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Highlights from the European society of cardiology congress 2020

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After another exciting conference, this article highlights some of the many studies presented. Below, we start with some of the clinically impactful studies that demonstrated statistically significant primary endpoint results.

Early rhythm control in patients with early atrial fibrillation reduced cardiovascular events

Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) was a multicenter, open, 1:1 randomized study that tested a strategy of early rhythm control therapy versus usual care in patients diagnosed with atrial fibrillation within one year [1]. The study enrolled patients diagnosed ≤ 12 months before enrollment who met one of the following criteria: (1) age > 75 years; (2) a prior history of stroke or transient ischemic attack; or (3) the presence of two other high-risk conditions. Early rhythm control included antiarrhythmic drugs and/or atrial fibrillation ablation, as well as cardioversion for persistent atrial fibrillation. The primary outcome was a composite of cardiovascular (CV) death, stroke, heart failure (HF) hospitalization, or acute coronary syndrome. A total of 2789 patients were randomized. The trial was stopped for efficacy at a median follow up of 5.1 years.

The mean age was 70 years and 46% were female. Patients were enrolled a median of 36 days after the first diagnosis of atrial fibrillation. In the early rhythm control group, 94.8% received an antiarrhythmic drug or underwent atrial fibrillation ablation. The primary outcome occurred less often with early rhythm control (HR 0.79, 0.66 to 0.94, P = 0.005). The absolute difference in risk was 1.1 events per 100 person-years. These findings favoring a strategy of early rhythm control versus rate control might be explained by having patients enrolled shortly after diagnosis of atrial fibrillation, use of modern atrial fibrillation ablation techniques, and guidance on the safe use of antiarrhythmic drugs [2].

Empagliflozin demonstrates additional evidence of efficacy in heart failure

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) was a 1:1 randomized, double-blinded, parallel-group, placebo-controlled study testing empagliflozin 10 mg daily versus placebo in chronic HF patients enriched for greater severity of left ventricular (LV) systolic dysfunction than in past trials [3]. Enrollment criteria included: (1) age ≥ 18 years and (2) LV ejection fraction (LVEF) ≤ 40%. Those with LVEF 31–40% needed to have a history of HF hospitalization within 12 months or higher levels of N-terminal prohormone natriuretic peptide (NT-preBNP). The primary outcome was a composite of CV death or hospitalization for HF. A total of 3730 patients were randomized. Median duration of follow-up was 16 months.

The mean age was 67 years, mean LVEF was 27%, median NT-proBNP was 1907 pg/ml, 50% had diabetes mellitus, 48% had chronic kidney disease stage III or worse. The primary outcome occurred in 19.4% in the empagliflozin group and 24.7% in the placebo group (HR 0.75, 0.65 to 0.86, P < 0.001) (Table 1). The effect of empagliflozin on the primary outcome was consistent across subgroups, including the presence of diabetes or the concomitant use of sacubitril-valsartan. These data support the findings of the DAPA-HF trial and suggest that sodium-glucose cotransporter 2 (SGLT2) inhibitors have a beneficial effect on HF outcomes as well as renal function in a chronic HF population regardless of the presence of diabetes [4].

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Table 1 Efficacy outcomes for empagliflozin in EMPERIOR-Reduced

	Empagliflozin	Placebo	HR (95% CI)	*P* value
CV death or hospitalization for HF	361 (19.4)	462 (24.7)	0.75 (0.65–0.86)	< 0.001
Hospitalization for HF	246 (13.2)	342 (18.3)	0.69 (0.59–0.81)	
CV death	187 (10.0)	202 (10.8)	0.92 (0.75–1.12)	
Total HF hospitalizations	388	553	0.70 (0.58–0.85)	< 0.001
Mean slope of Δ in eGFR per year	0.55 ± 0.23	− 2.28 ± 0.23	1.73 (1.10–2.37)	< 0.001

CV cardiovascular, *CI* confidence intervals, *HR* hazard ratio, *eGFR* estimated glomerular filtration rate (units of ml/min/1.73 m^2)

Ground-breaking trial demonstrates broad benefits with mavacamten for patients with symptomatic hypertrophic obstructive cardiomyopathy

Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM) was a phase 3, 1:1 randomized, double-blind trial which tested the first-in-class, selective allosteric inhibitor of cardiac myosin ATPase compared to placebo [5]. Inclusion criteria were: (1) diagnosis of hypertrophic obstructive cardiomyopathy (HOCM); (2) peak left ventricular outflow tract (LVOT) gradient ≥ 50 mm Hg at rest; (3) LVEF ≥ 55%; and (4) New York Heart Association (NYHA) class II–III symptoms. Mavacamten was started at 5 mg daily with blinded dose titrations at weeks 8 and 14. Dose adjustment was done to achieve target plasma concentrations between 350 and 700 ng/ml and reduction in LVOT gradient to < 30 mm Hg. The primary composite endpoint measured at week 30 was either ≥ 1.5 mL/kg/min in pVO_2 and ≥ 1 NYHA class reduction or ≥ 3.0 mL/kg/min in pVO_2 without worsening of NYHA class. The study cohort was 251 randomized patients.

The mean age of partici pants was 58·5 years, 73% had NYHA class II symptoms at baseline and 92% were on a β blocker or calcium channel blocker. The primary endpoint occurred in 37% on mavacamten and 17% on placebo (19.4%, 8.7–30.1, P = 0·0005). All other secondary endpoints were also significantly improved with mavacamten. Remarkably, complete response to therapy defined as reduction in all LVOT gradients to < 30 mm Hg and achieving NYHA class I was seen in 27% on mavacamten compared to < 1% on placebo. This study was the first significant validation of efficacy from a compound targeting the primary pathophysiology of HOCM [6].

Colchicine now also demonstrates efficacy in patients with chronic coronary artery disease

The second Low Dose Colchicine (LoDoCo2) trial tested whether colchicine, an anti-inflammatory drug that inhibits tubulin polymerization and alters leukocyte responsiveness, reduces cardiovascular outcomes in patients with chronic coronary artery disease (CAD) [7]. Enrollment criteria included: (1) age 35–82 years; (2) CAD on coronary angiography or a coronary artery calcium score of ≥ 400 Agatston units; and (3) clinically stable condition for ≥ 6 months. Exclusion criteria were moderate-to-severe renal impairment, severe heart failure, or history of known side effects from colchicine. After a run-in period, patients were 1:1 randomized to colchicine 0.5 daily versus placebo. The primary end point was a composite of CV death, spontaneous myocardial infarction (MI), ischemic stroke, or ischemia-driven coronary revascularization. A total of 5522 patients underwent randomization. Median follow-up was 28.6 months.

The mean age was 66 years, 15.3% were female, and statin use was 94%. The primary endpoint occurred in 6.8% of patients in the colchicine group and in 9.6% of patients in the placebo group (HR 0.69, 0.57–0.83, P < 0.001) (Table 2). The results of this trial indicate potential anti-inflammatory benefit from colchicine in consistent with those from the LoDoCo and COLCAT trials. Of note, the benefits of colchicine occurred on top of standard of care therapies. These benefits appeared early and appeared to accrue over time [8].

Table 2 Key endpoints in LoDoCo2 with hierarchical testing

	Colchicine (%)	Placebo (%)	HR (95% CI)	*P* Value
CV death, MI, ischemic stroke, or ischemic-driven revascularization	6.8	9.6	0.69 (0.57–0.83)	< 0.001
CV death, MI, or ischemic stroke	4.2	5.7	0.72 (0.57–0.92)	0.007
MI or ischemia-driven revascularization	5.6	8.1	0.67 (0.55–0.83)	< 0.001
CV death or MI	3.6	5.0	0.71 (0.55–0.92)	0.01
Ischemia-driven revascularization	4.9	6.4	0.75 (0.60–0.94)	0.01
MI	1.1	1.5	0.70 (0.53–0.93)	0.01
Ischemic stroke	0.6	0.9	0.66 (0.35–1.25)	0.20
All-cause death	2.6	2.0	1.21 (0.86–1.71)	No test
CV death	0.7	0.9	0.80 (0.44–1.44)	No test

CV cardiovascular, *MI* myocardial infarction, *CI* confidence intervals, *HR* hazard ratio

Less bleeding after transcatheter aortic valve implantation with aspirin monotherapy than with aspirin plus clopidogrel

The POPular TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) tested aspirin versus aspirin plus 3 months of clopidogrel on bleeding in patients undergoing TAVI. Exclusion criteria: (1) no indication for long-term oral anticoagulation and (2) recent coronary artery stent implantation (< 3 months for drug-eluting stent and < 1 month for bare metal stent). A total of 690 patients were 1:1 randomized in this open-label study. The two primary outcomes were all bleeding and non-procedure-related bleeding over 12 months [9].

The mean age was 80 years and 48.7% were female. Bleeding of any type occurred in 15.1% of the aspirin alone arm and in 26.6% of the aspirin plus clopidogrel group (RR 0.57, 0.42–0.77, P = 0.001). Non-procedure-related bleeding occurred in 15.1% and 24.9% of each arm, respectively (RR 0.61, 0.44–0.83, P = 0.005). Aspirin monotherapy was also associated with a lower incidence of CV death, stroke, MI, or non-procedure-related bleeding. Guideline recommendations for aspirin and clopidogrel following TAVI may now warrant revision.

Other conference highlights

There were also many important studies with non-statistically significant findings, but important clinical implications. These are discussed briefly in the following paragraphs.

BRACE CORONA trial investigated continuing vs suspending Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in patients diagnosed with Coronavirus disease 2019 (COVID-19) [10]. This trial enrolled a total of 659 patients hospitalized with COVID-19 and on chronic therapy with ACEIs or ARBs and randomized them to suspension of ACEI/ARB vs continued use of those medications. Days alive and outside of the hospital at 30 days (primary outcome) and all-cause death at 30 days (secondary outcome) were not statistically different in those groups. Of note, patients who were hemodynamically unstable, on mechanical ventilation, on more than 3 antihypertensives, were taking sacubitril/valsartan, or had a history of hospitalization for decompensated heart failure in the prior 12 months were excluded from this study.

BAMI trial compared intracoronary infusion of bone marrow-derived mononuclear cells with standard therapy in patients with acute ST elevation myocardial infarction (STEMI) who underwent successful reperfusion therapy [11]. This randomized, open-label trial enrolled 375 eligible patients and did not show any statistically significant difference in all-cause mortality at 2 years (primary outcomes) and cardiovascular death or hospitalization due to heart failure (secondary endpoint) between the study groups [12].

DUBIUS trial compared downstream vs upstream administration of P_2Y_{12} inhibitors in patients with non-ST elevation acute coronary syndrome (NSTE-ACS) undergoing percutaneous coronary intervention (PCI) [13]. This randomized, open-label trial randomized patients to pretreatment with ticagrelor before undergoing angiography (upstream P_2Y_{12} inhibition) vs treatment with P_2Y_{12} inhibitors after angiography and prior to PCI (downstream P_2Y_{12} inhibition). Patients in the downstream P_2Y_{12} inhibition treatment group were further randomized to receive ticagrelor vs prasugrel. Between the treatment groups, there was no significant difference in the primary outcome defined as a composite of death from vascular causes, non-fatal myocardial infarction, non-fatal stroke and major or fatal bleeding at 30 days after randomization. Of Note, this trial excluded patients who were on chronic oral anticoagulation [14].

ATPCI trial evaluated anti-anginal treatment with trimetazidine vs placebo in patients with recent successful PCI [15]. A total of 6007 patients within 30 days following a successful PCI for stable or unstable coronary artery disease

were randomized to receive trimetazidine 35 mg twice daily or matching placebo. Patients were followed up for a median of 47.5 months and there was no significant difference in the primary composite endpoints defined as cardiac death, hospital admission for cardiac events, or persistent angina requiring adding, switching, or increasing the dose of antianginal medications or leading to coronary angiography [16].

REALITY trial compared a restrictive red blood cell transfusion strategy vs a liberal strategy in patients with recent acute myocardial infarction (AMI) and anemia. Patient with AMI and hemoglobin (Hb) ≤ 10 g/dL and > 7 g/dL were enrolled and those with cardiogenic shock, post PCI or CABG AMI, life-threatening or massive bleeding, history of transfusion in the previous 30 days and history of malignant hematologic disease were excluded from the study. A total of 666 patients were randomized in a 1:1 fashion to transfusion with either a liberal strategy (defined as transfusion when Hb ≤ 10 g/dL with a goal of > 11 g/dL) or a restrictive strategy (defined as transfusion when Hb ≤ 8 g/dL with a goal of 8–10 g/dL). The primary endpoint defined as the 30-day composite of all-cause mortality, non-fatal stroke, non-fatal recurrent MI, and emergency revascularization prompted by ischemia was not statistically different between the arms and indicated noninferiority of the restrictive strategy.

Finally, we encourage readers to explore the broader content of the ESC presentations for other interesting studies and other topics of interest. As an example, the 2020 ESC provided new guidelines on Atrial Fibrillation [17], Non-ST-Segment Elevation Acute Coronary Syndromes [18], Sports Cardiology and Exercise in Patients with Cardiovascular Disease [19] and Adult Congenital Heart Disease [20].

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