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REVIEWS AND SCIENTIFIC MEETINGS AND NEW RESEARCH IMPLICATIONS (S. VIRANI, SECTION EDITOR)

Highlights of Cardiovascular Disease Studies Presented at the 2021 American Heart Association Scientific Sessions

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Abstract

Purpose of Review This review highlights major studies across a broad array of topics presented at the virtual 2021 American Heart Association (AHA) Scientific Sessions.

Recent Findings. Assessed studies examine a remotely delivered hypertension and lipid program in 10,000 patients across a diverse healthcare network; a cluster-randomized trial of a village doctor-led intervention for hypertension control; empagliflozin in heart failure with preserved ejection fraction (EMPEROR-Preserved); efficacy and safety of empagliflozin in hospitalized heart failure patients (EMPULSE); icosapent ethyl versus placebo in outpatients with coronavirus disease 2019 (PREPARE-IT 2); clinical safety, pharmacokinetics, and low-density lipoprotein cholesterol-lowering efficacy of MK-0161, an oral proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor; and effects of aspirin on dementia and cognitive impairment in the ASCEND trial.

Summary Research presented at the 2021 AHA Scientific Sessions emphasized the importance of interventions for cardiovascular disease prevention.

Keywords Aspirin · Atherosclerotic cardiovascular disease · Cardiovascular prevention · Empagliflozin · Heart failure

Abbreviations

ACS	Acute coronary syndrome
ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	Atherosclerotic Cardiovascular Disease
BP	Blood pressure
CAD	Coronary artery disease
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
HF	Heart failure

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HFE	Heart failure events
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HHF	Hospitalization for heart failure
HR	Hazard ratio
HTN	Hypertension
IPE	Icosapent ethyl
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire Total Symptom Score
LDL-C	Low-density lipoprotein cholesterol
MI	Myocardial infarction
OR	Odds ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
RRR	Relative risk reduction
SBP	Systolic blood pressure
SGLT-2	Sodium-glucose cotransporter 2
TICSm	Telephone Interview for Cognitive Status
VF	Verbal fluency

Introduction

The 2021 American Heart Association (AHA) Scientific Sessions featured several noteworthy clinical trials pertaining to cardiovascular disease (CVD) prevention and treatment. Reviewed studies assess a remotely delivered hypertension and lipid program in 10,000 patients across a diverse healthcare network; a cluster-randomized trial of a village doctor-led intervention; empagliflozin in heart failure with preserved ejection fraction (HFpEF; EMPEROR-Preserved) [1••]; icosapent ethyl (IPE) versus placebo in outpatients with coronavirus disease 2019 (COVID-19; PREPARE-IT 2); clinical safety, pharmacokinetics, and low-density lipoprotein cholesterol-lowering efficacy of MK-0161, an oral proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor; and effects of aspirin on dementia and cognitive impairment in the ASCEND trial. Like prior publications, we will discuss the significance and clinical implications of select research presentations [2–4]. A table summarizing the studies discussed is included at the end of this manuscript (Table 1).

A remotely delivered hypertension and lipid program in 10,000 patients across a diverse healthcare network

Study Overview

Disparities in cardiovascular disease management are apparent in the undertreatment of hypertension (HTN) and hypercholesterolemia [5–7]. Despite available treatment options, up to half of the patients with modifiable cardiovascular risk factors do not receive adequate medical care [8, 9]. To overcome this clinical challenge, a focus on remote health has emerged. Still, there is concern regarding the "digital health divide" whereby those who are less likely to connect to healthcare via digital means experience a barrier to care which may exacerbate health inequities [10–13]. The Digital Care Transformation Study regarding lipid and hypertension control was designed to address these gaps in care by means of a remote program.

Within the Mass General Brigham health system, patients in need of HTN or low-density lipoprotein cholesterol (LDL-C) optimization were identified by provider referral and electronic health record screening. A remote care delivery platform was enabled by a team of non-licensed navigators and pharmacists who gathered data and provided education, prescriptions based on clinical algorithms, and communicated decisions remotely. HTN management was enabled by WiFi, cellular, and Bluetooth devices. Personalized remote care was delivered without in-person visits with physicians. Program oversight was provided by specialists and primary care physicians. Outcomes of interest included reductions in blood pressure (BP) and LDL-C from baseline to completion of the program.

Enrollment totaled 11,000 patients of whom 12% were > 75 years of age, 55% were female, 29% were non-White, and 8% were non-English speaking. Twenty-nine percent had established atherosclerotic cardiovascular disease (ASCVD), 22% had diabetes without ASCVD, 26% had LDL > 190 without diabetes or ASCVD, and 23% were deemed high-risk primary prevention. The mean change in BP from program baseline to exit was a change of 10/6 mmHg for all enrolled patients and 12/6 mmHg in patients who completed the program and achieved maintenance. Ninety-two percent of patients who completed the program reached their guideline-recommended BP goals as defined by the ACC/AHA in this patient population as a BP target of < 130/80 mmHg. Significant reductions in LDL-C were noted in all enrolled patients, 45 mg/dL change in cholesterol, with even more pronounced reduction in LDL-C noted in those who completed the program, 70 mg/dL representing a 50% drop from baseline. Ninety-four percent of patients who completed the program achieved their LDL-C guideline-directed goals as determined by the ACC/AHA guidelines. Benefits remained consistent when analyzed across race, ethnicity, and primary language subgroups. Engagement and retention were also similar across each of these subgroups.

Table 1 Summary of major randomized clinical trials pertaining to cardiovascular disease prevention at the 2021 American Heart Association Scientific Sessions

Clinical trial	Study design & population	Treatment arm	Control arm	Primary outcome	Results
A remotely delivered hypertension and lipid program in 10,000 patients across a diverse healthcare network	- Prospective study - 11,000 patients: 12% older than 75yo, 55% female, 29% non-White, and 8% non-English speaking	29% with established ASCVD, 22% had diabetes without ASCVD, 26% had LDL > 190 without diabetes or ASCVD, and 23% were deemed high-risk primary prevention	None	Reduction in BP and LDL-C	Mean change in BP of 10/6 mmHg for all enrolled patients and 12/6 mmHg in patients who completed the program. 92% and 94% of patients who completed the program reached guideline-recommended BP goals and LDL-C goals, respectively
EMPEROR-Preserved	- Randomized, double-blind, placebo-controlled trial - Participants aged ≥ 18 years with NYHA, class II–IV HF with EF > 40% with NT-BNP (> 300 pg/ml in sinus rhythm and > 900 pg/ml in atrial fibrillation)	Empagliflozin 10 mg daily	Placebo	The composite primary endpoint was time to first event of adjudicated CV death or adjudicated HHF	Primary endpoint was reduced by 17% in the empagliflozin group versus placebo in the LVEF ≥ 50% group (6.7 versus 8.0 events/100 patient-years; HR 0.83, 95% CI: 0.71, 0.98; *p*-value 0.024). This was driven by a 22% reduction in the first HHF in the empagliflozin group versus placebo in the LVEF ≥ 50% group (4.5 versus 5.7 events/100 patient-years; HR 0.78, 95% CI: 0.64, 0.95; *p*-value 0.013). The reduction in CV death in the empagliflozin group versus placebo was not statistically significant (3.0 versus 3.4 events/100 patient-years; HR 0.89, 95% CI: 0.70, 1.13; *p*-value 0.34)
The China Rural Hypertension Control (CRHC) study	Cluster-randomized control trial of patients > 40 years of age with hypertension	Village physicians trained to treat hypertension based on 2017 ACC/AHA guidelines	No training for village physician	Proportion of patients with BPs < 130/80 mmHg at 18 months	Primary outcome of BP < 130/80 mmHg at 18 months was lower in the intervention group at 57.0% compared to 19.9% in the usual care group with a group difference of 37% (95% CI 34.8 to 39.1%; *p*-value < 0.001)

Table 1 (continued)

Clinical trial	Study design & population	Treatment arm	Control arm	Primary outcome	Results
PREPARE-IT 2	Pragmatic randomized control trial	8 g IPE daily for 3 days, then 4 g daily on days 4 to 28	Placebo	COVID-19-related hospitalization (meeting indications for or actual hospitalization) or death up to 28 days	Lower rate of the primary endpoint among IPE versus placebo treatment arms, but difference was not statistically significant
EMPULSE	- Multi-center, randomized, double-blind, and 90-day superiority trial - Patients > 18 years of age who were hospitalized for acute decompensated heart failure	Empagliflozin 10 mg daily within 1 to 5 days of hospitalization	Placebo	Composite of death, number of HFE, time to first HFE, and change from baseline KCCQ-TSS score after 90 days of treatment	Stratified win ratio 1.36 (95% CI: 1.09– 1.68; *p*-value 0.005) Rate of death was 4.2% in the intervention group compared to 8.3% in the placebo group HF events for intervention groups were 10.6% while HF events 14.7% on the placebo group Time to all-cause death or first HFE was reduced by 35% (HR 0.65 with 95% CI 0.43–0.99; $p = 0.042$) Placebo adjusted mean difference of KCCQ-TSS at day 90 was 4.5 points (95% CI: 0.3–8.6; $p = 0.034$)
MK-0616, an oral PCSK9 inhibitor	Randomized control trial **First phase 1 trial:** 60 healthy male participants ages 18–65 Mean age was 38, and all except 2 participants were White **Second phase 1 trial:** 40 men and women ages 18–65 already on statin therapy. 27 patients were male, mean age 57 years, 40% White, and 85% taking statin	**First phase 1 trial:** MK-0616 10–300 mg once daily **Second phase 1 trial:** MK-0161 10 or 20 mg once daily, administered with 2 different doses of sodium caprate	**First phase 1 trial:** Placebo **Second phase 1 trial:** Placebo	**First phase 1 trial:** Assessing pharmacokinetics of MK-0616, looking at the effect of permeation enhancers, food effect, and effect of various capsule formulations on the pharmacokinetics **Second phase 1 trial:** magnitude of LDL-C lowering effect from baseline	**First phase 1 trial:** The permeation enhancer was noted to improve absorption, with nearly identical results between labrasol and sodium caprate, and a negative food effect was observed with a meal consumed within 30 min prior to a dose **Second phase 1 trial:** LDL-C levels decreased by about 65% from baseline in participants receiving MK-0616

Table 1 (continued)

Clinical trial	Study design & population	Treatment arm	Control arm	Primary outcome	Results
Effects of aspirin on dementia and cognitive impairment in the ASCEND trial	Double-blind, randomized controlled trial Patients ≥ 40 years of age with any type of diabetes and without known cardiovascular disease	Aspirin 100 mg	Placebo	The primary outcome was broad dementia outcome (reported cases of dementia, cognitive impairment, delirium/confusion, dementia medications, referral to memory clinic, geriatric psychiatry). Narrow dementia outcome -people with dementia. At the final follow-up, a cognitive function test (z-score) was done based on either Telephone Interview for Cognitive Status (TICSm) and verbal fluency (VF) or the Healthy Minds test developed by the UK Biobank	9% non-significant reduction in the broad dementia outcome among patients on aspirin compared to placebo [aspirin 7.1% (548/7714), placebo 7.8% (598/7713); rate ratio 0.91 (0.81, 1.02)] 11% non-significant reduction in the narrow dementia outcome among patients on aspirin compared to placebo [aspirin 3.3% (254/7714), placebo 3.7% (283/7713); rate ratio 0.89 (0.75, 1.06)] No statistically significant difference in the meta-analyzed cognitive score (TICSm and VF or Healthy Minds) among patients on aspirin versus placebo [Mean (SE) cognitive z-score, aspirin ($n=4535$) 0.004 (0.015) versus placebo ($n=4480$) −0.002 (0.015); cognitive z-score difference 0.012, 95% CI (−0.016, 0.0390]

Clinical Implication

In the modern era, undertreatment of hypertension and hypercholesterolemia remains a persistent problem. The present trial, representing a diverse patient cohort, demonstrated clinically meaningful reductions in BP and LDL-C through remote patient care. Even small changes in BP (1–2 mmHg) have been shown to have a significant impact on population rates of cardiovascular disease [14•], and this trial demonstrates a remarkable mean change in BP of 10/6mHg for all enrolled participants. Moreover, LDL-C was lowered by 45 mg/dL in all enrolled participants. This reduction in these two extremely prevalent and important cardiovascular risk factors can translate into fewer ASCVD events. Remote patient care remains a very attractive option especially in the era of the COVID-19 pandemic. The incorporation of patient navigators enabled remote patient contact and education thereby expanding access to care. The algorithmically directed care supported by physicians and managed by pharmacists allowed for automated workflows, streamlined communication, and tailored medical therapy to reach guideline-directed targets. This system design and remote care delivery platform is timely and of crucial importance to practically apply management guidelines and improve patient care.

While impressive results are noted for those patients who completed the program, it is important to note that most patients in both the HTN and lipid program became unreachable over the course of the program. Still, engagement and retention were similar across race, ethnicity, and primary language subgroups. Future studies will need to continue to optimize techniques to keep patients actively engaged in similar remote programs without being lost to follow-up.

A cluster-randomized trial of a village doctor-led intervention

Study Overview

The China Rural Hypertension Control (CRHC) study is a cluster-randomized trial to evaluate the effectiveness of a standard treatment protocol based on the 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension treatment guidelines on hypertension control and cardiovascular events. The investigators selected 326 villages from 3 provinces in China which included a total of 33,995 participants aged ≥ 40 years with an untreated BP ≥ 140/90 mm Hg or treated BP ≥ 130/80 mm Hg or with an untreated BP ≥ 130/80 mm Hg and a history of cardiovascular disease, diabetes mellitus, or chronic kidney disease. The villages were randomly assigned to a treatment group where the physicians were trained to manage hypertension (163 villages) or usual management group (163 villages). In the treatment group, the village physicians were trained on standard BP measurement, received support from other physicians (primary care physicians and hypertension specialists), and received performance-based financial incentives. The enrolled patients in the treatment group received health coaching on home BP monitoring, lifestyle changes, and adherence to medication as well as discounted or free anti-hypertensive medication. The primary outcome measure was the proportion of patients with BPs < 130/80 mmHg at 18 months. The secondary outcomes were the proportion of patients with BP < 140/80 mmHg at 18 months and change in systolic and diastolic BP from baseline to 18 months. Intention to treat analysis was conducted.

The primary outcome of the proportion of patients with BP < 130/80 mmHg at 18 months was lower in the intervention group at 57.0% compared to 19.9% in the usual care group with a group difference of 37% (95% CI 34.8 to 39.1%; p-value < 0.001). Secondary outcomes including change in BP from baseline to 18 months was − 26.3/ − 14.6 mmHg (systolic/diastolic) in the intervention group compared to − 11.8/ − 7.5 mmHg (systolic/diastolic) in the usual care group with a net difference of − 14.5/ − 7.1 mmHg (95% CI: − 15.7 to − 13.3 mmHg; p-value < 0.001 for SBP and 95% CI: − 7.7 to − 6.5 mmHg; p-value < 0.001 for DBP). The proportion of patients with BP < 140/90 mmHg at 18 months was 77.3% for the intervention group compared to 44.5% in the usual care group (p-value < 0.001). The results were consistent by age, sex, education, and percent of anti-hypertensive medication use.

Clinical Implication

The prevalence of hypertension in China is high and increasing. A recent national survey in 2014 showed 27.8% of Chinese adults with hypertension, and only 5.5% of hypertensive patients in rural China had their BP controlled. Village doctors with appropriate training could play an important role in hypertension control in rural China. This trial showed a significant decrease in BP which was sustained at 18 months. This implementation strategy could be scaled up in rural China and other low resource settings for hypertension control which can overall help improve cardiovascular disease burden.

EMPEROR-Preserved: empagliflozin in heart failure with preserved ejection fraction (HFpEF) patients

Study Overview

The EMPEROR-Preserved trial previously showed that empagliflozin, a sodium-glucose cotransporter 2 (SGLT-2) inhibitor, reduced the combined risk of cardiovascular (CV) death and heart failure (HF) hospitalizations among patients with HF with left ventricular ejection fraction (LVEF) > 40% regardless of diabetes status [1••]. In this current study, these results were further stratified by baseline LVEF ≥ 50% (true HFpEF) versus LVEF 41 to 49% (heart failure with mid-range ejection fraction; HFmrEF). The aim was to assess the effects of empagliflozin, in addition to standard therapy, in patients with LVEF ≥ 50% in the EMPEROR-Preserved trial versus patients with LVEF 41–49% and to compare them to the other relevant trial results. This phase 3, double-blind, placebo-controlled trial recruited a total of 5988 patients, aged ≥ 18 years, with class II to IV heart failure (HF), with or without type 2 DM with NT-BNP (> 300 pg/ml in sinus rhythm and > 900 pg/ml in atrial fibrillation). Participants were randomized in a 1:1 fashion to receive either empagliflozin 10 mg ($n = 2997$) or matching placebo ($n = 2991$). The composite primary endpoint was time to first event of adjudicated CV death or adjudicated hospitalization for heart failure (HHF). The secondary endpoints were the first and recurrent adjudicated HHF events and the slope of change in estimated glomerular filtration rate (eGFR).

The mean age of LVEF ≥ 50% group ($n = 4005$; 67%) was 72.8 years whereas that of the LVEF 41–49% group ($n = 1983$; 33%) was 70.1 years ($p < 0.001$). There were 50% ($n = 2019$) women in the LVEF ≥ 50% group whereas the LVEF 41–49% group had 33% ($n = 657$) women ($p < 0.001$). Both the groups had around 50% patients with diabetes (48% in HFpEF, 52% in HFmrEF; $p = 0.004$). The standard HF therapy for both the groups included ACE inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors (79% in HFpEF, 85% in HFmrEF, p-value 0.001), beta blocker (84% in HFpEF, 90% in HFmrEF, $p < 0.001$), mineralocorticoid antagonist (33% HFpEF, 47% in HFmrEF, p-value < 0.001), and diuretics (81% in HFpEF, 79% in HFmrEF, p-value 0.041). The primary endpoint was reduced by 17% in the empagliflozin group versus placebo in the LVEF ≥ 50% group (6.7 versus 8.0 events/100 patient-years; hazard ratio [HR] 0.83, 95% confidence interval [CI]: 0.71–0.98; p-value 0.024). This was driven by a 22% reduction in the first HHF in the empagliflozin group versus placebo in the LVEF ≥ 50% group (4.5 versus 5.7 events/100 patient-years; HR 0.78, 95% CI: 0.64–0.95; p-value 0.013). The reduction in CV death in the empagliflozin group versus placebo was not statistically significant (3.0 versus 3.4 events/100 patient-years; HR 0.89, 95% CI: 0.70, 1.13; p-value 0.34). Similarly, the change in all-cause mortality in empagliflozin versus placebo (6.1 versus 6.1 events/100 patient-years; HR 1.02, 95% CI: 0.86–1.21; $p = 0.84$) and total HHF (6.8 versus 7.9 events/100 patient-years; HR 0.83, 95% CI: 0.66–1.04; $p = 0.11$) in the LVEF ≥ 50% group was not statistically significant.

In the HFmrEF patients with LVEF 41–49% group receiving empagliflozin versus placebo, the primary endpoint was reduced by 29% (7.2 versus 10 events/100 patient-years; HR 0.71, 95% CI: 0.57–0.88; $p = 0.002$; p for interaction 0.27), driven by a statistically significant reduction in first HHF of 42% (3.8 versus 6.5 events/100 patient-years; HR 0.58, 95% CI: 0.44–0.77; $p < 0.001$; p for interaction 0.093). Total HHF in the LVEF 41–49% group was reduced by 43% in the empagliflozin group versus placebo (5.8 versus 10.1 events/100 patient-years; HR 0.57, 95% CI: 0.42–0.79; p-value < 0.001) (p for interaction 0.06). The 8% reduction in CV death and 4% reduction in all-cause mortality in the LVEF 41–49% group were not statistically significant (HR 0.92, 95% CI: 0.69–1.22; $p = 0.54$ and HR 0.96, 95% CI: 0.78–1.19; p-value 0.72, respectively). At week 52, the change from baseline in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) quality of life in the empagliflozin versus placebo in the LVEF ≥ 50% group was 4.24 versus 2.78 ($p = 0.006$), while in LVEF 41–49% group, it was 4.86 versus 3.3 ($p = 0.043$; p-value for interaction 0.92). Similarly, there was a significant improvement in KCCQ total score and overall summary score in all patients who received empagliflozin versus placebo.

When patients with LVEF > 50% in the EMPEROR-Preserved trial ($n = 3501$) were compared to similar patients in the PARAGON-HF trial ($n = 4067$) [9], patients in the EMPEROR-Preserved trial had a significant reduction in first HHF or CV death (HR 0.82; 95% CI 0.69–0.98, $p = 0.0263$ versus HR 0.94; 95% CI 0.82–1.08, $p = 0.38$). When compared to placebo, the difference in the slope of decline in GFR with empagliflozin in the LVEF ≥ 50% group over time was 1.24 ml/min/1.73 m^2 per year ($p < 0.0001$).

Clinical Implication

The EMPEROR-Preserved trial demonstrates the superiority of empagliflozin over placebo in the reduction of composite endpoint of the first event of CV death or HF hospitalization patients with LVEF ≥ 50%. The benefit was primarily driven by a reduction in HF hospitalization–related events and not mortality. These benefits appeared irrespective of the baseline EF. This is the first large-scale study to demonstrate

significant improvement in patients with true HFpEF with drug therapy.

EMPULSE: efficacy and safety of empagliflozin in hospitalized heart failure patients

Study Overview

The purpose of this study was to assess the clinical benefit, safety, and tolerability of empagliflozin on hospitalized patients for acute decompensated heart failure. This was a multi-center, randomized, double-blind, and 90-day superiority trial. Inclusion criteria included patients over 18 years of age who were currently hospitalized for a primary diagnosis of acute decompensated heart failure (regardless of ejection fraction or a diagnosis type 2 diabetes mellitus), elevated NT-proBNP > 1600 pg/mL or BNP > 400 pg/mL, and with treatment of intravenous diuretics such as 40 mg of furosemide or equivalent. Inclusion criteria also included clinical stability with systolic BP > 100 mmHg, no increase in intravenous diuretic dose prior to randomization, no intravenous vasodilators, and no intravenous inotropic drugs. Key exclusion criteria included cardiogenic shock, current hospitalization for acute heart failure from an acute myocardial infarction, pulmonary embolism, or cerebrovascular accident. Interventions such as major cardiac procedures such as percutaneous coronary intervention transcatheter aortic valve intervention, MitraClip placement, cardiac resynchronization therapy, or cardiac mechanical support implantation. Patients with eGFR < 20 mL/min/1.73m^2 or requiring dialysis, type 1 diabetics, or history of ketoacidosis were excluded from the study as well. Patients were randomized to the control arm or treatment arm with empagliflozin 10 mg greater than 24 h and less than 5 days of hospitalization.

The primary outcome measure was a clinical benefit which was composite of death, number of heart failure events (HFE), time to first HFE, and change from baseline Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) after 90 days of treatment. Baseline characteristics of the intervention group and placebo group were similar with an average age of the patients around 70 years of age. One-third of the patients had LVEF > 40%, one-third had LVEF ≤ 40%, and one-third admitted for de novo HF. The primary analysis was assessed by a stratified win ratio. The win ratio was performed by a computer as it randomly picked one patient from the placebo group and one patient from the treatment group. It then checks if a patient died and if death was in the placebo group, then the patient in the treatment group had won. If there was a tie, the computer would then check the frequency of HHF. A tie in this category would lead the computer to pick time to first HFE and then another tie would lead the computer to evaluate the KCCQ-TSS score.

The stratified win ratio was 1.36 (95% CI: 1.09–1.68; p-value 0.0054) and death was 4.2% in the intervention group compared to 8.3% in the placebo group. HFE for intervention groups were 10.6% while HF events were 14.7% in the placebo group. Primary endpoint by subgroup analysis also showed consistent effects of empagliflozin including among those with de novo HF, acute on chronic HF, with lower or higher ejection fraction than 40%, or with or without diabetes mellitus. Time to all-cause death or first HFE was reduced by 35% (HR 0.65, 95% CI 0.4–0.99; $p = 0.042$). Placebo adjusted mean difference of KCCQ-TSS at day 90 was 4.5 points (95% CI 0.3–8.6; $p = 0.0347$). Body weight change from baseline to day 90 was a reduction by 1.5 kg in the intervention group compared to placebo (95% CI − 2.8 to − 0.3; $p = 0.0137$). Adverse events that took place were similar in the intervention and placebo groups. Patients treated with empagliflozin during their hospitalization were 36% more likely to experience a clinical benefit compared to patients on placebo.

Clinical Implication

Over the last few years, SGLT-2 inhibitors have shown benefit in patients with HF irrespective of ejection fraction or diabetes status. The EMPULSE trial adds to the increasing body of evidence in SGTL-2 inhibitors in HF therapy as it was the first trial to test inpatients with decompensated HF regardless of ejection fraction or diabetes mellitus status. Initiation of empagliflozin versus placebo in patients hospitalized for acute HF resulted in a significant clinical benefit within 90 days, fewer deaths or HFE, improvement in quality of life, greater reduction in body weight, and benign safety profile.

PREPARE-IT 2: icosapent ethyl (IPE) versus placebo in outpatients with COVID-19

Study Overview

PREPARE-IT 2 is a pragmatic trial assessing IPE versus placebo in non-hospitalized patients with COVID-19 to reduce hospitalization rates and major clinical complications. Included participants were ≥ 40 years of age with confirmed COVID-19 diagnosis within 7 days of symptom onset. Exclusion criteria encompassed hospitalization requirement, contraindication to treatment drug, pregnant or breastfeeding women, anticoagulant administration, or hemorrhagic diathesis. Patients in the treatment arm received 8 g of IPE daily for the first

3 days followed by 4 g daily on days four to 28. Those randomized to the placebo arm received a placebo capsule with identical dosing schedules as the active group. The primary study outcome was COVID-19-related hospitalization or death up to 28 days. For the primary outcome, hospitalization entailed meeting indications for inpatient admission per the blinded investigator or actual hospitalization. The key secondary outcomes included COVID-19-related actual hospitalization or death assessed up to 28 days. Other secondary endpoints entailed not alive or not out of the hospital at day 28, new requirement of mechanical ventilation, total evens (non-fatal myocardial infarction [MI] or non-fatal stroke or death), and total mortality. Investigators calculated a sample size of 2000 participants based on 90% power to detect a 30% relative risk reduction (RRR) in the active group if the 28-day composite rate (indication for hospitalization or death) among controls was 18%, assuming a 5% dropout and total significance alpha level of 0.05.

Of the 2052 patients included in the study, approximately 53% were female and the average age was 53 years. The most commonly reported symptoms were fatigue, cough, and fever. The primary outcome was experienced by 110 of 986 patients in the treatment arm (11.16%) and 135 of 1030 patients in the placebo arm (13.69%) without significant difference noted between the two groups (HR 0.84, 95% CI 0.65–1.08; $p=0.17$). Similarly, there was no significant difference related to the key secondary outcome among the 53 of 986 patients in the treatment arm (5.38%) and 70 of 1030 patients in the placebo arm (6.80%; HR 0.78, 95% CI 0.55–1.12; $p=0.18$). Other secondary endpoints measured also did not show significant differences between the treatment versus placebo arms: not alive or not out of the hospital at day 28 (10 vs. 14 patients; odds ratio [OR] 0.74, 95% CI 0.29–1.81; $p=0.54$), new requirement of mechanical ventilation (8 vs. 11 patients; OR 0.76, 95% CI 0.26–2.08; $p=0.65$), non-fatal myocardial infarction MI or non-fatal stroke or death (4 vs. 11 patients; OR 0.38, 95% CI 0.09–1.28; $p=0.12$), total mortality (4 vs. 8 patients; OR 0.52, 95% CI 0.11–1.95; $p=0.39$), and in-hospital length of stay (9 vs. 7 days; mean difference 3 days, 95% CI 1–5; $p=0.01$). Regarding safety, IPE was well-tolerated without significant differences between the active and placebo arms. In terms of drug discontinuation rate, there was a significant difference seen among active treatment (70 of 989 patients [7.08%]) versus placebo (39 of 1030 [3.79%]) groups ($p=0.001$). Statistically significant reasons for such stopping the study included patient discontinuation (active: 25 of 989 patients [2.43%], placebo: 12 of 1030 patients [1.21%]; $p=0.030$) and both adverse event and patient discontinuation (active: 16 of 989 patients [1.55%], placebo: 3 of 1030 patients [0.30%]; $p=0.002$).

Clinical Implication

Overall, despite lower observed rates of COVID-19-related hospitalization and death among patients in the IPE treatment versus placebo arm, no statistically significant difference was seen between the two groups. This trend of lower rates and odds remained consistent for other measured secondary endpoints. However, both primary and key secondary endpoints did not reach statistical significance likely due to the underpowered study. Additionally, there was a slightly higher discontinuation rate among those in the active treatment arm even though IPE was generally well-tolerated without significant differences in reported adverse events when compared to placebo. Future investigations with a larger patient population to achieve higher statistical power are needed to determine if IPE has a role in COVID-19 management.

The clinical safety, pharmacokinetics, and LDL-C-lowering efficacy of MK-0616 an oral PCSK9 inhibitor

Study Overview

Despite available therapies directed at cholesterol lowering, millions of patients with hypercholesterolemia do not achieve LDL-C treatment targets. The addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition to statin therapy decreases LDL-C by at least an additional 50%, making it possible to achieve very low LDL-C levels and decrease ASCVD events [15, 16]. Currently available PCSK9 inhibitors, alirocumab and evolocumab, are underused due to cost, insurance authorization, and the need for biweekly or monthly injections. Still, their clinical utility for high-risk patients in need of aggressive secondary prevention or those with familial hypercholesterolemia has been powerful [17]. Currently, there are no orally bioavailable PCSK9 inhibitors given the difficulty to find small molecules that can disrupt the interaction of LDL receptors and the PCSK9 protein.

This study included two small phase 1 randomized double-blind placebo-controlled trials looking at dosage, safety, and pharmacokinetics of MK-0616 used in conjunction with agents to improve gastrointestinal absorption. The first trial involved a population of 60 healthy male participants ages 18–65 who were randomized to receive once-daily doses ranging from 10 up to 300 mg of MK-0616 or placebo. The mean age was 38 years, and all except 2 participants were White. Outcomes of interest included assessing pharmacokinetics of MK-0616, looking at the effect of permeation enhancers, food effect, and effect of various capsule formulations on the

pharmacokinetics. Percent change in free PCSK9 in the plasma was measured. Patients were monitored for any serious side effects. The second trial involved the addition of MK-0616 to the treatment regimen of 40 men and women ages 18–65 with hypercholesterolemia already on moderate- to high-intensity statin therapy for at least 3 months. These patients were studied for 14 days with the primary outcome of interest being the magnitude of LDL-C-lowering effect from baseline. Twenty-seven patients were male, mean age was 57, 40% of patients were White, and 85% of patients were taking moderate- to high-intensity statin. Patients were randomized to receive once-daily dose of 10 or 20 mg of MK-0616 administered with 2 different doses of sodium caprate versus placebo and with meal.

Results from the first trial demonstrated no deaths or serious adverse events. Treatment-related adverse events were mild. These included abdominal discomfort, diarrhea, dyspepsia, headache, and maculopapular rash. The permeation enhancer was noted to improve absorption, with nearly identical results between labrasol and sodium caprate, and a negative food effect was observed with a meal consumed within 30 min prior to a dose. Of the studied dosages, there was more than a 90% maximal reduction of free PCSK9 in the plasma for 24 h despite only 2% oral bioavailability. Similarly, in the second trial, there were no deaths or serious adverse events. LDL-C levels decreased by about 65% after 14 days of therapy in participants receiving MK-0616.

Clinical Implication

These early phase 1 results show highly effective LDL-C lowering with MK-0616, therapy on top of statins. The safety profiles in these trials demonstrated excellent tolerability and no serious adverse events. MK-0616 single doses reduced free PCSK9 by more than 90%, and in multiple doses, MK-0616 reduced LDL-C by 65% after 14 days. As an oral PCSK9 inhibitor, MK-0616 has the potential to overcome barriers to treatment and allow more patients to achieve LDL-C goals and lower cardiovascular disease risk. Importantly, future studies will need to incorporate more diverse populations with more women and various race/ethnic and age groups represented. Adherence to this therapy in the long term also remains to be demonstrated. Real-world efficacy will need to be assessed given the meal-time separation required to achieve maximal results. The cost will need to be determined and may significantly limit availability. While cardiovascular outcomes have yet to be studied regarding this therapy, this orally bioavailable therapy may have significant clinically meaningful effects with future approval.

Effects of aspirin on dementia and cognitive impairment in the ASCEND trial

Study Overview

The ASCEND trial previously showed that the use of aspirin in primary prevention among patients with diabetes reduced major adverse vascular events like myocardial infarction, strokes/transient ischemic attacks (TIAs), and death from any vascular cause [18•]. However, this benefit was offset by an increase in major bleeding. Aspirin may prevent cognitive decline by a reduction in ischemic strokes and TIAs but the increase in intracranial bleeds and microbleeds may worsen cognitive impairment. Prior studies did not convincingly demonstrate the effect of aspirin in impacting dementia or cognitive decline. The ASCEND trial was a double-blind, randomized controlled trial, conducted on patients ≥ 40 years of age with any type of diabetes and without known cardiovascular disease. A total of 15,480 participants without baseline dementia were randomized in a 2×2 factorial design to aspirin 100 mg versus placebo (and omega-3 fatty acids 1 g capsule/day versus placebo). Patients were followed up for 7.4 years during the trial and 1.8 years post-trial, with $> 99\%$ follow-up completed for morbidity and mortality. The primary outcome of this analysis was broad dementia outcome which included reported cases of dementia, cognitive impairment, delirium/confusion, dementia medications, or referral to memory clinic or geriatric psychiatry. The narrow dementia outcome included reported cases with dementia during the study. At the final follow-up, a cognitive function test (z-score) was done based on either Telephone Interview for Cognitive Status (TICSm) and verbal fluency (VF) or the Healthy Minds test developed by the UK Biobank. The dementia outcomes were derived from hospitalizations or serious events reported by participants, the International Classification of Disease 10^{th} revision code diagnoses in electronic hospital admission data and death records, and other indications of cognitive impairment in follow-up and electronic records.

The mean age for participants in both the aspirin and the placebo group was 63 years. Males constituted 63% of the participants in both groups and both groups had 94% patients with type 2 diabetes and 62% patients with hypertension. The rest of the demographic characteristics including BMI, statin use, and HBA1c were similar in both groups. Observational analyses of the risk of dementia associated with non-fatal events or major bleeds were conducted. Poisson regression analyses were done using 2-year intervals of age at risk spent with or without event. Analyses were adjusted for the number of non-dementia-related hospitalizations $(0, 1, \geq 2)$ during the interval,

randomized treatment allocation, sex, prior diseases, and baseline predictors of dementia including a hospital diagnosis–based frailty score. Dementias that were diagnosed after a disabling stroke or intracranial bleed were excluded.

For participants who had a serious vascular events (myocardial infarction, ischemic strokes, and TIAs), there was an increase in the risk of dementia (rate ratio for the broad dementia outcome = 2.4, 95% CI 1.97–2.92). For participants with major bleed, there was nearly a twofold increase in the risk of dementia (rate ratio for the broad dementia outcome = 1.96, 95% CI 1.49–2.56). Revascularization did not significantly affect dementia risk (rate ratio for the broad dementia outcome = 0.91, 95% CI 0.68–1.23). There was a 9% non-significant reduction in the broad dementia outcome among patients on aspirin compared to placebo [aspirin 7.1% (548/7714), placebo 7.8% (598/7713); rate ratio 0.91, 95% CI 0.81–1.02)]. There was an 11% non-significant reduction in the narrow dementia outcome among patients on aspirin compared to placebo [aspirin 3.3% (254/7714), placebo 3.7% (283/7713); rate ratio 0.89, 95% CI 0.75–1.06]. There was no statistically significant difference in the meta-analyzed cognitive score (TICSm and VF or Healthy Minds) among patients on aspirin versus placebo [mean (SE) cognitive z-score, aspirin ($n = 4535$): 0.004 (0.015) versus placebo ($n = 4480$): − 0.002 (0.015); cognitive z-score difference 0.012, 95% CI − 0.016 to 0.039].

Clinical Implication

There was no statistically significant effect of aspirin on dementia outcomes. However, with the wide confidence intervals, the results excluded proportional harms of > 2% and benefits of > 19%. In order to assess any modest proportional 15–18% benefits of 5 to 7 years of aspirin use, larger trials, with a higher number of incident dementia cases, are required.

Conclusion

The 2021 AHA Scientific Sessions included several noteworthy trials that further the field of cardiovascular disease prevention and treatment. Overall, optimization of primary and secondary prevention is imperative in saving lives, preserving quality of life, and decreasing associated costs for patients and the healthcare system.

Notable findings regarding advancements in technologically driven remote management of CVD, lipid-lowering management therapies, and SGLT2 inhibitor use in HF reinforce the need to continually advance the field of cardiovascular medicine. With that said, further research to assess the clinical applicability of these findings is needed.

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Declarations

Conflict of Interest *Michelle T. Lee, Jerin George, Hunaina Shahab, Melody Hermel, Jamal S. Rana:* None.
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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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•• Of major importance

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