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

Highlights of Cardiovascular Disease Prevention Studies Presented at the 2022 European Society of Cardiology Congress

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Abstract

Purpose of Review Focused review of select studies presented at the 2022 European Society of Cardiology Congress.

Recent Findings Included studies assessed the effects of aspirin and omega-3 fatty acid supplements on heart failure (ASCEND study); the impact of icosapent ethyl on ST-elevation MI incidence (REDUCE-IT); air temperature's effect on cardiovascular mortality (EXHAUSTION project); LVEF outcomes after troponin-guided neurohormonal blockade for the prevention of anthracycline toxicity; efficacy of routine stress testing after high-risk PCI (POST-PCI trial); influenza vaccine among patients with acute coronary syndromes (VIP-ACS trial); empagliflozin in patients with acute myocardial infarction (EMMY); effects of comprehensive imaging-based cardiovascular screening on death and cardiovascular events (DANCAN-VAS); safety of long-term evolocumab in patients with established atherosclerotic cardiovascular disease (FOURIER-OLE); and use of a cardiovascular polypill as a global strategy to improve secondary prevention (SECURE).

Summary Research presented at the 2022 ESC Congress highlighted many novel applications of preventative and treatment strategies in cardiology, including the effects of environmental risk factors on the incidence of cardiovascular disease.

Keywords Empagliflozin · Heart failure · Cardiovascular disease · Prevention · Acute coronary syndrome · Evolocumab · PCSK-9 inhibitor

Abbreviations

ACS	Acute coronary syndrome
AF	Atrial fibrillation
ARB	β-Adrenergic receptor blocker

Topical Collection on *Reviews and Scientific Meetings and New Research Implications*.

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ASCVD	Atherosclerotic cardiovascular disease
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence interval
CK	Creatine kinase
cMRI	Cardiac MRI
CO	Carbon monoxide
COVID-19	Coronavirus disease 2019
CV	Cardiovascular
CVD	Cardiovascular disease
CT	Computed tomography
DHA	Docosahexaenoic acid
ECMO	Extra corporeal membrane oxygenation
EPA	Eicosapentaenoic acid
ESC	European Society of Cardiology
eGFR	Estimated glomerular filtration rate
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
hs-cTnI	High sensitivity cardiac Troponin-I
HTN	Hypertension
ICCU	Intensive cardiac care unit
IPE	Icosapent Ethyl
KCCQ	Kansas City Cardiomyopathy Questionnaire
LDL-C	Low-density lipoprotein cholesterol
LMEM	Linear mixed effect model
LVEDV	Left ventricular end diastolic volume
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end systolic volume
MACE	Major adverse cardiovascular event
MAE	Major adverse event
MI	Myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal-pro hormone B-type natriuretic peptide
OR	Odds ratio
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PPM	Parts-per-million
RAASi	Renin-angiotensin-system inhibitor
SGLT-2	Sodium-glucose cotransporter 2
STEMI	ST-segment elevation myocardial infarction

Introduction

The 2022 European Society of Cardiology (ESC) Congress featured several notable trials regarding CV disease (CVD) incidence, prevention, and management. Included studies assessed the effects of aspirin and omega-3 fatty acid supplements on HF (ASCEND study): the impact of icosapent ethyl on ST-elevation MI incidence (REDUCE-IT); air temperature's effect on cardiovascular mortality (EXHAUSTION project); LVEF outcomes of troponin-guided neurohormonal blockade for the prevention of anthracycline toxicity; efficacy of routine stress testing after high-risk PCI (POST-PCI trial); influenza vaccine among patients with acute coronary syndromes (VIP-ACS trial); empagliflozin in patients with acute myocardial infarction (EMMY); effects of comprehensive imaging based cardiovascular screening on death and cardiovascular events (DANCANVAS); safety of long-term evolocumab in patients with established atherosclerotic cardiovascular disease (FOURIER-OLE); and use of a cardiovascular polypill as a global strategy to improve secondary prevention (SECURE). As with prior publications, the significance and clinical implications of select presentations is discussed [1–3]. Finally, a table summarizing the studies discussed is included (Table 1).

Effects of Aspirin and Omega-3 Fatty Acid Supplements on Heart Failure in the ASCEND Study

The role of aspirin, if any, in preventing HF is unclear. The ASCEND trial published in 2018 demonstrated that aspirin use reduced serious vascular events in patients with diabetes; however, the associated bleeding hazard offset its benefits [4•].

This study aimed to assess the effects of aspirin versus placebo and separately, of omega 3 fatty acids versus placebo in patients over the age of 40 with diabetes and no prior CVD history at baseline. The primary outcome was a composite of hospitalizations for HF or death due to HF. Secondary outcomes included individually hospitalizations for HF or death due to HF. Patients in the original ASCEND trial were randomized to aspirin 100 mg daily versus placebo. Data was collected via participant reporting as well as routinely collected health care data. Researchers searched ICD-10 codes specific for HF prior to randomization.

ASCEND was a double-blind, placebo-controlled, randomized 2×2 factorial design trial with 7740 patients in each arm with a mean follow-up of 7.4 years. Average age was 63 and 63% were male. Regarding the effects of aspirin on HF hospitalization or death, there was no significant

Table 1 Summary of major randomized clinical trials on cardiovascular disease prevention at the 2022 European Society of Cardiology Congress

Clinical trial	Study design and population	Treatment arm	Control arm	Primary outcome	Results
ASCEND	Randomized parallel trial of patients over the age of 40 with diabetes and no known cardiovascular disease	Aspirin 200 mg daily	Placebo	Primary outcome was a composite of hospitalizations for heart failure or death due to heart failure	There was no statistically significant effect of aspirin on hospitalization or death from heart failure ($p=0.85$) There was no statistically significant effect of omega 3 fatty acids on hospitalization or death due to heart failure. ($p=0.15$)
REDUCE-IT	1:1 randomized trial in statin-treated men and women ≥ 45 years with established cardiovascular disease or diabetes plus 1 or more risk factors	IPE (2 g twice daily with food) with	Placebo	Myocardial infarction incidence	Overall, MI incidence for IPE vs. placebo: 8.6% vs. 12.0% ($p<0.0001$). HR 0.69 (95% CI 0.58–0.81) ST-segment elevation MI (STEMI): 2.7% vs. 3.9% ($p=0.0008$). HR 0.60 (0.44–0.81) NSTEMI: 5.9% vs. 7.8% ($p=0.001$). HR 0.73 (95% CI 0.60–0.89)
The EXHAUSTION project	5 cohorts from Sweden, Norway, UK, Germany, and Italy	Stage 1: cohort specific analysis (time stratified case cross over design comparing temperature on case versus control days to measure effect modification in the form of odds ratio Stage 2: random effect meta-analysis	Stage 1: cohort specific analysis (time stratified case cross over design comparing temperature on case versus control days to measure effect modification in the form of odds ratio	Mortality including death from cardiovascular disease, ischemic heart disease and cerebrovascular disease and morbidity in form of myocardial infarction and cerebrovascular events	Results showed increased cardiovascular mortality (−4.8 vs 4.7 with OR 1.19 (95% CI 1.04–1.36), ischemic heart disease mortality (-4.8 vs 4.6 with OP 1.22 (95% CI 1.07–1.38), coronary morbidity (− 8.9 vs. 2.4 with OR 1.04 (1.01–1.08) with short-term cold exposure, however, no effect was observed with heat exposure Patients with ages > 65 years and female sex were potentially more susceptible to the effects of cold temperature on new-onset ischemic heart disease

Table 1 (continued)

Clinical trial	Study design and population	Treatment arm	Control arm	Primary outcome	Results
Cardiac CARE	Multicenter prospective randomized open-label blinded end point trial of combination β-adrenergic receptor blocker and renin-angiotensin-system inhibitor therapy in patients receiving anthracycline chemotherapy associated with myocardial injury	Standard of care plus combination candesartan and carvedilol therapy	Standard of care	Change in LVEF on cardiac magnetic resonance imaging from baseline to 6 months after the completion of anthracycline	There was no difference in mean LVEF change post anthracycline chemotherapy The absolute decline in LVEF for each of the 3 groups were: − 2.9% in the low-risk non-randomized group, − 4.2% in the randomized treatment group, and − 4.3% in the randomized standard of care group Change in hs-cTnl concentration from baseline to 2 months post anthracycline chemotherapy demonstrated no difference between groups with and without adjustment
The post-PCI trail	Multicenter, open-label, randomized trial in high-risk patients undergoing PCI	Routine stress testing at 12 months after PCI ($n = 849$)	Standard of care	A composite of major cardiovascular events including death from any cause, myocardial infarction, or hospitalization for unstable angina at 2 years post-PCI	There was no difference in the composite primary outcomes between the two groups, with 46 of 849 patients (5.5%) in routine stress testing patients and 51 of 857 patients (6.0%) in standard care (HR 0.90 (95% CI 0.61–1.35) $p = 0.62$)
VIP-ACS	A randomized, open-label, blinded trial in patients hospitalized for acute coronary syndrome	Double dose quadrivalent influenza vaccine given during the hospitalization	Standard dose quadrivalent influenza vaccine given in the outpatient setting 30 days post randomization	The primary outcome was a hierarchical composite of all-cause death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure hospitalization, urgent coronary revascularization, and hospitalization for respiratory infections, which was changed from the original time to event analysis to a win ratio due to effects of the COVID-19 pandemic on recruitment and event rates	Primary outcome: HR 0.97 [95% CI 0.75–1.24], $P = 0.79$ Win ratio 1.02 [95% CI 0.79–1.32], $P = 0.84$ The results in pre-specified subgroups were consistent with the primary result

Table 1 (continued)

Clinical trial	Study design and population	Treatment arm	Control arm	Primary outcome	Results
EMMY	Randomized, double-blind, placebo-controlled trial, performed across 11 sites in Austria from 2017 until 2022 including 476 patients aged 18–80, eGFR > 45, with first intake of study medication ≤ 72 h after MI with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia or imaging evidence of new regional wall motion abnormality	Empagliflozin 10 mg daily	Placebo	Change in NT-proBNP levels from randomization to week 26	Relative reduction in NT-proBNP levels at week 26 (comparison empagliflozin vs placebo) of − 15% (95% CI: − 4.4% to − 23.6%), $p = 0.026$. At visit 2 (6 weeks), there was a − 10.6% relative reduction in NT-proBNP levels that was not statistically significant, $p = 0.075$ At visit 3 (12 weeks) there was a − 13.3% relative reduction in NT-proBNP levels (95%-CI: − 22.5% to -3.0%), p = 0.021
The FOURIER-OLE trial	Open-label extended study ($n = 6635$)	Evolocumab every 2 or 4 weeks	N/A	The primary outcome was the incidence of adverse events and Major adverse cardiovascular events including cardiovascular mortality, myocardial infarction, or stroke	Low serious adverse events (< 10%), injection site reactions (0.4%), new-onset diabetes (1.2%), drug-related allergic reactions (0.6%), muscle-related events (1.2%), hemorrhagic stroke (0.04%) 23% reduction in CV death [HR 0.77, 95% CI 0.60–0.99, $p = 0.04$]. $p = 0.04$) 15% reduction in the composite endpoint of CV death, MI, stroke, unstable angina or coronary [HR 0.85, 95% CI 0.75–0.96, $p = 0.008$] and 20% reduction composite CV death, MI, or stroke [HR 0.80, 95% CI 0.68–0.93, $p = 0.03$]

Table 1 (continued)

Clinical trial	Study design and population	Treatment arm	Control arm	Primary outcome	Results
DANCAVAS	Community based, randomized controlled trial consisting of men aged 65–74, living in municipalities in Denmark, who were identified and included in the study with no exclusion criteria, and participants were either invited to screening (1/3 of patients) or were not invited (2/3 of patients)	Invited to screening, a program including ECG-gated non-contrast CT scan to detect coronary artery calcium, atrial fibrillation, and aortic and iliac aneurysms; four-limb blood pressure measurements for peripheral arterial disease and hypertension, and blood samples to test for diabetes and cholesterol	Not invited to screening	All-cause mortality	All-cause mortality occurred in 2,106 (12.6%) in the screened group vs. 3915 (13.1%) in the non-invited group (HR = 0.95 (0.9–1.00), $p = 0.062$) When stratified for age, all-cause mortality for the 65–69-year age group did show a clinically significance in the screened group (HR = 0.89 (0.83–0.96), $p = 0.004$); though no difference in the 70–74-year age group (HR = 1.01 (0.94–1.09), $p = 0.747$)
SECURE	Phase 3, randomized, controlled clinical trial across 7 countries consisting of patients who had experienced a type 1 MI within the previous 6 months and were either older than 75 years of age or at least 65 years of age with diabetes mellitus, mild or moderate kidney dysfunction, previous MI, previous coronary revascularization, or previous stroke	Fixed dose combination polypill consisting of aspirin (100 mg), rampril (2.5, 5, or 10 mg) and atorvastatin (20 or 40 mg)	Standard of care	CV death, nonfatal type 1 MI, nonfatal ischemic stroke, or urgent revascularization	Significantly lower risk of MACE than usual care with a primary outcome event occurring in 9.5% in the polypill group vs. 12.7% in the usual care group HR 0.76 [95% CI 0.60–0.96], $P = 0.02$ A secondary outcome event was detected in 8.2% of patients in the polypill group vs. 11.7% of patients in the usual care group HR 0.70 [95%CI, 0.54–0.90], $P = 0.005$

effect on the composite outcome with 3.4% of patients in the aspirin group and 3.4% in the placebo group developing the composite endpoint, with a rate ratio of 0.98 (confidence interval (CI) 0.83–0.17) and $p = 0.85$. This was also reflected in the HF hospitalizations with a rate ratio of 1 (CI 0.84–1.19) and death from HF with rate ratio of 0.98 (CI 0.64–1.48). For omega-3 fatty acids [1 g daily, 840 mg of marine fatty omega-3 acids with 460 mg of eicosapentaenoic acid (EPA) and 380 mg docosahexaenoic acid (DHA)] versus placebo (olive oil), 3.2% of patients in the omega arm developed the primary composite outcome, compared to 3.6% in the placebo group. While the primary composite outcome did not achieve significance ($p = 0.15$), it was associated with a proportional 26% risk reduction and up towards a 5% increase in risk. The authors reported a trend towards fewer hospitalizations for HF with 2.9% in the treatment arm as compared to 3.4% in the placebo arm that did not reach statistical significance.

Clinical Implication

This study attempted to assess the use of medications that demonstrate an improvement in serious vascular outcomes and determine whether any of those benefits may overlap into the HF realm. While this was a negative outcome trial, it is helpful in laying out the limitations and benefits of these commonly used medications and defining their roles within the CV field. More research on this topic, including subgroup analysis of benefit between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) is needed. Furthermore, the dosing and type of omega-3 fatty acid and the placebo selection are important as seen in the REDUCE-IT and JELIS trials that showed a CVD benefit with higher doses of EPA. Similarly, the net-benefit for aspirin may accrue predominantly in middle-aged individuals at moderate to high risk of CVD, but low risk of bleeding.

REDUCE-IT: Significant Reduction In ST-Elevation MI with Icosapent Ethyl

Study Overview

Management of patients with hypertriglyceridemia is not well established. The effect of omega-3 fatty acids has been previously studied in patients with high triglycerides with conflicting results on CV events [5]. The REDUCE-IT trial aimed to assess the safety and benefit of icosapent ethyl (IPE) in statin-treated patients aged ≥ 45 with baseline triglycerides > 135 and < 500 mg/dL and at high risk or with established CVD (patients with diabetes and one or more risk factors for CVD) [6]. The study cohort was randomized in a 1:1 fashion and stratified by primary vs. secondary prevention, use of ezetimibe, and geographic region. Seventy percent of the cohort had a previous CV event, and 94% were on moderate or high intensity statin.

In the REDUCE-IT trial, the use of 2 g twice daily IPE was associated with more favorable outcomes (CV events, CV mortality, plus all-cause mortality in a separate analysis for the US subgroup) compared to a pharmaceutical-grade mineral oil placebo. In this current sub analysis from REDUCE-IT, myocardial infarction (MI) incidence for IPE vs. placebo was 8.6% vs. 12.0% ($p < 0.0001$) with a hazard ratio (HR) of 0.69 (95% CI 0.58–0.81). ST-segment elevation MI (STEMI) incidence was 2.7% vs. 3.9% ($p = 0.0008$) with a HR of 0.60 (0.44–0.81), and non-ST-segment elevation MI (NSTEMI) incidence was 5.9% vs. 7.8% ($p = 0.001$) with a HR of 0.73 (95% CI 0.60–0.89).

Clinical Implication

The REDUCE-IT trial demonstrated a beneficial effect of IPE after several negative trials utilizing other formulations and doses of omega-3 fatty acids failed to show benefit or reduction in CV event rates. It is noteworthy that the dose of purified EPA levels used in the trial was significantly higher [4 g/daily] compared to prior trials. Newer results are important as they show a reduction in clinically meaningful MI events. IPE was associated with overall higher rates of atrial fibrillation (AF) and peripheral edema. There was no statistically significant difference in in all-cause mortality in the overall cohort but a significant reduction in the US subgroup favoring IPE. Current guidelines have not included IPE use for all patients treated with statins, but it seems favorable to consider its use in patients with high levels of triglycerides with established CVD or diabetes in addition to another risk factor.

Short-term Effects of Air Temperature on CV Mortality and Morbidity Across Five European Cohorts: Results of the EXHAUSTION Project

Study Overview

Unfavorable temperatures were estimated to account for 1.96 million deaths (1.01 million in male and 1.95 in female subjects) worldwide in 2019, mainly due to CVD [1]. There is little information about how individual characteristics may influence effect modification. A limited number of studies have examined the effects of air temperature on an individual level.

Five European cohorts including participants from Italy, Germany, the UK, Norway, and Sweden were examined for the short-term associations between unfavorable temperature

and CV mortality and morbidity as part of the EXHAUSTION project [7]. Statistical analysis was performed in two stages including stage 1 with cohort specific analysis (time stratified case cross over design comparing temperature on case versus control days) to measure effect modification in the form of OR) and stage 2 with random effect meta-analysis.

There were 2.28 million participants, mean age was 52 years (except for participants from Sweden with a mean age of 71 years), and 50% were female. Outcomes were mortality including death from CVD, ischemic heart disease, and cerebrovascular disease, and morbidity in form of MI and cerebrovascular events. High temperature was defined as an increase in air temperature from 75 to 99th percentile and cold temperature was defined as a decrease in air temperature from 25th to 1st percentile. Results showed an increased CV mortality (−4.8 vs. 4.7 with OR 1.19 (95% CI 1.04–1.36), ischemic heart disease mortality (−4.8 vs. 4.6 with OR 1.22 (95% CI 1.07–1.38), coronary morbidity (−8.9 vs. 2.4 with OR 1.04 (1.01–1.08) with short-term cold exposure (with an approximately 10 °C temperature drop, from 5 to −5 °C); however, no effect was observed with high temperature. It was noted that patients with ages > 65 years and female sex were potentially more susceptible to the effects of cold temperature on new-onset ischemic heart disease.

Clinical Implication

The EXHAUSTION TRIAL shows that short-term cold exposure leads to significantly higher risk of CV mortality and morbidity at the individual level, especially for patients with age > 65 years and females. However, with heat exposure no detrimental effects were observed on CV outcomes. Clinical guidance and CV risk assessment should be tailored to patients' environmental exposures.

Cardiac CARE—A Randomized trial of Troponin-guided Neurohormonal Blockade for the Prevention of Anthracycline Cardiotoxicity

Study Overview

Cardiac CARE was a multicenter, prospective, randomized, open-label, blinded end point trial of combination β-adrenergic receptor blocker (ARB), and renin-angiotensin-system inhibitor (RAASi) therapy in patients receiving anthracycline chemotherapy associated with myocardial injury. Inclusion criteria were a diagnosis of breast cancer or non-Hodgkin lymphoma scheduled for high-dose anthracycline therapy. Patients scheduled for anti-HER2 therapy and those with established systolic dysfunction, HF, or poorly controlled HTN were excluded. The primary outcome was the change in LVEF on cardiac MRI (cMRI) from baseline to 6 months after completion of chemotherapy. For secondary analysis, change in LVEF over the 6-month study period was analyzed in low-risk patients to ascertain the specificity of high sensitivity cardiac troponin-I (hs-cTnI) for identifying participants whose LVEF did not decline. Sample size was planned at 23 patients per group to detect a difference of 5 LVEF percentage points between groups, at 90% power.

All patients had baseline cMRI scan and hs-cTnI quantification as well as hs-cTnI quantification before each chemotherapy cycle. Patients with elevated hs-cTnI in the upper tertile were randomized 1:1 to receive standard of care plus combination candesartan and carvedilol therapy (treatment group) or standard of care alone (standard of care group). Repeat cMRI was performed 6 months after completion of chemotherapy in all study patients [8].

Of 191 patients enrolled, 57 were randomized and 118 were not randomized. In the randomized high-risk groups, the groups were well balanced with percent female patients (79 and 78%), average age (54 years old in both groups), number of patients with non-Hodgkin lymphoma (41 vs. 46%), number of patients with breast cancer (59 vs. 54%), mean planned epirubicin dose (469 and 479 mg/m^2), percent undergoing radiotherapy (57 and 54%), and LVEF at baseline (70 and 69%). The low-risk non-randomized group notably had fewer patients with non-Hodgkin lymphoma (21%) and lower mean planned epirubicin dose (424). Median hs-cTnI in ng/l was 2 in both randomized high-risk groups and 0.5 in the low-risk non-randomized group.

Between the randomized groups, there was no difference in mean LVEF change post anthracycline chemotherapy even after controlling for age, LVEF at baseline, and cumulative anthracycline dose. The absolute decline in LVEF for each of the 3 groups were −2.9% in the low-risk non-randomized group, −4.2% in the randomized treatment group, and −4.3% in the randomized standard of care group. Change in hs-cTnl concentration from baseline to 2 months post anthracycline chemotherapy demonstrated no difference between groups with and without adjustment.

Clinical Implication

Prior studies of preventative neurohormonal therapy have demonstrated some cardioprotective benefit for patients undergoing anthracycline chemotherapy [9]. In the Cardiac CARE trial, neurohormonal blockade did not prevent a fall in LVEF on cMRI or myocardial injury in high-risk patients with elevated hs-cTnI during anthracycline chemotherapy. Moreover, hs-cTnI lacked the specificity to identify low-risk participants that did not experience a decline in LVEF. These findings do not support the recently released ESC cardio-oncology treatment guidelines which advocate cTnI monitoring for surveillance of anthracycline cardiotoxicity

and cardioprotective therapy with neurohormonal blockade [10••]. Long-term studies are needed to clarify the utility of routine biomarker monitoring to inform preventative treatment of overt HF after anthracycline chemotherapy. Diagnostic aid from appropriate imaging such as echocardiography with global longitudinal strain analysis or cMRI may necessary in the meantime.

Follow-up Strategy of Routine Functional Testing or Standard Care in High-risk Patients After PCI: the Post-PCI Trial

Study Overview

After PCI, there are limited data to guide follow-up surveillance. The POST-PCI trial examined the clinical outcomes of a strategy of routine stress testing among high-risk patients who had undergone successful PCI [11].

This open-label-pragmatic randomized trial involved 11 sites in South Korea. Participants were > 19 years of age with high-risk anatomical or clinical characteristics who underwent successful PCI. High-risk anatomical characteristics were defined as a left main disease, lesion at bifurcation and ostium, chronic total occlusion, restenotic lesion, multivessel disease, or lesion length ≥ 32 mm. High-risk clinical characteristics were defined as the presence of diabetes, chronic renal disease with serum creatinine > 2 or end-stage renal disease on dialysis, and acute coronary syndrome with positive cardiac biomarkers. Exclusion criteria were patients with cardiogenic shock on admission, patients being treated with bare metal stents or balloon angioplasty only, lactating and/or pregnant patients, patients with life expectancy < 1 year, patients participating in another drug or device investigational study, and patients unable to consent themselves or participate in follow-up. The primary outcome was a composite of major CV events including death from any cause, MI, or hospitalization for unstable angina at 2 years post-PCI. Patients were randomized 1:1 to either routine stress testing at 12 months after PCI ($n = 849$) or standard care ($n = 857$). The mean age was 64 years and 79% were females. Of the routine functional testing group, 92.5% (723) underwent stress testing at 12 months, and in the standard care group, 9% (69) underwent stress testing at 12 months given other clinical indications.

At 2 years, there was no difference in the composite primary outcomes between the two groups, with 46 of 849 patients (5.5%) in routine stress testing patients and 51 of 857 patients (6.0%) in standard care (HR 0.90 (95% CI 0.61–1.35) $p = 0.62$). There was also no difference in secondary outcomes including death or MI [3.2% vs. 2.5%, HR 0.71 (95% CI 0.43–1.17)], any hospitalization [25.5% vs. 22.8%, HR 1.12 (95% CI 0.92–1.36)], invasive coronary angiography (12.3% vs. 9.3%, difference 2.99 percentage points; 95% CI, − 0.01 to 5.99), and repeat revascularization at 2 years (8.1% vs. 5.8%, difference, 2.23 percentage points; 95% CI, − 0.22 to 4.68) in routine functional testing versus standard of care for high-risk patients undergoing PCI respectively.

Clinical Implication

POST-PCI trial including high-risk patients undergoing PCI showed no difference in clinical outcomes, including ischemic CV events or death from any cause in patients having active surveillance with routine functional testing vs standard care at 2 years.

Influenza Vaccine Among Patients with Acute Coronary Syndromes: the VIP-ACS Trial

Study Overview

The study blindly randomized patients who were hospitalized for ACS to double dose quadrivalent vaccine during hospitalization versus standard dose vaccine in the outpatient setting and looked at a composite outcome or all-cause death, MI, stroke, hospitalization for unstable angina, HF hospitalization, urgent coronary revascularization, and hospitalization for respiratory infections.

The VIP-ACS trial randomized 1801 participants after an ACS to receive a double dose influenza vaccine while hospitalized versus the standard dose influenza vaccine after hospital discharge and within 30 days after randomization. In the 12-months follow-up, the study failed to show any significant difference in the primary composite end point (all-cause death, myocardial infarction, stroke, hospitalization for unstable angina, HF hospitalization, urgent coronary revascularization, and hospitalization for respiratory infections HR 0.97 [95% CI 0.75–1.24], $P = 0.79$. Due to the COVID-19 pandemic's effect on recruitment, the analysis was changed from the originally planned time to event analysis to a win ratio analysis to account for the reduced sample size—this resulted in a win ratio of 1.02 [95% CI 0.79–1.32], $P = 0.84$.

Clinical Implication

The overall number of hospitalizations due to influenza infections in VIPS-ACS was low, and not different between the study groups. The study was also impacted by the COVID-19 global pandemic with very strict respiratory precautions and quarantine requirements. The preventive measures used from masking to shutdowns could have contributed to the incidence of influenza and may have reduced the effect size that the authors initially anticipated. Influenza vaccinations are still recommended for patients with recent

ACS; however, the timing of such vaccinations does not seem to impact outcomes.

Empagliflozin in Patients with ACUTE MYOCARDIAL INFARCTION (EMMY)

Study Overview

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors have shown reduced risk for hospitalization for HF, CV, and all-cause mortality in patients with both chronic HFrEF and HFpEF [12]. MI is a major cause of incident HF. The EMMY trial aimed to determine whether empagliflozin in addition to guideline recommended post MI therapy initiated within 72 h after PCI with a large acute MI, with or without diabetes, would result in a larger decline in N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) levels and larger improvement in LVEF [13].

This was an investigator initiated, randomized, double-blind, placebo-controlled trial, performed across 11 sites in Austria from 2017 until 2022. Participants were 18–80 years old, had estimated glomerular filtration rate (eGFR) > 45 ml/min/1.73m^2, not hypotensive before first drug administration with blood pressure (BP) > 110/70 mmHg, had first intake of study medication ≤ 72 h after MI after performance of coronary angiography. Patients were admitted with an MI defined as creatine kinase (CK) > 800 U/l and a troponin level > 10 × the upper limit of normal with at least one of the following: symptoms of ischemia, electrocardiographic changes indicative of new ischemia, or imaging evidence of new regional wall motion abnormality. Patients were excluded if they had any other form of diabetes other than type 2 diabetes, had history of diabetic ketoacidosis, pH < 7.32, hemodynamic instability, had acute symptomatic urinary tract or genital infections, were previously treated with SGLT-2 inhibitors within the 4 weeks prior, allergic to SGLT2 inhibitors, had > 1 episode of severe hypoglycemia in last 6 months on insulin or sulfonylurea or were females of childbearing potential without adequate contraception. Patients were randomized to empagliflozin 10 mg/day vs. placebo, with follow-up visits at 6 weeks, 12 weeks, 26 weeks, and a follow-up safety phone call 4 weeks after the final visit.

The primary outcome was a change in NT-proBNP levels from randomization to week 26. Secondary outcomes included changes in NT-proBNP levels from randomization to week 6, changes in LVEF from randomization to weeks 6 and 26, changes in echocardiographic parameters for diastolic dysfunction, changes in left ventricular end systolic (LVESV), and end diastolic volume (LVEDV), and changes in ketone body, HgbA1c, and body weight.

Five hundred and sixty-eight patients were assessed, 476 were randomized with 237 in the empagliflozin arm, and 239 in the placebo arm, for the final analysis without data imputation 212 were in empagliflozin arm and 209 in the placebo arm. Baseline characteristics, medications, and laboratory parameters were well balanced between the two groups.

The percent change in log-transformed NT-proBNP from baseline showed a relative reduction in NT-proBNP levels at week 26 (comparison empagliflozin vs. placebo) of − 15% (95% CI: − 4.4% to − 23.6%), $p = 0.026$. At visit 2 (6 weeks), there was a − 10.6% relative reduction in NT-proBNP levels that was not statistically significant, $p = 0.075$. At visit 3 (12 weeks), there was a − 13.3% relative reduction in NT-proBNP levels (95% CI: − 22.5% to − 3.0%), $p = 0.021$. Secondary efficacy analysis of NT-proBNP levels at week 26 in empagliflozin vs placebo showed similar results, − 15% (95% CI: − 12.5% to − 17.3%) and − 16% (95% CI: − 2.0% to − 28.1%), respectively. Ejection fraction, *E*/e', LVESV, and LVEDV at 26 weeks were assessed and showed an absolute percentage difference of 1.5% greater (95% CI: 0.2% to 2.9%), $p = 0.029$ for LVEF, mean reduction of 6.8% greater (95% CI: 1.3% to 11.3%), $p = 0.015$ for *E*/*e*', 7.5 ml lower volume (95% CI: 3.4% to 11.5%), $p = 0.0003$ for LVESV, and 9.7 ml lower volume (95% CI: 3.7% to 15.7%), $p = 0.0015$ for LVEDV in the empagliflozin group compared with placebo.

Safety parameters were assessed and noted 3 cases of death, all in the empagliflozin arm—one was a large MI with severe HF, the second was due to lung cancer, and the third was a case of cardiogenic shock due to coronary occlusion, none of which were assessed to be due to the empagliflozin. There were more urinary infections in the empagliflozin arm vs. placebo.

Clinical Implication

SGLT2 inhibitors are emerging as powerful therapies in CV care, especially as guideline directed medications for HF. The implications of these medications in acute MI remains unknown. The EMMY trial showed a greater reduction in NT-proBNP, improvement of function and structural echocardiographic parameters after an acute MI after 26 weeks of treatment with empagliflozin compared to placebo. Empagliflozin, when initiated immediately after an acute MI, might be a promising treatment option to prevent HF, and is being investigated in ongoing CV outcome trials.

Long-term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease: Primary Results of the FOURIER-OLE Studies

Study Overview

Long-term data on the safety and efficacy of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is lacking.

The FOURIER trial demonstrated a reduced risk of major adverse CV adverse events at a follow-up of 2.2 years with evolocumab therapy without any significant benefit of CV mortality [14•]. The FOURIER-OLE trial was an open-label extension of the parent FOURIER trial that was conducted on stable 27,564 ASCVD patients with low-density lipoprotein cholesterol (LDL-C) ≥ 70 mg/dl or non-HDL-C of ≥ 100 mg/dl on optimized dose of a statin [15].

In the parent FOURIER trial, patients were randomized to evolocumab either every 2 or 4 weeks (13,784 patients) or placebo (13,780 patients). Enrolled in FOURIER-OLE and continued therapy with evolocumab every 2 or 4 weeks regardless of whether they were originally randomized to evolocumab or placebo in the parent trial were 6635 patients. Of the 6635 patients enrolled in FOURIER-OLE, there were two groups that were compared: 3355 (50.6%) who were originally randomized in the parent trial to treatment with evolocumab and 3280 (49.4%) who were originally randomized to placebo. Median follow-up time was 5.5 years. The primary outcome was the incidence of adverse events and major adverse CV events (MACE) including CV, MI, or stroke were also explored in this study. Median age was 62 years with 30% female.

Results showed that evolocumab use, in patients on optimized statin therapy, provides sustained LDL-C reduction. The median LDL-C was 30 mg/dl for the study population in aggregate at 12 weeks after the start of FOURIER-OLE (with similar results irrespective of original treatment assignment). At that time, the achieved LDL-C was < 70 mg/dl in 87.3%, < 55 mg/dl in 80.3%, < 40 mg/dl in 63.2%, and < 20 mg/dl in 26.6% of patients. Patients sustained this low-level LDL-C at the end of 5-year follow-up. This trial demonstrated evolocumab is well tolerated with low serious adverse events (10%), injection site reactions (0.4%), drug-related allergic reactions (0.6%), muscle-related events (1.2%), rhabdomyolysis/myopathy event (0.04%), new-onset diabetes (1.2%), cataract formation (0.74%), and hemorrhagic stroke (0.04%). Patients who were randomized to evolocumab use in the parent trial, when they continued its use in the open-label FOURIER-OLE trial, had 23% reduction in CV death when compared to patients who were randomized to placebo in the parent trial (HR 0.77, 95% CI 0.60–0.99, $p = 0.04$). In the extended FOURIER-OLE trial, a 15% reduction in the primary endpoint of FOURIER trial (composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) was noted (16.7% in patients who were randomized to placebo in parent trial vs. 14.6% in patients who were randomized to evolocumab in the parent trial) [HR 0.85, 95% CI 0.75–0.96, $p = 0.008$]. Likewise, a 20% reduction was noted in the key secondary endpoint of composite CV death, MI, or stroke (11.4% in patients who were randomized to placebo in parent trial vs. 9.2% in who were randomized to evolocumab in parent trial) [HR 0.80, 95% CI 0.68–0.93, $p = 0.003$]. This demonstrates that clinical benefit of PCSK-9 inhibition not only grew over time, it persisted without adverse events. Similar to prior statin trials, a legacy effect was observed as demonstrated by an accrual of CV benefit in patients randomized to evolocumab in the parent trial as opposed to those patients originally randomized to placebo. Additionally, a lag in the onset of clinical benefit of LDL-C lowering was noted similar to previously documented lag effect noted with all of the major LDL-C-lowering drugs classes.

Clinical Implication

Evolocumab, a fully human antibody, when used on top of an optimized level of statin therapy sustains low LDL-C levels on a long-term basis. To prevent MIs and CV deaths in patients with established ASCVD, this strategy has been demonstrated to be safe, well tolerated, and effective. Therapy should be initiated as early as possible to achieve optimal benefit given the legacy and lag effects observed.

DANCAVAS—Screening and Intervention to Prevent Cardiovascular Disease

Study Overview

CVD is the main cause death and the main cause of premature death among males, though data are divergent on the benefits of routine CV screening. The investigators of this trial aimed to investigate effects of comprehensive imaging base CV screening on death and CV events.

This was a community based, randomized controlled trial consisting of men aged 65–74, living in municipalities in Denmark, who were identified and included in the study with no exclusion criteria, and participants were either invited to screening (1/3 of patients) or were not invited (2/3 of patients). Those screened went through a program including electrocardiographic-gated non-contrast computed tomography (CT) scan to detect coronary artery calcium, AF, and aortic and iliac aneurysms; four-limb BP measurements for peripheral arterial disease and HTN, and blood samples to test for diabetes and cholesterol. The primary outcome was all-cause mortality. Secondary outcomes included stroke, MI, amputation due to vascular disease, aortic dissection, and aortic rupture. A post hoc defined composite outcome of all-cause mortality, stroke, and MI was also included.

Identified men were 46,611, 16,736 of which were invited to screening and were analyzed for outcomes, 29,790 of which were not invited to screening and were analyzed for outcomes, with a median follow-up time of 5.6 years. Of note, only 63% of the invited group attended the screening. Analysis was performed using intention to treat principle. Baseline characteristics were well matched between

groups. Primary outcome of all-cause mortality occurred in 2106 (12.6%) in the screened group vs. 3915 (13.1%) in the non-invited group (HR = 0.95 (0.9–1.00), $p = 0.062$). When stratified for age, all-cause mortality for the 65–69 year age group did show a clinically significance in the screened group (HR = 0.89 (0.83–0.96), $p = 0.004$); though no difference in the 70–74 year age group (HR = 1.01 (0.94–1.09), $p = 0.747$). Secondary outcomes revealed a significant difference in stroke with 1169 (7.0%) in the invited group vs. 2228 (7.5%) in the non-invited group (HR = 0.93 (0.86–0.99), $p = 0.035$), and a non-significant difference in MI with 431 (2.6%) in the invited group vs. 844 (2.8%) in the non-invited group (HR = 0.91 (0.81–1.03), $p = 0.134$). There was a clinically significant difference in the post hoc composite outcome of death, stroke, or MI with 3335 (19.9%) in the invited group vs. 6308 (21.2%) in the non-invited group (HR = 0.93 (0.89–0.97), $p < 0.001$.

The authors explained why this difference might have been seen with explanatory outcomes showing more antiplatelet agents were initiated in the screened group (HR = 3.12, $p < 0.001$), as were lipid lowering therapy (HR = 2.54, $p < 0.0010$). Though no difference was observed between anticoagulants, hypertensive agents, or antidiabetic medications. Safety outcomes demonstrated no statistically significant differences between the groups.

Clinical Implication

Comprehensive imaging-based CV screening among men aged 65 to 74 years did not significantly reduce all-cause mortality at 5 years. However, subgroup analyses indicated that the younger age group (65–69 years) may benefit from screening. Results show a potential use of routine screening in patients 65–69 years old and highlight that appropriate selection of patients to be screened is essential.

Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE)

Study Overview

The efficacy of CVD medications is limited by suboptimal adherence. This study randomized patients from seven different countries with MI within the previous 6 months to a fixed dose combination polypill consisting of aspirin (100 mg), rampril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg) or standard care consisting of treatment according to current clinical guideline. The primary composite outcome was CV death, nonfatal type 1 MI, nonfatal ischemic stroke, or urgent revascularization, and the key secondary endpoint was a composite of CV death, nonfatal type 1 MI, or nonfatal ischemic stroke [16].

The SECURE trial randomized 2499 patients and followed them for a median of 36 months. Included patients had experienced a type 1 MI within the previous 6 months and were either older than 75 years of age or at least 65 years of age with one of the following comorbidities: diabetes mellitus, mild or moderate kidney dysfunction, previous MI, previous coronary revascularization, or previous stroke. Patients on oral anticoagulation were excluded.

The study demonstrated a significantly lower risk of MACE than usual care with a primary outcome event occurring in 9.5% in the polypill group vs. 12.7% in the usual care group HR 0.76 [95% CI 0.60–0.96], $p = 0.02$. A secondary outcome event was noted in 8.2% of patients in the polypill group vs. 11.7% of patients in the usual care group HR 0.70 [95%CI, 0.54–0.90], $p = 0.005$. At 24 months, adherence remained high in the polypill group at 74.1% and lower in the usual care group at 63.2% (risk ratio, 1.17; 95% CI, 1.10–1.25). Results remained consistent across pre-specified subgroups and safety outcomes were equivalent between groups.

Clinical Implications

The use of a polypill for secondary CVD prevention in older patients is a safe strategy to reduce recurrent CV events. In part, the success is due to increased adherence to medication. This study demonstrates the potential to reduce recurrent CV events on a global scale.

Conclusion

The 2022 European Society of Cardiology Congress included several significant trials that advance the field of cardiovascular disease prevention and management. A deeper understanding of risk factors for CVD as well as tools to screen for, prevent, and treat CVD hold promise to reduce the burden of CVD which remains the leading cause of mortality worldwide. While these studies generate optimism for reducing morbidity and mortality in CVD, future studies are warranted to determine applicability of these findings.

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Declarations

Conflict of Interest Melody Hermel, Megan Pelter, Timothy Jordan, Azka Latif, Mohammad Gad: None. Salim S. Virani: Honorarium, American College of Cardiology (Associate Editor for Innovations,

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•• Of major importance

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