Cardiology News / Recent Literature Review / Second Quarter 2021

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ESC Digital **Congress** 27-30/8/2021

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

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

AHA Scientific 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

Systemic Lupus Erythematosus (SLE) Patients Have a Higher Associated Risk of Heart Failure (HF) and Other Cardiovascular (CV) Outcomes Compared with Matched Control Subjects

Among 3,411 SLE patients (median age: 44.6 years; 86% women) who were matched with 13,644 controls, over a median of 8.5 years, absolute 10-year risks of outcomes were: HF, 3.71% vs 1.94%; atrial fibrillation, 4.35% vs 2.82%; ischemic stroke, 3.75% vs 1.92%; MI, 2.17% vs 1.49%; venous thromboembolism, 6.03% vs 1.68%; and the composite of ICD implantation/ventricular arrhythmias/cardiac arrest, 0.89% vs 0.30% (SLE patients, vs control subjects). SLE with subsequent HF was associated with higher mortality compared with HF without SLE (adjusted hazard ratio: 1.50) (Yafasova A et al, *J Am Coll Cardiol* 2021;77:1717-27).

Worse Long-Term Outcomes of Patients with Late Presentation of ST-Segment Elevation Myocardial Infarction (STEMI)

Of 13,707 patients (2011-2015), 5,826 consecutive patients diagnosed with STEMI within 48 h of symptom onset were categorized as late (12-48 h; n = 624) or early (<12 h; n = 5,202) presenters. Late presenters had worse clinical outcomes (180-day mortality: 10.7% vs. 6.8%; 3-year mortality: 16.2% vs. 10.6%; both log-rank $p < 0.001$), whereas presentation at ≥12 h of symptom onset was not independently associated with increased mortality after STEMI. The use of invasive interventional procedures decreased from the first (<12 h) to the second (12-24 h) 12-h interval of symptom-to-door time ("no primary PCI strategy" increased from 4.9% to 12.4%, and "no PCI" from 2.3% to 6.6%; both $p < 0.001$). Mortality rates increased from the first to the second 12-h interval of symptom-to-door time (from 6.8% to 11.2% for 180-day mortality; from 10.6% to 17.3% for 3-year mortality; all $p < 0.05$) (Cho KH et al, *J Am Coll Cardiol* 2021;77:1859-70).

High Dietary Sodium (HS) Intake Increases Plasma Volume, Lowers Standing Plasma Norepinephrine, and Decreases Δ Heart Rate in Patients With Postural Tachycardia Syndrome (POTS)

Among 14 POTS patients and 13 healthy control subjects (HC), age 23-49 years, enrolled in a crossover study with 6 days of low (LS) (10 mEq/d) or high sodium (HS) (300 mEq/d) diet, in POTS, the HS diet reduced upright heart rate and Δ heart rate compared with the LS diet. Total blood volume and plasma volume (PV) increased, and standing norepinephrine decreased with the HS compared with the LS diet. However, upright heart rate, Δ heart rate, and upright norepinephrine remained higher in POTS than in controls on the HS diet, despite no difference in the measured PV (Garland EM et al, *J Am Coll Cardiol* 2021; 77:2174-84).

Poorer Outcomes for STEMI after TAVI: Very High In-Hospital and Mid-Term Mortality / Longer Door-To-Balloon Times and Higher PCI Failure Rate, Partially Due to Coronary Access Issues

Among 118 patients presenting with STEMI at a median of 255 days after TAVI, median door-to-balloon time was higher in TAVI patients (40 min vs. 30 min; $p = 0.003$). Procedural time, fluoroscopy time, dose-area product, and contrast volume were also higher in TAVI patients ($p<0.01$). PCI failure occurred more frequently in patients with previous TAVI (16.5% vs. 3.9%; $p < 0.001$), including 5 patients in whom the culprit lesion was not revascularized owing to coronary ostia cannulation failure. In-hospital and late (median of 7 months) mortality rates were 25.4% and 42.4%, respectively (20.6% and 38.2% in primary PCI patients), and estimated glomerular filtration rate <60 ml/min (hazard ratio-HR: 3.02; $p = 0.004$), Killip class ≥2 (HR: 2.74; $p = 0.004$), and PCI failure (HR: 3.23; $p = 0.005$) determined an increased risk (Faroux L et al, *J Am Coll Cardiol* 2021;77:2187-99).

Stroke Complicating Infective Endocarditis (IE) After TAVI: Occurred in 1 of 10 Patients With IE / A History of Stroke, Short Time Between TAVI and IE, Vegetation Size, Valve Prosthesis Type, and Residual Aortic Regurgitation Conferred a High Risk / Stroke Increased In-Hospital and 1-Year Mortality Rates / Surgical Treatment Failed to Improve Outcomes

Data from 569 patients who developed definite IE following TAVI from 59 centers in 11 countries indicated that a total of 57 (10%) patients had a stroke during IE

hospitalization, with no differences in causative microorganism between groups. Stroke(S)-IE patients exhibited higher rates of acute renal failure, systemic embolization, and persistent bacteremia ($p<0.05$). Prior stroke before IE, residual aortic regurgitation ≥moderate after TAVI, balloon-expandable valves, IE within 30 days after TAVI, and vegetation size >8 mm conferred a higher risk of stroke during the index IE hospitalization ($p<0.05$). Stroke rate in patients with no risk factors was 3.1% and increased up to 60% in the presence of >3 risk factors. S-IE patients had higher rates of in-hospital mortality (54.4% vs. 28.7%; $p<0.001$) and overall mortality at 1 year (66.3% vs. 45.6%; $p<0.001$). Surgical treatment was not associated with improved outcomes in S-IE patients (in-hospital mortality: 46.2% in surgical vs. 58.1% in no surgical treatment; p = NS) (del Val D et al, *J Am Coll Cardiol* 2021;77: 2276-87).

4-Year Study of Out-Of-Hospital Cardiac Arrests (OHCAs): Only 1/3 Were Sudden, of Which One-Half Were Resuscitated to Hospitalization & 1 in 5 Survived to Discharge / Arrhythmic Cause Predicted Survival and ~One-Half of Nonsurvivors Had Non-Arrhythmic Causes/Early Identification of Non-arrhythmic Sudden Cardiac Arrests (SCAs) (e.g., Neurologic Emergencies) May be a Target to Improve OHCA Survival

Among 734 OHCAs over 48 months, 239 met SCA criteria, 133 (55.6%) were resuscitated to hospitalization, and 47 (19.7%) survived to discharge. Arrhythmic causes accounted for many more resuscitated SCAs (92 of 133, 69.1%), particularly among survivors (43 of 47, 91.5%), than WHO-defined SCDs in POST SCD (293 of 525, 55.8%; $p<0.004$ for both). Among resuscitated SCAs, arrhythmic cause, ventricular tachycardia/fibrillation initial rhythm, and white race were independent predictors of survival. None of the resuscitated SCAs due to neurologic causes survived (Ricceri S et al, *J Am Coll Cardiol* 2021;77:2353-62).

Data From 5 Landmark ICD Trials Suggest That the Underlying Arrhythmic Substrate Rather Than the ICD Therapy is the More Important Determinant of Mortality in ICD Recipients

Data on 5,516 ICD recipients from 5 landmark ICD trials (MADIT-II, MADIT-RISK, MADIT-CRT, MADIT-RIT, RAID) indicated that a first appropriate ICD shock was associated with increased risk of subsequent mortality with or without concomitant occurrence of inappropriate shock during follow-up (hazard ratio -HR: 2.78 and 2.31; $p<0.001$ and $p=0.12$), whereas inappropriate shock alone was not associated with mortality risk (HR: 1.23; p=NS). Similarly, ICD therapy for VT ≥200 bpm or VF was associated with increased risk of death with or without concomitant therapy for VT <200 bpm (HRs: 2.25 and 2.62; both $p < 0.001$), whereas appropriate therapy for VT <200 bpm or inappropriate therapy (regardless of etiology) did not reach statistical significance. Combined assessment showed that appropriate ICD shocks for VF, shocks for fast VT (≥200 bpm) without prior antitachycardia pacing (ATP), as well as shocks for fast VT delivered after failed ATP, were associated with the highest risk of subsequent death (HR: all >2.8; $p<0.001$) (Aktas MK et al, *J Am Coll Cardiol* 2021;77:2453-62).

Urinary Dickkopf-3 (uDKK3), a Stress-Induced Renal Tubular Epithelium–Derived Glycoprotein: A Biomarker Predicting Both Acute Kidney Injury (AKI) and Persistent Kidney Dysfunction

Contrast-associated-AKI occurred in 64 of the 458 patients (14%), and baseline uDKK3/uCr ≥491 pg/mg was the best threshold for its prediction. Persistent kidney dysfunction occurred in 57 of the 458 patients (12%) and baseline uDKK3/uCr ≥322 pg/mg appeared as the best threshold for its prediction (Roscigno G et al, *J Am Coll Cardiol* 2021;77:2667-76).

Combining a DASH (Dietary Approaches To Stop Hypertension) Dietary Pattern With Sodium Reduction Lowered 2 Distinct Mechanisms of Subclinical Cardiac Damage: Injury and Strain, Whereas DASH Alone Reduced Inflammation

Among 412 participants (mean age 48 years; 56% women, 56% Black; mean baseline systolic/diastolic BP 135/86 mmHg) DASH (vs. control) reduced hs-cTnI by 18% and hs-CRP by 13%, but not NT-proBNP. In contrast, lowering sodium from high to low levels reduced NT-proBNP independently of diet (19%), but did not alter hs-cTnI and mildly increased hs-CRP (9%). Combining DASH with sodium reduction lowered hs-cTnI by 20% and NT-proBNP by 23%, whereas hs-CRP was not significantly changed compared with the high sodium-control diet (Juraschek SP et al, *J Am Coll Cardiol* 2021;77:2625-34).

Use of Glycated Hemoglobin Can Identify Subclinical Atherosclerosis (SA) in People Without Diabetes

Among 3,973 middle-aged individuals from the PESA (Progression of Early Subclinical Atherosclerosis) study, with no history of CV disease and with HbA1c in the nondiabetic range, HbA1c showed an association with the multiterritorial extent of SA (odds ratio: 1.05, 1.27, 1.27, 1.36, 1.80, 1.87, and 2.47 for HbA1c 4.9-5.0%, 5.1-5.2%, 5.3-5.4%, 5.5-5.6%, 5.7-5.8%, 5.9-6.0%, and 6.1-6.4%, respectively; reference HbA1c ≤4.8%; $p<0.001$). The association was significant in all pre-diabetes groups and

even below the pre-diabetes cut-off (HbA1c 5.5%-5.6% odds ratio: 1.36; p=0.033). High HbA1c was associated with an increased risk of SA in low-risk individuals (p < 0.001), but not in moderate-risk individuals (p=0.335) (Rossello X et al, *J Am Coll Cardiol* 2021;77:2777–2791).

Left Atrial (LA) Thrombus Prevalence is High in Subgroups of Anticoagulated Patients With AF/AFL, Who May Benefit From Routine Pre-Procedural TEE Use Before Cardioversion or Catheter Ablation

In 35 studies (N=14,653), the mean-weighted LA thrombus prevalence was 2.73%. LA thrombus prevalence was similar for VKA- and DOAC-treated patients (2.8% vs 3.12%; p=0.674). Patients with non-paroxysmal AF/AFL had a 4-fold higher LA thrombus prevalence compared with paroxysmal patients (4.81% vs 1.03%; p<0.001). LA thrombus prevalence was higher among patients undergoing cardioversion vs ablation (5.55% vs 1.65%; p<0.001). Patients with CHA_2DS_2-VASc scores ≥3 had a higher LA thrombus prevalence compared with patients with scores ≤2 (6.31% vs 1.06%; p<0.001) (Lurie A et al, *J Am Coll Cardiol* 2021;77:2875-86).

Dilated Cardiomyopathy (DCM): LGE CMR is a Strong Predictor of Ventricular Arrhythmia (VA) or Sudden Death / Specific High-Risk LGE Distributions Were Identified / A New Clinical Algorithm Integrating LGE and LVEF Significantly Improved the Risk Stratification for VA and Sudden Death

In 1,165 patients over a median of 36 months, LGE was an independent and strong predictor of VA (hazard ratio: 9.7; p<0.001). This association was consistent across all strata of LVEF. Epicardial LGE, transmural LGE, and combined septal and free-wall LGE were all associated with heightened risk. A simple algorithm combining LGE and 3 LVEF strata (i.e., ≤20%, 21-35%, >35%) was superior to LVEF with the 35% cutoff (Harrell's C statistic: 0.8 vs. 0.69; area under the curve: 0.82 vs 0.7; p<0.001) and reclassified the arrhythmic risk of 34% of patients with DCM. LGE-negative patients with LVEF 21-35% had low risk (annual event rate 0.7%), whereas those with high-risk LGE distributions and LVEF >35% had higher risk (annual event rate 3%; p=0.007) (Di Marco A et al, *J Am Coll Cardiol* 2021;77:2890-2905).

Nonischemic Cardiomyopathy (NICM): Myocardial Scar and LVEF are Risk Markers for All-Cause and Cardiac Death / Whereas Myocardial Scar Has Strong and Incremental Prognostic Value for SCD Risk Stratification, LVEF Has no Incremental Prognostic Value Over Clinical Measures

Among 1020 patients with NICM, over a median of 5.2 years, 277 (27%) patients died. On survival analysis, LVEF ≤35% and scar were strongly associated with all-cause (log-rank test *P*=0.002 and *P*<0.001, respectively) and cardiac death (*P*=0.001 and *P*<0.001, respectively). Whereas scar was strongly related to sudden cardiac death (SCD; *P*=0.001), there was no significant association between LVEF ≤35% and SCD risk (*P*=0.57). On multivariable analysis, LVEF and scar are independent risk markers of all-cause and cardiac death. The addition of LVEF provided no incremental prognostic value for SCD; conversely, scar extent demonstrated significant incremental prognostic value (Klem I et al, *Circulation* 2021;143:1343-58).

CABANA: In AF Patients With Stable Heart Failure and Mostly Preserved LVEF, Catheter Ablation Produced Important Improvements in Survival, Freedom From AF Recurrence, and Quality Of Life Relative to Drug Therapy

Of the 778 patients with heart failure enrolled in CABANA, 378 were assigned to ablation and 400 to drug therapy. LVEF at baseline was available for 571 patients (73%); 9.3% had an LVEF <40% and 11.7% an LVEF of 40-50%. In the intention-to-treat analysis, the ablation arm had a 36% relative reduction in the primary composite end point (hazard ratio-HR, 0.64) and a 43% relative reduction in all-cause mortality (HR, 0.57) compared with drug therapy alone over a median of 48.5 months. AF recurrence was decreased with ablation (HR, 0.56). The adjusted mean difference for quality-of-life summary score was 5.0 points, favoring the ablation arm (Packer DL et al, *Circulation* 2021;143:1377–1390).

Higher Intakes of Fruit and Vegetables Conferred Lower Mortality / The Risk Reduction Plateaued at ≈5 Servings of Fruit and Vegetables Per Day

Among 66,719 women from the Nurses' Health Study (1984–2014) and 42,016 men from the Health Professionals Follow-up Study (1986–2014), free from cardiovascular disease (CVD), cancer, and diabetes at baseline, nonlinear inverse associations were observed of fruit and vegetable intake with total mortality and cause-specific mortality attributable to cancer, CVD, and respiratory disease (all $P_{nonlinear}$<0.001). Intake of ≈5 servings/d of fruit and vegetables, or 2 servings of fruit and 3 servings of vegetables, was associated with the lowest mortality, and above that level, higher intake was not associated with additional risk reduction. In comparison with the reference level (2 servings/d), daily intake of 5 servings of fruit and vegetables was associated with hazard ratios of 0.87 for total mortality, 0.88 for CVD mortality, 0.90 for cancer mortality, and 0.65 for respiratory disease mortality. Higher intakes of most subgroups of fruits and

vegetables were associated with lower mortality, with the exception of starchy vegetables such as peas and corn. Intakes of fruit juices and potatoes were not associated with mortality (Wang DD et al, *Circulation* 2021;143: 1642-54).

DAPA-HF: Dapagliflozin Reduced the Risk of Total (First and Repeat) Heart Failure (HF) Hospitalizations and Cardiovascular (CV) Death / Time-To-First Event Analysis Underestimated the Benefit of Dapagliflozin in HF and Reduced Ejection Fraction (HFrEF)

Of 2371 participants randomly assigned to placebo, 318 experienced 469 hospitalizations for HF; of 2373 assigned to dapagliflozin, 230 patients experienced 340 admissions. In a multivariable model, factors associated with a higher risk of recurrent HF hospitalizations included higher heart rate, higher N-terminal pro-B-type natriuretic peptide, and NYHA class. The rate ratio for the effect of dapagliflozin on recurrent HF hospitalizations or CV death was 0.75 (P=0.0002), according to one model, while in another model, the rate ratio for total HF hospitalizations was 0.71 (P<0.0001), and 0.81 for CV death (P=0.0282) (Jhund PS et al, *Circulation* 2021;143:1962-72).

Cardiac Late Sodium Channel Current (Late-I_{Na}) is a Molecular Target in the Heart for the Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitor Empagliflozin, Contributing to Cardioprotection

The SGLT2 inhibitor empagliflozin reduced late-I_{Na} in cardiomyocytes from mice with heart failure and in cardiac Nav1.5 sodium channels containing the long QT syndrome 3 mutations R1623Q or ΔKPQ. Empagliflozin, dapagliflozin, and canagliflozin are all potent and selective inhibitors of H_2O_2-induced late-I_{Na} with little effect on peak sodium current. In mouse cardiomyocytes, empagliflozin reduced the incidence of spontaneous calcium transients induced by the late-I_{Na} activator veratridine in a similar manner to tetrodotoxin, ranolazine, and lidocaine. There is indication that empagliflozin binds to Nav1.5 in the same region as local anesthetics and ranolazine. In an acute model of myocardial injury, perfusion of isolated mouse hearts with empagliflozin or tetrodotoxin prevented activation of the cardiac NLRP3 (nuclear-binding domain-like receptor 3) inflammasome and improved functional recovery after ischemia. (Phlippaert K et al, *Circulation* 2021;143:2188-2204).

TTM2 Trial: In Patients With Coma After Out-Of-Hospital Cardiac Arrest, Targeted Hypothermia Did Not Lead to a Lower Incidence of Death by 6 Months Than Targeted Normothermia

A total of 1900 adults with coma who had had an out-of-hospital cardiac arrest of presumed cardiac or unknown cause were randomly assigned to undergo targeted hypothermia at 33°C, followed by controlled rewarming, or targeted normothermia with early treatment of fever (body temperature, ≥37.8°C). Among 1850 patients evaluated for the primary outcome (death from any cause at 6 months), at 6 months, 465 of 925 patients (50%) in the hypothermia group had died, as compared with 446 of 925 (48%) in the normothermia group (relative risk with hypothermia, 1.04; P=NS). Of the 1747 patients in whom the functional outcome was assessed, 488 of 881 (55%) in the hypothermia group had moderately severe disability or worse (modified Rankin scale score ≥4), as compared with 479 of 866 (55%) in the normothermia group (relative risk with hypothermia, 1.00). Arrhythmia resulting in hemodynamic compromise was more common in the hypothermia group (24% vs 17%, P<0.001) (Dankiewicz J et al, *N Engl J Med* 2021; 384:2283-94).

LAAOS III: Among Patients With Atrial Fibrillation Who Had Undergone Cardiac Surgery, Most of Whom Continued Antithrombotic Therapy, the Risk of Ischemic Stroke or Systemic Embolism Was Lower With Concomitant Left Atrial Appendage (LAA) Occlusion Performed During Surgery

Among patients (mean age 71 years, mean CHA_2DS_2-VASc score 4.2) randomly assigned to undergo (n=2379) or not undergo (N=2391) occlusion of the LAA during surgery (92.1% received the assigned procedure, and at 3 years, 76.8% continued to receive oral anticoagulation), over a mean of 3.8 years, stroke or systemic embolism occurred in 114 participants (4.8%) in the occlusion group and in 168 (7%) in the no-occlusion group (hazard ratio, 0.67; P=0.001). The incidence of perioperative bleeding, heart failure, or death did not differ significantly between the trial groups (Whitlock RP et al, *N Engl J Med* 2021; 384:2081-91).

ADAPTABLE: No Differences in Cardiovascular Events or Major Bleeding Between Patients Assigned to 81 mg and Those Assigned to 325 mg of Aspirin Daily

Among 15,076 patients followed for a median of 26.2 months, death, hospitalization for MI, or hospitalization for stroke occurred in 590 patients (7.28%) in the 81-mg group and 569 patients (7.51%) in the 325-mg group (hazard ratio-HR, 1.02). Hospitalization for major bleeding occurred in 53 patients (0.63%) in the 81-mg group and 44 patients (0.60%) in the 325-mg group (HR, 1.18). Patients assigned to 325 mg had a higher incidence of dose switching than those assigned to 81 mg (41.6% vs 7.1%) and fewer median days of exposure to the assigned dose (434 days vs 650 days) (Jones WS et al, *N Engl J Med* 2021; 384:1981-90).

The Human Homologue (hsa-miR-Chr8:96) of a Newly Identified microRNA Could be Used to Distinguish Patients With Myocarditis from Those With MI

A microRNA specific for myocarditis was identified first in mice via microRNA microarray analyses and quantitative PCR assays in sorted CD4+ T cells and type 17 helper T (Th17) cells after inducing experimental autoimmune myocarditis or myocardial infarction (MI). The human homologue for this microRNA was then identified and its expression compared in plasma obtained from patients with acute myocarditis. It was confirmed that Th17 cells, characterized by the production of interleukin-17, are a characteristic feature of myocardial injury in the acute phase of myocarditis. The microRNA mmu-miR-721 was synthesized by Th17 cells and was present in the plasma of mice with acute autoimmune or viral myocarditis but not in those with acute MI. The human homologue, designated hsa-miR-Chr8:96, was identified in 4 independent cohorts of patients with myocarditis. The area under the receiver-operating-characteristic curve for this novel microRNA for distinguishing patients with acute myocarditis from those with MI was 0.927. The microRNA retained its diagnostic value in models after adjustment for age, sex, ejection fraction, and serum troponin level (Blanco-Domínguez R et al, *N Engl J Med* 2021; 384:2014-27).

SPRINT / Final Report: Among Patients at Increased CV Risk, Targeting a Systolic Blood Pressure <120 vs <140 mmHg Resulted in Lower Rates of MACE and Lower All-Cause Mortality / Rates of Some Adverse Events Were Higher in the Intensive-Treatment Group

Among 9361 patients at increased risk for CV disease without diabetes or previous stroke randomly assigned to adhere to an intensive treatment target (systolic BP <120 mmHg) or a standard treatment target (systolic BP <140 mm Hg), at a median of 3.33 years, the rate of the primary outcome (MI, other ACS, stroke, acute decompensated heart failure, or death from CV causes) and all-cause mortality during the trial were lower in the intensive-treatment group than in the standard-treatment group (rate of the primary outcome, 1.77% per year vs. 2.40% per year; hazard ratio-HR, 0.73; all-cause mortality, 1.06% per year vs. 1.41% per year; HR, 0.75). Serious adverse events of hypotension, electrolyte abnormalities, acute kidney injury or failure, and syncope were significantly more frequent in the intensive-treatment group. When trial and post-trial follow-up data were combined (3.88 years in total), similar patterns were found for treatment benefit and adverse events; however, rates of heart failure no longer differed between the groups. (SPRINT Research Group, *N Engl J Med* 2021; 384:1921-1930).

PURE: A Diet With a High Glycemic Index Was Associated With an Increased Risk of Cardiovascular (CV) Disease and Death

Among 137,851 participants aged 35-70 years living on 5 continents, 8780 deaths and 8252 major CV events occurred over a median of 9.5 years. After adjustments comparing the lowest and highest glycemic-index quintiles, it was found that a diet with a high glycemic index was associated with an increased risk of a major CV event or death, both among participants with preexisting CV disease (hazard ratio-HR, 1.51) and among those without such disease (HR, 1.21). A high glycemic index also conferred an increased risk of CV death. The results with respect to glycemic load were similar to the findings regarding the glycemic index among the participants with CV disease at baseline, but the association was not significant among those without preexisting CV disease (Jenkins DJA et al, *N Engl J Med* 2021; 384:1312-22).

ACTION: Use of Therapeutic-Dose Direct Oral Anticoagulants (DOACs) Should be Avoided in COVID-19 Patients in the Absence of an Evidence-Based Indication for Oral Anticoagulation as Such Therapy Does Not Improve Clinical Outcomes and Increases Bleeding Compared With Prophylactic Anticoagulation

Among 3331 patients screened, 615 were randomly allocated to the therapeutic anticoagulation group (n=311) or to the prophylactic anticoagulation group (n=304) (576 or 94% were clinically stable and 39 or 6% clinically unstable). One patient, in the therapeutic group, was lost to follow-up. The primary efficacy outcome (time to death, duration of hospitalization, or duration of supplemental oxygen to day 30) was not different between the 2 groups (34.8% vs 41.3%; ratio 0·86, p=0·40). Consistent results were seen in clinically stable and clinically unstable patients. The primary safety outcome of major or clinically relevant non-major bleeding occurred in 26 (8%) patients assigned therapeutic anticoagulation and 7 (2%) assigned prophylactic anticoagulation (relative risk 3.64, p=0.0010). Allergic reaction to the study medication occurred in 2 (1%) and 3 (1%) patients, respectively (Lopes RD et al, *Lancet* 2021; 397 (10291):2253-63).

RECOVERY: In Hospitalized COVID-19 Patients With Hypoxia and Systemic Inflammation, Tocilizumab Improved Survival and Other Clinical Outcomes, Regardless of the Amount of Respiratory Support and in Addition to the Benefits of Systemic Corticosteroids

Tocilizumab, a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits the binding of

IL-6 to both membrane and soluble IL-6 receptors, blocking IL-6 signaling and reducing inflammation, was assessed in 4116 adults of 21,550 patients enrolled into the RECOVERY trial, including 3385 (82%) patients receiving systemic corticosteroids. Overall, 621 (31%) of the 2022 patients allocated tocilizumab and 729 (35%) of the 2094 patients allocated to usual care died within 28 days (rate ratio 0.85; p=0·0028). Consistent results were seen in all prespecified subgroups. Patients allocated to tocilizumab were more likely to be discharged from hospital within 28 days (57% *vs* 50%; rate ratio 1.22; p<0.0001). Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (35% *vs* 42%; risk ratio 0.84; p<0.0001) (RECOVERY Collaborative Group, *Lancet* 2021; 397 (10285):1637-45).

Meta-Analysis: Guided Selection of Antiplatelet Therapy Improved Both Composite and Individual Efficacy Outcomes With a Favorable Safety Profile, Driven by a Reduction in Minor Bleeding, Supporting Use of Platelet Function or Genetic Testing to Optimize the Choice of Agent in Patients Undergoing PCI

Meta-analysis of 11 randomized controlled trials and 3 observational studies with data for 20,743 patients, indicated that compared with standard therapy, guided selection of antiplatelet therapy conferred a reduction in major adverse CV events (RR 0.78, p=0.015) and reduced bleeding, although not statistically significant (RR 0.88, p=0.069). CV death (RR 0.77, p=0.049), MI (RR 0.76, p=0.021), stent thrombosis (RR 0.64, p=0.011), stroke (RR 0.66, p=0.010), and minor bleeding (RR 0.78, p=0.0030) were reduced with guided therapy compared with standard therapy. Risks of all-cause death and major bleeding did not differ between guided and standard approaches. Outcomes varied according to the strategy used, with an escalation approach associated with a significant reduction in ischemic events without any trade-off in safety, and a de-escalation approach associated with a significant reduction in bleeding, without any trade-off in efficacy (Galli M et al, *Lancet* 2021;397(10283):1470-83)

Copenhagen General Population Study/The Physical Activity Paradox: Higher Leisure Time Physical Activity Reduced MACE and All-Cause Mortality Risk, While Higher Occupational Physical Activity Increased Risks, Independent of Each Other

Among 104,046 women and men, aged 20–100 years, over a median 10-year follow-up, 7913 (7.6%) MACE and 9846 (9.5%) deaths occurred from all causes. Compared to low leisure time physical activity, multivariable adjusted (for lifestyle, health, living conditions, and socioeconomic factors) hazard ratios-HRs for MACE were 0.86 for moderate, 0.77 for high, and 0.85 for very high activity; corresponding values for higher occupational physical activity were 1.04, 1.15, and 1.35, respectively. For all-cause mortality, corresponding HRs for higher leisure time physical activity were 0.74, 0.59, and 0.60, and for higher occupational physical activity 1.06, 1.13, and 1.27, respectively. Similar results were found within strata on lifestyle, health, living conditions, and socioeconomic factors, and when excluding individuals dying within the first 5 years of follow-up. Levels of the two domains of physical activity did not interact on risk of MACE ($P = 0.40$) or all-cause mortality ($P = 0.31$) (Holtermann A et al, *Eur Heart J* 2021;42: 1499–1511).

Among Critically Ill Adults With COVID-19, Early Therapeutic Anticoagulation Did Not Affect Survival in the Target Trial Emulation

Among 3239 critically ill adults with COVID-19 (median age 61 years; 64.5% men), a total of 204 patients (6.3%) developed venous thromboembolism (VTE), and 90 (2.8%) developed a major bleeding event. Independent predictors of VTE were male sex and higher D-dimer level on ICU admission. Among the 2809 patients included in the target trial emulation, 384 (11.9%) received early therapeutic anticoagulation. Over 27 days, patients who received early therapeutic anticoagulation had a similar risk for death as those who did not (hazard ratio, 1.12) (Al-Samkari H, et al, *Ann Intern Med* 2021; 2021;174:622-32).

EARNEST-PVI: PVI Plus Complex Fractionated Atrial Electrogram (CFAE) and Linear Ablation Strategy Was Equivalent to PVI Alone in Persistent AF

Among 497 patients with persistent AF who underwent initial catheter ablation randomly assigned to either PVI alone (PVI-alone group, n=249) or PVI plus CFAE and/or linear ablation (PVI-plus group, n=248; linear ablation 85%, CFAE 15%), indicated that over 1 year, freedom from recurrence occurred in 71.3% of patients in the PVI-alone group and in 78.3% in the PVI-plus group (hazard ratio 1.56, non-inferior $P = 0.3062$). Complication rates were 2% vs 3.6%, respectively ($P = 0.199$) (Inoue K et al, *EP Europace* 2021;23: 565-74).

High-Power Short-Duration (HPSD) RFA Has Better Procedural Efficacy vs Conventional RFA With Comparable Safety and Shorter Procedural Duration

A meta-analysis of 15 studies involving 3718 patients (2357 in HPSD RFA and 1361 in conventional RFA) showed that freedom from arrhythmia was higher in HPSD RFA when compared with conventional RFA (odds ratio-OR 1.44; $P = 0.009$]. Acute PV reconnection was lower

(OR 0.56, $P = 0.005$) and first-pass isolation was higher (OR 3.58, $P < 0.001$) with HPSD RFA. There was no difference in complications (P = NS). Total procedure duration (mean difference -MD −37.35 min, $P < 0.001$], fluoroscopy duration (MD −5.23 min, $P = 0.001$), and RF ablation time (MD −16.26 min, $P < 0.001$) were all lower in HPSD RFA. HPSD RFA also had higher freedom from atrial arrhythmia in the subgroup analysis of patients with paroxysmal AF (OR 1.80; $P < 0.001$), studies with ≥50 W protocol in the HPSD RFA group (OR 1.53; $P = 0.02$) and studies with contact force sensing catheter use (OR 1.65; $P = 0.002$) (Ravi V et al, *EP Europace* 2021;23:710-21).

Cryoballoon Procedures are Fast with a Benign Safety Profile / Shorter Time-to-Isolation (TTI) and Longer Freeze Durations Confer Better Results

Ablation of paroxysmal (PAF) or persistent AF (persAF) with 2nd generation cryoballoon, luminal esophageal temperature monitoring (cut-off of 15°C), and phrenic nerve (PN) monitoring (during ablation of septal PVs), freeze duration set at 240 s with a bonus application in case of delayed (> 75 s) TTI, was performed in 1017 patients (58% male, 66 ± 12 years old, 70% with PAF; mean procedure time 69 ± 25 min, TTI recorded in 77% of PVs at a mean of 48 ± 31 s). There occurred 0.2% cardiac tamponade, 4.8% PN injury (1.6% of PN palsy). Among 725 patients with follow-up data, 84% with PAF and 75% with persAF were in sinus rhythm at 1 year. Shorter freezing duration and longer TTI predicted recurrence (Bordignon S et al, *EP Europace* 2021;23:868-77).

ASPREE: In Adults ≥65 Years of Age, Statin Therapy Was Not Associated With Incident Dementia, (Mild Cognitive Impairment (MCI), or Declines in Individual Cognition Domains

Among 18,846 participants ≥65 years of age in a randomized trial of aspirin, who had no prior CV events, major physical disability, or dementia initially, followed for 4.7 years, statin use vs nonuse was not associated with dementia, MCI, or their subclassifications or with changes in cognitive function scores over time (p >0.05 for all). No differences were found in any outcomes between hydrophilic and lipophilic statin users. Baseline neurocognitive ability was an effect modifier for the associations of statins with dementia (p for interaction < 0.001) and memory change (p for interaction = 0.02) (Zhou Z et al, *J Am Coll Cardiol* 2021:77 3145-56).

Important Review and Other Articles

● **2021 ACC/AHA Key Data Elements and Definitions for Heart Failure** (Bozkurt B et al, *J Am Coll Cardiol* 2021;77: 2053-2150**)**

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)

● **Cardiovascular Risk** in Patients with **Psoriasis** (Garshick MS et al, *J Am Coll Cardiol* 2021;77:1670-80)

● **Antithrombotic therapy in COVID-19** (Talasaz AH et al, *J Am Coll Cardiol* 2021;77:1903-21)

● Clinical Approach to **Cardiovascular Toxicity of Oral Antineoplastic Agents** (Rao VU et al, *J Am Coll Cardiol* 2021;77:450-500)

● **Transcatheter Mitral Valve Replacement** (Alperi A et al**,** *J Am Coll Cardiol* 2021;77:3058–3078)

● 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)