

# Highlights from Studies in Cardiovascular Disease Prevention Presented at the Digital 2020 European Society of Cardiology Congress: Prevention Is Alive and Well

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Accepted: 16 September 2020 / Published online: 3 October 2020

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## Abstract

**Purpose of Review** The review highlights selected studies related to cardiovascular disease (CVD) prevention that were presented at the 2020 European Society of Cardiology (ESC) Congress—The Digital Experience.

**Recent Findings** The studies reviewed include clinical trials on novel RNA interference-based lipid-lowering therapies AKCEA-APOCIII-L<sub>Rx</sub> and vupanorsen (AKCEA-ANGPTL3-L<sub>Rx</sub>); the EVAPORATE trial assessing the effects of icosapent ethyl on coronary plaque volume progression; the LoDoCo2 trial evaluating the efficacy of low-dose colchicine in cardiovascular disease risk reduction among patients with chronic coronary artery disease; as well as the EMPEROR-Reduced trial evaluating cardiovascular and renal outcomes with empagliflozin in patients with heart failure and reduced ejection fraction. In addition, we review the BPLTTC analysis on blood pressure treatment across blood pressure levels and CVD status and discuss findings from the BRACE CORONA study that examined continuing versus suspending angiotensin-converting enzyme inhibitor or angiotensin receptor blockers in patients on these antihypertensive medications who were hospitalized with COVID-19 infection.

**Summary** The studies presented at the 2020 digital ESC Congress highlight the continuing advancements in the field of CVD prevention.

**Keywords** Cardiovascular disease prevention · APOCIII · ANGPTL3 · Colchicine · Empagliflozin · COVID-19

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This article is part of the Topical Collection on *Reviews and New Research Implications*

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## Introduction

Novel advancements in the field of cardiovascular disease (CVD) prevention were recently showcased at the 2020 European Society of Cardiology Congress (ESC Congress 2020).

Due to the ongoing coronavirus disease 2019 (COVID-19) pandemic, the scientific session was held on a digital platform, allowing for the presentation and discussion of the latest science in cardiology despite the COVID-19 outbreak. Below, we summarize findings from seven major studies relevant to

CVD prevention that were presented at ESC Congress 2020 (Table 1).

The studies include clinical trials of novel lipid-lowering therapies AKCEA-APOCIII- $L_{Rx}$  and vupanorsen (AKCEA-ANGPTL3- $L_{Rx}$ ). We further highlight data from the Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy (EVAPORATE) study that evaluated the effect of icosapent ethyl on coronary plaque volume; findings from the Low Dose Colchicine 2 (LoDoCo2) trial assessing the efficacy of colchicine in cardiovascular disease risk reduction among patients

**Table 1** Summary of the trials reviewed in this article

Study	Intervention	Design	N	Follow-up duration	Principle findings
AROPOC 331001 (8)	SiRNA targeting APOC3	Open-label, phase I clinical trial in healthy human volunteers	12	16 weeks	Mean max change: 1. APOC3: -94% 2. TG: -75% 3. LDL-C: -25% 4. apoB: -33% 5. HDL-C: +75% No SAE. 2/12 (17%) with ISR
AROANG1001 [1]	SiRNA targeting ANGPTL3	Open-label, phase I clinical trial in healthy human volunteers	12	16 weeks	Mean max change: 1. ANGPTL3: -96% 2. TG: -72% 3. LDL-C: -50% 4. apoB: -49% 5. non-HDL-C: -54% 6. HDL-C: -47% No SAE. Headache and URI most common AE
EVAPORATE [2]	Icosapent ethyl 4 g daily	Randomized, double-blind, placebo-controlled trial	80	18 months	Change in LAP volume: $-0.3 \pm 1.5 \text{ mm}^3$ in IPE vs. $0.9 \pm 1.7 \text{ mm}^3$ in placebo, $p = 0.006$
LoDoCo2 [3]	Colchicine 0.5 mg daily	Randomized, double-blind, placebo-controlled trial	5522	28.6 months	Primary composite endpoint (CV death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization): HR 0.69, 95% CI 0.57–0.83, $p < 0.001$
BPLTTC [4]	Blood pressure lowering	Meta-analysis of individual-level data from 48 clinical trials of blood pressure lowering	348,854	4 years	10% risk reduction in major CV outcomes, 13% lower risk for stroke, 7% for ischemic heart disease, 14% for HF, and 5% for death per 5 mmHg reduction in SBP
EMPEROR-Reduced [5]	Empagliflozin 10 mg daily	Randomized, double-blind, placebo-controlled trial	3730	16 months	Primary composite endpoint (CV death or HF hospitalization): HR 0.75, 95% CI 0.65–0.86, $p < 0.001$
BRACE CORONA [6]	Continuing vs. suspending ACEI/ARB	Phase IV randomized trial	659	30 days	Primary outcome (days alive and out of hospital at 30 days): $21.9 \pm 8.0$ mean days in continuing ACEI/ARB group vs. $22.9 \pm 7.1$ mean days in suspending ACEI/ARB group (mean difference between groups was -1.1 days, 95% CI -2.33–0.17). Mean ratio 0.95, 95% CI 0.90–1.01, $p = 0.09$

Abbreviations: AE serious adverse events, apoB apolipoprotein B, apoC-III apolipoprotein C-III, ANGPTL3 angiopoietin-like protein 3, HDL-C, high-density lipoprotein cholesterol, TG triglycerides, non-HDL-C non-high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, SAE serious adverse events, ISR injection site reactions, URI upper respiratory tract infection, LAP low-attenuation plaque, IPE icosapent ethyl, CV cardiovascular, MI myocardial infarction, HR hazard ration, CI confidence interval, HF heart failure, SBP systolic blood pressure, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker

with chronic coronary artery disease; as well as the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced) trial evaluating cardiovascular (CV) and renal outcomes with empagliflozin in heart failure. In addition, we review the Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) analysis on blood pressure treatment across blood pressure levels and CVD status. Finally, we outline findings from the Angiotensin Receptor Blockers and Angiotensin-converting Enzyme Inhibitors and Adverse Outcomes in Patients With COVID19 (BRACE CORONA) trial that examined continuing versus suspending angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) in patients hospitalized with COVID-19 infection. In this review, we will provide concise summaries of the major findings from these studies, put these findings in the context of what is known on the topic, and discuss their clinical implications [7–9].

### RNA Interference Therapies Targeting Novel Triglyceride Pathways: ARO-APOC3 and ARO-ANG3

Lipoprotein lipase (LPL) is a key enzyme involved in the clearance of triglycerides (TG) and triglyceride-rich lipoproteins (TGRL) from the blood circulation. Apolipoprotein C-III (apoC-III) and angiopoietin-like protein 3 (ANGPTL3) are hepatic secretory proteins that inhibit the activity of LPL and consequently increase TG levels. ApoC-III also decreases the uptake and clearance of TGRL via LPL-independent mechanisms, with an associated increase in very low-density lipoprotein (VLDL) and decrease in high-density lipoprotein (HDL). Loss of function mutations in ANGPTL3 results in reduction in low-density lipoprotein (LDL), VLDL, HDL, and TG. Mendelian randomization studies have shown that polymorphisms of the genes encoding these proteins are causally associated with atherosclerotic cardiovascular disease (ASCVD) [10, 11]. Considerable interest has been shown in the development of novel agents for these potential therapeutic targets [12].

RNA interference (RNAi) or post-transcriptional gene silencing is a biological process whereby small RNA molecules inhibit gene expression or translation by binding to and neutralizing messenger RNA (mRNA) molecules. Anti-sense oligonucleotide (ASO) and small interfering RNA (siRNA) are two types of RNAi technology currently being employed to target production of apoC-III and ANGPTL3 and thereby, lower levels of TG. siRNA is a double-stranded RNA, which upon entry into the cytoplasm, hybridizes and degrades mRNA [13].

### Study Overview: RNAi Targeting apoC-III with ARO-APOC3 in Healthy Volunteers

ARO-APOC3 is a siRNA that inhibits the production of apoC-III. This in turn increases the hydrolysis of TGRL via LPL, resulting in increased uptake and clearance of TGRL with an overall reduction in TG and VLDL and increase in HDL-C. AROAPOC331001 is the first in human study to evaluate the efficacy, safety, and tolerability of ARO-APOC3 in healthy volunteers [14].

In an open-label clinical trial, 12 healthy volunteers were administered 10 mg ( $n = 4$ ), 25 mg ( $n = 4$ ), and 50 mg ( $n = 4$ ) of ARO-APOC3 by subcutaneous injection on day 1 and day 29 (week 4). Over a 16-week follow-up period, repeat doses of ARO-APOC3 demonstrated substantial and durable mean reductions in apoC-III levels by 73% with 10 mg, 90% with 25 mg, and 94% with 50 mg dosage and fasting TG levels by 58% (10 mg), 70% (25 mg), and 75% (50 mg), respectively. Fasting low-density lipoprotein cholesterol (LDL-C) levels were reduced by 20–25%, apolipoprotein B (apoB) levels by 28–33%, while high-density lipoprotein cholesterol (HDL-C) levels increased by 30–74%. Moreover, there was a reduction in both fasting TG levels as well as post-prandial lipemia.

ARO-APOC3 had a favorable safety and tolerability profile. All adverse events (AE) were mild, with the most common being diarrhea (33%). Local injection site reactions occurred in 2/12 (17%) of the participants with most injection site AE resolving within 48 h. There were no reported serious AEs and no clinically significant changes in platelets, bilirubin, creatinine, or liver enzymes.

### Study Overview: RNAi Targeting ANGPTL3 with ARO-ANG3 in Healthy Volunteers

ARO-ANG3 is a siRNA directed to hepatocytes where it specifically degrades the mRNA of ANGPTL3, resulting in gene silencing. AROANG1001 is a first in human study carried out in healthy volunteers to study the pharmacokinetics, safety, and tolerability of ARO-ANG3 [1].

In an open-label trial, 12 healthy volunteers were administered 100 mg ( $n = 4$ ), 200 mg ( $n = 4$ ), and 300 mg ( $n = 4$ ) of multiple subcutaneous doses of ARO-ANG3 on day 1 and day 29 (week 4). Substantial and durable mean reductions were demonstrated in ANGPTL3 levels by 81% (100 mg), 86% (200 mg), and 96% (300 mg) and fasting TG by 62% (100 mg), 72% (200 mg), and 67% (300 mg), respectively. It also demonstrated a mean maximum reduction in LDL-C by 50%, apoB by 42%, non-HDL-C by 54%, and HDL-C by 47% and showed improvement in post-prandial lipemia.

ARO-ANG3 was well-tolerated without any serious adverse events with no significant discontinuation of the study medication. The most common adverse events were headache (5/12, 42%), upper respiratory tract infection (4/12, 33%), and

vascular access bruising/swelling (4/12, 33%). Injection site reactions occurred in 2/12 participants (17%). There were no clinically significant adverse effects on the levels of platelets, total bilirubin, creatinine, or transaminases.

## Clinical Implications

There is increasing recognition of the causal role of TGRL in the pathogenesis of ASCVD and TG as a potential marker for increased ASCVD risk. As a result, there has been a growing focus on developing TG-lowering strategies with potential for CV benefit. Pharmacological inhibition of apoC-III with ARO-APOC3 produced favorable lipid changes, with substantial and durable reduction in TG, apoC-III, and LDL-C; increase in HDL-C; and improvement in post-prandial lipemia. Similarly, a repeated dose of ARO-ANGPTL3 also demonstrated significant dose-dependent reduction in fasting ANGPTL3, TG, LDL-C, apoB, and non-HDL-C. One difference was a decrease, as opposed to increase, in HDL-C. Furthermore, both ARO-APOC3 and ARO-ANGPTL3 demonstrated acceptable safety and tolerability profile without any serious adverse events. In individuals treated with optimal statin and other evidence-based lipid-lowering therapies, considerable residual ASCVD risk persists [15••]. ApoC-III and ANGPTL3 inhibition have the potential to effectively treat combined hyperlipidemia and decrease residual risk in patients with ASCVD beyond current guideline-recommended standard of care. In addition, significant LDL-C reduction with ANGPTL3 inhibition appears to be independent of the LDL receptor pathway. Therefore, ANGPTL3 inhibitors may serve as an important adjunct in the treatment of homozygous FH patients with mutations in the LDL receptor pathway [16]. While the results from both of these studies are promising, they should be viewed with caution as this technology is novel, and we await more data from future phase II and III clinical trials to ascertain their effects on CV outcomes and establish long-term efficacy, safety, and tolerability before this technology can be integrated into routine clinical practice.

## Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients with Elevated Triglycerides on Statin Therapy: Final Results of the EVAPORATE Trial

Icosapent ethyl (IPE) is a highly purified form of eicosapentaenoic acid. In the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT), individuals with either established ASCVD or with diabetes and additional CV risk factors on stable statin therapy (with or without ezetimibe) were randomized to IPE 4 g daily versus placebo. Over a median follow-up period of 4.9 years, participants in the IPE group showed reduced adverse CV

outcomes when compared with placebo (4.3% vs. 5.2%; hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.66 to 0.98,  $p = 0.03$ ) [17•]. The EVAPORATE trial examined the effect of IPE on coronary plaque progression among patients with persistently elevated triglycerides on statin therapy [2]. The present study sought to clarify the mechanism of benefit of IPE which was shown to reduce CV events in the REDUCE-IT trial.

## Study Overview

EVAPORATE was a randomized, double-blind, placebo-controlled trial of 80 patients aged 30–85 years with known coronary atherosclerosis (narrowing of  $\geq 20\%$  in 1 coronary artery by either invasive angiography or coronary computed tomography angiography CTA), elevated fasting triglyceride levels (135–499 mg/dL), and LDL-C levels between  $\geq 40$  and  $\leq 115$  mg/dL. Patients were required to be on statin therapy, with or without ezetimibe, and demonstrated adherence to therapeutic lifestyle changes including diet and exercise. The IPE dose was 2 g twice daily with food. The primary endpoint was the change in low-attenuation plaque (LAP) volume measured using multidetector computed tomography (MDCT) angiography at 18 months. Percent change in plaque characteristics was compared using multiple linear regression adjusted for baseline plaque, age, sex, diabetes status, hypertension, and baseline triglyceride levels using an intention-to-treat analysis.

The mean age of study participants was  $57 \pm 6$  years, 54% men, 82% white, 69% with diabetes mellitus, 77% with hypertension, and 43% with prior cigarette smoking history. Mean triglyceride level was  $259 \pm 78$  mg/dL, with no significant differences between the 2 groups. Change in LAP volume was significantly lower among those treated with IPE ( $-0.3 \pm 1.5$  mm<sup>3</sup>) versus mineral oil placebo ( $0.9 \pm 1.7$  mm<sup>3</sup>) ( $p = 0.006$ ). Other plaque characteristics were also improved in the IPE group including change in total plaque volume ( $-9\%$  vs.  $+11\%$ ,  $p = 0.002$ ), change in total non-calcified plaque volume ( $-19\%$  vs.  $+9\%$ ,  $p = 0.0005$ ), change in fibrofatty plaque ( $-34\%$  vs.  $+32\%$ ,  $p = 0.0002$ ), change in fibrous plaque ( $-20\%$  vs.  $1\%$ ,  $p = 0.003$ ), and change in calcified plaque ( $-1\%$  vs.  $+15\%$ ,  $p = 0.053$ ). Notably, there were no significant differences in total cholesterol, LDL-C, high-density lipoprotein cholesterol, and triglyceride levels from baseline to follow-up between the two groups.

## Clinical Implications

The EVAPORATE trial demonstrates that IPE reduces CV outcomes likely, at least in part, by slowing the progression of high-risk atherosclerotic plaques. IPE decreased the progression of LAP, which reflects plaques that are more prone to rupture. Prior studies have demonstrated that statins and

proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors also reduce coronary plaque progression [18, 19]. The benefits of lipid-lowering drugs on CV outcomes are likely in part mediated by their effects on coronary plaques with a decrease in the number of plaques that are likely to rupture and a shift to and resultant increase in those that are more stable (calcified).

The clinical use of CCTA at present is mainly for risk prediction in the primary prevention of ASCVD. Coronary artery calcium (CAC) is assigned a IIA recommendation for additional risk stratification among intermediate-risk patients after evaluating risk-enhancing factors [20••]. At presents, only LDL-C is used to assess the response and adherence to lipid-lowering therapy. Future studies are warranted to investigate the potential role of CCTA or other measurements of atherosclerotic plaque progression among high-risk patients in order to document response to treatment. These benefits must be weighed against the inherent risks of contrast, exposure to radiation, and cost. The anatomic approach of evaluating sub-clinical atherosclerosis using CCTA and CAC is quite promising for both primary and secondary prevention of ASCVD.

### Colchicine in Patients with Chronic Coronary Disease: the LoDoCo2 Trial

Residual ASCVD risk exists even among patients who are optimally treated with guideline-directed medical therapy, including statins, antiplatelet agents, and treatment of other risk factors. A growing body of evidence suggests that increased inflammation is causally associated with risk for ASCVD [21]. The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) demonstrated that treatment of secondary prevention patients with elevated inflammation as measured by elevated high-sensitivity C-reactive protein (hs-CRP) with canakinumab resulted in significantly lower rates of recurrent cardiovascular events compared with placebo [22•]. The Low Dose Colchicine (LoDoCo) trial was an open-label study of 531 participants that showed a reduced risk for acute CVD events in individuals with chronic coronary artery disease treated with colchicine (HR 0.33, 95% CI 0.18–0.59,  $p < 0.001$ ) [23]. The Colchicine Cardiovascular Outcomes Trial (COLCOT) demonstrated the effect of colchicine for cardiovascular risk reduction among patients with recent myocardial infarction (MI) within the past 30 days [24•]. In COLCOT, cardiovascular event rates were 5.5% among patients in the colchicine group, compared with 7.1% in the placebo group (hazard ratio, 0.77; 95% CI 0.61 to 0.96;  $p = 0.02$ ). The LoDoCo2 trial built upon the results of the LoDoCo and COLCOT studies and examined the effect of colchicine on cardiovascular events among a large sample of patients with chronic/stable coronary artery disease (CAD) [3].

### Study Overview

LoDoCo2 was a randomized, double-blind, placebo-controlled trial of 5522 patients aged 35–82 years with stable coronary artery disease and no acute cardiovascular events in the 6 months prior to randomization. Patients were excluded if they had severe valvular heart disease, severe heart failure, moderate-to-severe renal impairment, or known side effects from colchicine. The presence of CAD was documented using prior invasive coronary angiography or CCTA or a CAC score of at least 400 Agatston units. All patients underwent a 1-month run-in phase where they received 0.5 mg of colchicine daily and then were subsequently randomized in a 1:1 fashion to receive 0.5 mg of colchicine once daily or matching placebo. The primary endpoint was a composite of CV death, spontaneous (nonprocedural) MI, ischemic stroke, or ischemia-driven coronary revascularization. Cox regression models were used to study the association between colchicine versus placebo and the primary outcomes using an intention-to-treat analysis.

The mean age of the study participants was  $66 \pm 8.6$  years, 15% were women, 12% were current smokers, and 18% had diabetes mellitus. The majority of patients treated with colchicine were on guideline-directed medical treatment of antiplatelets (67%), lipid-lowering drugs (97%), anticoagulants (12%), and antihypertensive agents (72% renin-angiotensin inhibitors, 61% beta-blocker, 23% calcium channel blocker). The majority of patients (84%) had a history of acute coronary syndrome with 68% having had an event at least 24 months before randomization. The distribution of baseline characteristics was equal between the 2 groups.

Over a median follow-up duration of 29 months, a total of 451 composite events occurred, with 6.8% in the colchicine group and 9.6% in the placebo group. The absolute event rates per 100 person-years were 2.5 and 3.6, respectively (HR 0.69, 95% CI 0.57–0.83,  $p < 0.001$ ). This was mainly driven by a reduction in MI and ischemia-driven coronary revascularization. Non-CV deaths occurred more frequently among the colchicine group, but this was not significant. There were similar rates of cancer diagnosis, hospitalization for infection, hospitalization for pneumonia, and hospitalization for a gastrointestinal reason in either group. Neutropenia and myotoxic effects were overall low in both groups and not significantly different. Gout occurred significantly less frequently among those treated with colchicine (cumulative incidence ratio, 0.40; 95% CI, 0.28 to 0.58). The effect of colchicine as compared with placebo was consistent in prespecified subgroup analyses.

### Clinical Implications

Results from the LoDoCo2 study further solidifies inflammation as an important risk for ASCVD and provides evidence

supporting use of anti-inflammatory agents to target this risk. Colchicine is a commonly prescribed, well-established medication, which may facilitate the repurposing of this agent for use in CVD prevention. Importantly, the safety of anti-inflammatory agents must be well established particularly with regard to non-cardiovascular outcomes. However, unlike canakinumab, which is known to target a specific inflammatory pathway, the mechanism of action for colchicine in the reduction of ASCVD remains unclear. Moreover, inflammatory markers such as hs-CRP were not measured routinely in LoDoCo2, and therefore, future studies are warranted to identify potential biomarkers that can be used to better stratify patients who most benefit from colchicine.

## Blood Pressure Lowering Treatment Trialists' Collaboration: BPLTTC Trial

### Study Overview

The BPLTTC trial sought to examine the effect of blood pressure lowering for the prevention of ASCVD outcomes among patients with normal blood pressure (BP). Prior studies have yielded inconsistent results leading to contradictory treatment recommendations.

BPLTTC researchers conducted a meta-analysis of individual-level data from 48 clinical trials worldwide [4]. The sample size included 348,854 participants, and the average duration of follow-up was 4 years. Participants were divided into 2 groups based on a prior diagnosis of ASCVD. Each group was further divided into 7 subgroups based on categories of systolic blood pressure (SBP) at study entry (< 120, 120–129, 130–139, 140–149, 150–159, 160–169, and  $\geq$  170 mmHg).

Each 5 mmHg reduction in SBP was associated with a 10% relative risk reduction of major cardiovascular outcomes including a 13% lower risk for stroke, 7% for ischemic heart disease, 14% for heart failure, and 5% for death. Importantly, there was no effect modification with respect to relative risk reduction (per 5 mmHg) by presence of ASCVD or SBP category at study entry. However, it should be noted that in patients with higher baseline SBP, achieving a greater magnitude of change in SBP will likely be associated with a greater absolute risk reduction in cardiovascular events.

### Clinical Implications

Current ACC/AHA hypertension guidelines from 2017 recommend initiation of BP-lowering therapy among patients with BP  $\geq$  140/90 mmHg or with 130–189/80–89 mmHg if they have clinical ASCVD or  $\geq$  10% estimated risk of ASCVD in those without prior ASCVD with a BP treatment goal of < 130/80 mmHg [25••]. Based on results of the

BPLTTC study, the decision to prescribe BP-lowering therapy may not be based on a prior diagnosis of ASCVD or current BP levels as there is no evidence that the effects of BP-lowering drugs differ by baseline SBP values even as low as < 120 mmHg among both primary and secondary prevention populations.

The BPLTTC study challenges the current paradigm of hypertension treatment. The current approach to BP lowering is not only based on BP criteria and clinical characteristics of patients including the presence of ASCVD but also incorporates risks of aggressive BP lowering including effects on kidney disease progression and serious safety outcomes such as falls. Furthermore, the effect of BP lowering on diastolic blood pressure (DBP) and its subsequent effect of cardiovascular outcomes needs to be further studied to document the safety of aggressive DBP lowering. Until more information is available, clinicians should continue to adhere to current guidance on BP lowering using a shared decision-making approach incorporating patient values and preferences. BP should be measured at every visit to assess response and adherence to treatment. Based on the present study, it may be reasonable to continue the present dose of BP-lowering drugs among patients who achieve SBP < 120 mmHg and are tolerating therapy well without side effects or adverse outcomes.

## EMPEROR-Reduced: Empagliflozin in Heart Failure with a Reduced Ejection Fraction, with and Without Diabetes

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a class of oral medications currently approved for the treatment of diabetes mellitus. Empagliflozin, canagliflozin, and dapagliflozin comprise the currently available SGLT2i agents [26]. The EMPA-REG study, a randomized controlled trial of 7020 participants with diabetes and established CVD, showed a decrease in risk of the composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke among individuals in the empagliflozin group compared with placebo (HR 0.86, 95% CI 0.74–0.99,  $p = 0.04$  for superiority) [27•]. Moreover, there was a significantly lower rate of cardiovascular death and heart failure hospitalization in the empagliflozin group compared with placebo. Findings from cardiovascular outcomes trials suggest that cardiovascular benefits, especially with respect to heart failure, are a class effect among SGLT2i [28, 29]. Since the original cardiovascular outcomes trials of SGLT2i, there has been immense interest in incorporating these agents in the treatment regimen for patients with heart failure with reduced ejection fraction (HFrEF). The rationale of the EMPEROR-Reduced study was to assess the efficacy of empagliflozin 10 mg daily in the reduction of cardiovascular death or heart failure in patients with heart failure and with or without diabetes [5].

## Study Overview

EMPEROR-Reduced was a randomized, placebo-controlled trial of 3730 patients, half of whom had diabetes mellitus. Participants were required to have class II, III, or IV heart failure and a left ventricular ejection fraction (LVEF)  $\leq 40\%$  on guideline-directed medical therapy. Participants with LVEF  $\geq 30\%$  also had to have a history of hospitalization for heart failure within the previous 12 months or a high level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP)  $\geq 1000$  pg/mL in those with EF 31–35%,  $\geq 2500$  pg/mL in those with EF of 36–40%, or  $\geq 600$  pg/mL in those with EF of  $\leq 30\%$ . The primary outcome was a composite of cardiovascular death or heart failure hospitalization. Key secondary outcome measures included first and recurrent heart failure hospitalizations as well as decline in estimated glomerular filtration rate (eGFR).

Over a median follow-up of 16 months, individuals in the empagliflozin group had significantly lower primary outcome events compared with placebo (HR 0.75, 95% CI 0.65–0.86,  $p < 0.001$ ; ARR 5.3%). There was no heterogeneity of effect based on diabetes status. Total heart failure hospitalization events were significantly lower in the empagliflozin group compared with placebo: 10.7 versus 15.5 events/100 patient-year (HR 0.70, 95% CI 0.58–0.85,  $p < 0.001$ ), as was the annual rate of decline in eGFR ( $-0.55$  vs.  $-2.28$  mL/min/1.73 m<sup>2</sup> of body-surface area/year,  $p < 0.001$ ). There was no significant difference in death from cardiovascular cause or death from any cause between the empagliflozin and placebo groups. With respect to safety, uncomplicated genital tract infection was more frequent in the empagliflozin group compared with placebo (1.7% vs. 0.6%), while rates of hypoglycemia and lower-limb amputation were not significantly different between groups.

## Clinical Implication

The findings of EMPEROR-Reduced are consistent with the recent DAPA-HF trial, which assessed the efficacy of dapagliflozin in reduction of cardiovascular death or heart failure hospitalization in patients with HFrEF with or without diabetes mellitus [30]. In EMPEROR-Reduced, the significance in the primary outcome was driven by a reduction in heart failure events. Importantly, there was a similar risk reduction noted among those with and those without diabetes mellitus. Current evidence suggests that empagliflozin confers significant cardiovascular and renal protection in patients with diabetes and HFrEF, showing reduction in risk for cardiovascular mortality and heart failure hospitalization. Results from EMPEROR-Reduced suggest that empagliflozin may also have a role in the treatment of HFrEF patients even without diabetes given the beneficial impact on heart failure hospitalization and renal outcomes.

## BRACE CORONA: Continuing Versus Suspending ACE Inhibitors and ARBs in COVID-19

Underlying CVD or cardiovascular risk factors increase risk for morbidity and mortality in patients infected with COVID-19 [31]. The renin-angiotensin-aldosterone system (RAAS) plays an important role in the mechanism of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) tissue invasion and pathogenesis. SARS-CoV-2 is thought to enter cells via surface bound angiotensin-converting enzyme 2 (ACE2), which then leads to downregulation of surface ACE2 and accumulation of angiotensin II. Increased levels of angiotensin II are associated with vasoconstriction, fluid accumulation, and fibrosis [32].

There has been uncertainty regarding the use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in patients with COVID-19. On the one hand, ACEI/ARB may enhance viral binding and entry by increasing the expression of ACE2 receptors. On the other hand, diminishing the production of angiotensin II with ACEI/ARB and increased generation of angiotensin [7–13] may attenuate inflammation and fibrosis; thus, their use may be protective [33]. The rationale of the BRACE CORONA trial was to compare the impact on adverse outcomes between hospitalized COVID-19 patients who were continued on their chronic ACEI/ARB regimen versus those who had these medications temporarily held [6].

## Study Overview

BRACE CORONA was a multi-center randomized trial of 659 patients hospitalized with a confirmed diagnosis of COVID-19 and who were on a chronic regimen of ACEI or ARB [34]. Patients who were hemodynamically unstable prior to confirmed diagnosis of COVID-19, those with decompensated heart failure hospitalization in the prior 12 months, those with more than 3 anti-hypertensive medications, and those using sacubitril-valsartan were excluded. Included participants were randomized 1:1 to either continued use of ACEI/ARB treatment or to temporarily suspending ACEI/ARB treatment for 30 days. The primary outcome was days alive and out of the hospital at 30 days.

At 30 days, 95.0% of the continuing ACEI/ARB group were alive and out of the hospital compared with 91.8% of the suspending ACEI/ARB group. There was no difference in primary outcome between the continuing ACEI/ARB ( $21.9 \pm 8.0$  mean days) and suspending ACEI/ARB ( $22.9 \pm 7.1$  mean days) groups (mean ratio 0.95, 95% CI 0.90–1.01,  $p = 0.09$ ). The mean difference between groups was ( $-1.1$  days, 95% CI  $-2.33$ – $0.17$ ).

## Clinical Implication

ACEI and ARB agents are well established, evidence-based therapy in the treatment of hypertension and heart failure. The BRACE CORONA trial provides clinical trial data showing that there is no clinical benefit in routinely withholding these agents in hospitalized patients with mild to moderate COVID-19 infections. Therefore, unless otherwise indicated, ACEI/ARB therapy should be generally continued in patients with COVID-19.

## Conclusion

The 2020 ESC Congress hosted several important clinical trials that demonstrate great strides within the field of CVD prevention and underscore the potential for further advancements.

## Compliance with Ethical Standards

**Conflict of Interest** SSV: Grant Support: Department of Veterans Affairs, World Heart Federation, Tahir and Jooma Family. Honorarium: American College of Cardiology (Associate Editor for Innovations, [acc.org](http://acc.org)).

SM: Personal fees from Amgen, Sanofi, Regeneron, Esperion, AstraZeneca, 89bio; Grants from Apple, Google, iHealth, Nokia, Maryland Innovation Initiative, American Heart Association, Aetna Foundation, PJ Schafer Memorial Fund, David and June Trone Family Foundation, Akcea Therapeutics, National Institutes of Health, outside the submitted work. In addition, SM has a pending patent on System of LDL-C Estimation. And he is a founder of and holds equity in Corrie Health, which intends to further develop the platform.

XJ, MAR, AH, and AA do not have any relevant disclosures.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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