive sleep apnea and CVD**: AHA Statement (Yeghiazarians Y et al, *Circulation* 2021;144:e56–e67)

● **Myocardial revascularization surgery** (Mack MJ et al**,** *J Am Coll Cardiol* 2021;78:365–383)

● **Percutaneous coronary revascularization** (Serruys PW et al, *J Am Coll Cardiol* 2021;78:384–407)

● **Chronic total occlusion crossing algorithm** (Wu EB et al, *J Am Coll Cardiol* 2021;78:840–853)

● **Cryoballoon ablation for atrial fibrillation** (Andrade JG et al, *J Am Coll Cardiol* 2021;78:914–930)

● **Device therapy in chronic heart failure** (Fudim M et al, *J Am Coll Cardiol* 2021;78:931–956)

● AHA Statement on **Invasive Management of Cardiogenic Shock** (Henry TD et al, *Circulation 2021;143:e815–e829*)

● AHA Statement on **Opioid-Associated Out-of-Hospital Cardiac Arrest** (Dezfulian C et al, *Circulation* 2021;143:e836-70)

● AHA Statement on **Obesity and Cardiovascular Disease** (Powell-Wiley TM et al, *Circulation* 2021;143:e984–e1010)

● **HDL** in the 21st Century (Rohatgi A et al, *Circulation* 2021;143:2293–2309)

● **"Pill-in-Pocket" Anticoagulation for Atrial Fibrillation:** Fiction, Fact, or Foolish? (Passman R et al, *Circulation* 2021; 143:2211-13)

● **Arrhythmogenic right ventricular cardiomyopathy** and **sports activity** (Gasperetti A, *Eur Heart J* 2021;42:1231–1243)

● HFA/EACVI/EHRA/EAPCI Position Statement on management of **secondary mitral regurgitation** in patients with heart failure (Coats AJS et al, *Eur Heart J* 2021;42: 1254-69)

● **Air Pollution** - impact on **Cardiovascular Disease**: A Joint Opinion from the WHF, ACC, AHA, ESC (Brauer M et al, *Eur Heart J* 2021;42: 1460–1463)

● **European position paper** on the management of patients with **patent foramen ovale**. Part II (Pristipino C et al, *Eur Heart J* 2021;42:1545-53) / for Part I, see *Eur Heart J* 2019;40:3182-95

● Diagnosis and treatment of **cardiac amyloidosis:** a position statement of the ESC Working Group (Garcia-Pavia P et al, *Eur Heart J* 2021;42: 1554-68)

● **COVID-19 & Acute Myocardial Injury and Infarction** (Manolis AS et al, J **Cardiovasc Pharmacol Ther** 2021 May 5;10742484211011026. doi: 10.1177/10742484211011026. Online ahead of print)

● **Perimitral atrial flutter** (Ioannidis P et al, *J Arrhythm* 2021;37:584-596)

● **Classification of Heart Failure** according to Ejection Fraction (Lam CSP & Solomon SD, *J Am Coll Cardiol* 2021;77: 3217-25)

AHA Statement-**Managing AF in patients with HFrEF** (Gopinathannair et al, *Circ Arrhythm Electrophysiol* 2021;14(6): HAE0000000000000078)

Mechanical Complications of Acute MI: A Scientific AHA Statement (Damluji AA et al, *Circulation 2021;144:e16–e35*)

Arrhythmias and Autonomic Disorders in Cardio-Oncology: an AHA Statement (Fradley MG et al, *Circulation. 2021;144:e41–e55*)

Myocarditis With COVID-19 mRNA Vaccines (Bozkurt B et al, *Circulation* 2021;144:471–484)

Diagnosis and Management of **Myocarditis in Children:** an **AHA Statement** (Law YM et al, *Circulation.* 2021;144:e123–e135)

● **Peripheral artery disease**, an **AHA Statement** (Criqui MH et al, *Circulation* 2021;144:e171–e191)

● **Polymorphic ventricular tachycardia** (Viskin S et al, *Circulation* 2021;144:823–839)

● **Coronary artery anomalies** (Gentile F et al, *Circulation* 2021;144:983–996)

● **Opioid Use and Its Relationship to Cardiovascular Disease and Brain Health:** an AHA advisory (Chow SL et al, *Circulation* 2021;144:e218–e232)

● **Peripartum cardiomyopathy** (Sliwa K et al, *Eur Heart J* 42:3094–3102).

● **Eradicating Tobacco**-A Joint Opinion from the ACC, AHA, ESC, and the WHF (Willett J et al. *Eur Heart J* 2021; 42:3044–3048)

● **2021 ESC Guidelines on CV disease prevention** (Visseren FLJ et al, *Eur Heart J* 2021;42:3227–37)

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

● **EHRA expert consensus statement and practical guide on optimal implantation technique for conventional pacemakers and ICDs** (Burri H et al, *EP Europace* 2021;23:983–1008)

● **Optimized implementation of cardiac resynchronization therapy** (Mullens W et al, *EP Europace* 2021;23:1324–1342)