



Highlights from Studies Presented at the Virtual American College of Cardiology Scientific Sessions 2021: Staying Updated with the Latest Advancements in Prevention

Vardhmaan Jain¹ · Mahmoud Al Rifai² · Dhruv Mahtta² · Jing Liu² · Aliza Hussain² · Salim S. Virani^{2,3} 

Accepted: 22 June 2021

© This is a U.S. government work and not under copyright protection in the U.S.; foreign copyright protection may apply 2021

Abstract

Purpose of Review This review highlights late-breaking science presented at the Virtual American College of Cardiology Scientific Sessions 2021 that demonstrated advancements in preventative cardiology and introduced novel therapeutic modalities for the management of chronic kidney disease, heart failure, and COVID-19.

Recent Findings The studies reviewed include clinical trials that assessed the use of dapagliflozin in patients with respiratory failure due to COVID-19 (DARE-19 trial); evinacumab for patients with severe hypertriglyceridemia and pancreatitis; effect of genotype-guided oral P2y12 inhibitors vs conventional clopidogrel on long-term ischemic outcomes after percutaneous coronary intervention (TAILOR-PCI trial); anticoagulation in patients hospitalized with COVID-19 (ACTION trial); atorvastatin vs placebo in patients with COVID-19 admitted to the ICU (INSPIRATION-S trial); rehabilitation therapy in older acute heart failure patients (REHAB-HF trial); and aspirin dosing: a patient-centric trial assessing benefits and long-term effectiveness (ADAPTABLE trial). In addition, we review the results of the American College of Cardiology Global Heart Attack Initiative (GHATI). Finally, we discuss the secondary analysis of the STRENGTH trial assessing the association of achieved levels of omega-3 fatty acid levels and major cardiovascular outcomes.

Summary The studies presented at the virtual American College of Cardiology Scientific Session 2021 represent remarkable contributions in the field of cardiovascular disease and prevention.

Keywords Dapagliflozin · Evinacumab · Aspirin · Rehabilitation · Severe hypertriglyceridemia · Omega-3 fatty acid

Introduction

The American College of Cardiology (ACC) Scientific Session 2021 was held virtually in the setting of the ongoing COVID-19 pandemic. Multiple late-breaking science and notable studies

pertaining to the latest updates in heart failure, prevention, anticoagulation, and cardiac rehabilitation were presented. In this review, we summarize some of their key findings.

The studies reviewed here include those looking at the benefits of sotagliflozin in risk reduction across the full spectrum of

Topical Collection on *Reviews and New Research Implications*

✉ Salim S. Virani
virani@bcm.edu

Vardhmaan Jain
jainv2@ccf.org

Mahmoud Al Rifai
Mahmoud.Alrifai@bcm.edu

Dhruv Mahtta
Dhruv.Mahtta@bcm.edu

Jing Liu
Jing.Liu@bcm.edu

Aliza Hussain
Aliza.Hussain@bcm.edu

¹ Department of Internal Medicine, Cleveland Clinic, Cleveland, OH, USA

² Section of Cardiology Department of Medicine, Baylor College of Medicine, Houston, TX, USA

³ Section of Cardiology Health Services Research and Development, Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Boulevard, Houston, TX 77030, USA

ejection fraction, including heart failure with preserved ejection fraction; effects of dapagliflozin on prevention of major clinical events and recovery in patients with respiratory failure due to COVID-19 (DARE-19); anticoagulation in patients hospitalized with COVID-19—the anticoagulation coronavirus trial (ACTION trial); atorvastatin vs placebo in patients with COVID-19 admitted to the ICU: the INSPIRATION-S trial; evinacumab for patients with severe hypertriglyceridemia and pancreatitis; achieved levels of omega-3 fatty acid levels and major cardiovascular outcomes: secondary analysis from the STRENGTH trial [1]; aspirin dosing: a patient-centric trial assessing benefits and long-term effectiveness (ADAPTABLE trial) [2]; and rehabilitation therapy in older acute heart failure patients (REHAB-HF) [3]. We also review the results of the effects of genotype-guided oral P2Y12 inhibitors vs conventional clopidogrel on long-term ischemic outcomes after percutaneous coronary intervention (TAILOR-PCI) and 1-year results from the American College of Cardiology Global Heart Attack Treatment Initiative (GHATI) [4]. As in prior publications, we aim to provide a summary for each of select major studies and their clinical implications [5–7].

Benefits of Sodium Glucose Co-transporter-1/2 Inhibition with Sotagliflozin Across the Full Spectrum of Ejection Fraction, Including Heart Failure with Preserved Ejection Fraction

Study Overview

In this analysis, Bhatt et al. used pooled patient-level data from 2 large, randomized trials, SCORED and SOLOIST-WHF [8•, 9•].

The SCORED trial was a multicenter randomized double-blind study comparing sotagliflozin to placebo among outpatients with diabetes and chronic kidney disease (estimated glomerular filtration rate, 25 to 60 ml per minute per 1.73 m² of body-surface area). The primary outcome was a composite of cardiovascular-related deaths, hospitalizations, or urgent visits for heart failure. The study population consisted of 10,584 patients who were followed for a median of 16 months. The event rate among those treated with sotagliflozin (200mg daily) was 5.6 per 100 person-years compared to 7.5 in the placebo arm which translated to a significant risk reduction with hazard ratio (HR), 0.74, and 95% confidence interval (CI), 0.63 to 0.88.

The SOLOIST-WHF trial was a multicenter randomized double-blind study comparing sotagliflozin (200 mg) to placebo among patients with diabetes mellitus who were recently hospitalized for worsening heart failure. The primary outcome was a composite of cardiovascular deaths and hospitalizations or urgent visits for heart failure. The study population

consisted of 1,222 patients who were followed for a median of 9 months. The event rate among those treated with sotagliflozin was 51.0 per 100 person-years compared to 76.3 in the placebo arm which translated to a significant risk reduction with HR 0.67 and 95% CI 0.52 to 0.85.

In the present pooled analysis, the researchers examined the effectiveness of sotagliflozin treatment stratified by baseline ejection fraction (EF) which was available in all except 22 patients. They performed this analysis both in the combined cohort consisted of 11,784 patients and in the subgroup of 4,500 patients who had a prior history of heart failure. In both groups, the authors found significant reductions in the primary outcomes regardless of EF at study entry. Among patients with an EF 40% or less, the risk reduction was 22% in both the overall cohort and heart failure group. Among patients with an EF 40 to 50%, sotagliflozin resulted in a risk reduction of 39% in the overall cohort and 43% in the heart failure group. The corresponding risk reduction among those with EF greater than 50% was 30% in the entire cohort and 33% in the heart failure group. These results were statistically significant and were similar for males and females.

Clinical Implications

Currently there are no disease-modifying treatments for heart failure with preserved EF (HFpEF) [10]. The TOPCAT trial suggested that spironolactone may potentially be beneficial, but this was only in post hoc analyses from the Americas [11]. Sacubitril-valsartan was also not found to be efficacious in the PARAGON-HF trial [12]. SGLT2 inhibitors hold much promise and may prove to be beneficial in this challenging group of patients. The current study shows that sotagliflozin may reduce adverse outcomes among HFpEF patients although it is unclear whether these results would also apply to heart failure patients without diabetes. The DELIVER trial examining the efficacy of dapagliflozin in HFpEF is currently under way and is expected to be completed in November 2021 [13]. Similarly, EMPEROR-Preserved aims to study the effect of empagliflozin in HFpEF patients, and results are expected to be released soon [14].

Effects of Dapagliflozin on Prevention of Major Clinical Events and Recovery in Patients with Respiratory Failure Due To COVID-19—Main Results from the DARE-19 Randomized Trial

Study Overview

The DARE-19 trial was a randomized, placebo-controlled trial examining the efficacy of dapagliflozin (10 mg daily) among noncritically ill hospitalized patients with COVID-19. Patients

were included if they were hospitalized with confirmed/suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for ≤ 4 days with O₂ saturation of $\geq 94\%$ on ≤ 5 L/min, chest X-ray findings consistent with COVID-19, and presence of at least 1 cardiovascular risk factor (hypertension, type 2 diabetes, atherosclerotic cardiovascular disease (ASCVD), heart failure, chronic kidney disease). The primary outcome was a composite of end-organ dysfunction or death. Secondary outcomes included kidney dysfunction and all-cause mortality.

A total of 1,250 patients were included (mean age 62 years, 43% women) and followed for up to 90 days. The primary outcome occurred in 11.2% of patients in the dapagliflozin arm vs 13.8% in the placebo group ($p = 0.17$) with a HR 1.09 and 95% CI 0.97 to 1.22. Secondary outcomes were also not significant: 7.7% vs 10.4% for kidney dysfunction and 6.6% vs 8.6% for all-cause mortality.

Clinical Implications

The results of this trial demonstrate that dapagliflozin does not significantly reduce organ dysfunction or death or improve recovery compared with placebo among noncritically ill hospitalized patients with COVID-19. Importantly, the trial included patients with and without type 2 diabetes. However, the sample size was small, follow-up duration was short, and very few patients had baseline heart failure or chronic kidney disease. It is conceivable that patients with heart failure and COVID-19 diagnosis could potentially benefit from dapagliflozin though a larger trial with longer follow-up is likely required. Further research examining the potential cardioprotective mechanisms of SGLT2 inhibitors in these patients is required to better understand the use of these agents for mitigating the burden of morbidity and mortality due to COVID-19 among heart failure patients.

Anticoagulation in Patients Hospitalized with COVID-19—the AntiCoagulation cOroNaviRus (ACTION) Trial

Study Overview

Arterial and venous thromboembolism have been reported in patients with COVID-19 [15, 16]. While studies have suggested that anticoagulation might improve clinical outcomes in patients with COVID-19, much remains unknown regarding the optimal strategy, such as patient selection, choice, and duration of anticoagulation therapy. The ACTION trial was a randomized clinical trial comparing the efficacy and safety of therapeutic versus prophylactic anticoagulation with rivaroxaban in preventing complications in hospitalized patients with COVID-19 and elevated D-dimer levels (above upper limit of normal).

Stable patients received rivaroxaban 20 mg daily, and unstable patients received enoxaparin 1mg/kg twice daily. The primary outcome of the study was a hierarchical analysis of mortality, duration of hospitalization, and duration of oxygen use through 30 days. Primary safety outcome includes major or clinically relevant non-major bleeding according to International Society on Thrombosis criteria. Key secondary outcomes include death, myocardial infarction, venous thromboembolism, stroke, or major adverse limb event.

Patients were included in the trial if they met the following inclusion criteria: age ≥ 18 years, hospitalized with a confirmed diagnosis of COVID-19 and duration of symptoms related to hospitalization ≤ 14 days, and elevated D-dimer at admission. Main exclusion criteria included indication for therapeutic anticoagulation at screening, eCrCl < 30 ml/min, platelets $< 50,000$ /mm³, use of P2Y₁₂ inhibitor or ASA > 100 mg daily, and very high risk of bleeding. A total of 615 patients were randomized to either therapeutic anticoagulation ($n=311$) or standard of care with in-hospital prophylactic dose anticoagulation ($n=304$). Within the therapeutic group, stable patients received rivaroxaban 20 mg po daily, while unstable patients received enoxaparin 1 mg/kg subcutaneously twice daily. This was followed by rivaroxaban 20 mg through 30 days in both groups, irrespective of duration of hospitalization. The primary outcome was analyzed with unmatched stratified win ratio, such that the therapeutic group wins when treatment patient survived 30 days and control has died and vice versa.

Among the enrolled patients, there were no significant differences in baseline characteristics such as age, gender, body mass index, as well as comorbidities such as chronic lung disease, diabetes, hypertension, and coronary disease between the therapeutic and the prophylactic groups. The primary outcome (hierarchical analysis of mortality, duration of hospitalization, and duration of oxygen use through 30 days) occurred in 34.8% of the therapeutic anticoagulation group and 41.3% of the prophylactic anticoagulation group (WR [95% CI] = 0.86 [0.59–1.22]). Among the efficacy outcomes, all-cause mortality was 11.3% in the therapeutic anticoagulation group compared to 7.6% in the prophylactic anticoagulation group [RR 1.49 (0.9–2.64)]. Composite thromboembolic outcome (myocardial infarction, venous thromboembolism, stroke, and major adverse limb event) occurred in 7.4% patients in the therapeutic anticoagulation group and 9.9% of the patients in the prophylactic anticoagulation group [RR 0/75 (0.45–1.26)]. For safety outcomes, the ISTH major bleeding or clinically relevant non-major bleeding was 8.4% in the therapeutic anticoagulation group compared to 2.3% in the prophylactic anticoagulation group [RR 3.64 (1.61–8.27)].

Clinical Implications

Overall, the trial showed that among patients hospitalized with COVID-19 with elevated D-dimers, in-hospital therapeutic

anticoagulation with rivaroxaban 20mg once daily for stable patients and enoxaparin for unstable patients followed by rivaroxaban through 30 days did not improve clinical outcomes but significantly increased bleeding compared with patients treated with prophylactic anticoagulation. The ACTION trial is unique in that it tested the effect of an oral anticoagulant and extended treatment for 30 days post discharge.

Atorvastatin vs Placebo in Patients with COVID-19 Admitted to the ICU: the INSPIRATION-S Trial

Study Overview

There has been limited high-quality evidence of the safety and efficacy of statin use in COVID-19 patients with evidence mostly related to observational studies [17]. In the HARP-2 trial, statins use had neutral results in the full population of intubated and ventilated patients with ARDS [18]. However, in a post hoc analysis of the baseline data of the HARP-2 trial, in hyperinflammatory sub-type of ARDS, simvastatin use was associated with decreased mortality when compared to placebo [19, 20]. The INSPIRATION-S trial sought to answer the question whether atorvastatin, compared with placebo, confers benefit to ICU patients with COVID-19.

INSPIRATION-S was a multicenter randomized clinical trial with a 2×2 factorial design in 11 hospitals in Iran. Patients with RT-PCR-confirmed COVID-19 admitted to ICU, with estimated survival of > 24 h, and meeting the study inclusion criteria were included in the study. Exclusion criteria included baseline liver function tests > 6 times upper normal limits, total creatine kinase > 500 U/L, acute liver disease (LFTs > 3 times upper normal limit plus histologic finding including cirrhosis or inflammation or necrosis), routine use of statins prior to the index hospitalization, or any previous documented statin intolerance. The primary outcome of the study was the composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or mortality within 30 days. The secondary efficacy outcomes include individual components of the primary efficacy outcome and ventilator-free days. The main safety outcomes include rise in liver enzymes > 3 times upper normal limit and clinically diagnosed myopathy. Additional safety outcomes include BARC 3 or 5 bleeding, severe thrombocytopenia.

A total of 605 patients were randomized to receive either atorvastatin 20mg daily (n= 303) versus placebo (n = 302). There were no significant differences in baseline characteristics between the two groups including age, gender distribution, BMI, coexisting conditions, medication history, as well as median laboratory values. The primary outcome occurred in 32.7% of patients receiving atorvastatin compared to 36.3% of patients receiving placebo (OR 0.84 (0.58–1.22), P value 0.35). Interestingly, in a subgroup analysis, those in the statin

group with symptom onset less than 7 days showed a significant reduction in the primary outcome compared with those in the placebo group [OR 0.6 (0.37, 0.99)]. Secondary efficacy outcomes (all-cause mortality, adjudicated venous thromboembolism individually) were all insignificant with a P value > 0.05 when comparing atorvastatin versus placebo group. Ventilator-free days (median, Q1, Q3) were 30 (10–30) in the atorvastatin group and 30 (4, 30) in the placebo group (P = 0.08). Major bleeding (Bleeding Academic Research Consortium [BARC] 3 or 5) was 3.7% in the atorvastatin group compared with 1.6% in the placebo group (p = 0.12).

Clinical Implications

Among patients with COVID-19 admitted to the ICU, atorvastatin 20mg daily compared with placebo did not result in significantly reduced risk of composite outcome of adjudicated venous or arterial thrombosis, treatment with ECMO, or all-cause mortality. The rate of thrombotic events in the study was lower than expected, and the study could not exclude a smaller treatment effect. Interestingly, a relatively low dose of atorvastatin was used in the study. The smaller treatment effect and positive findings within specific subgroups (such as those with symptom onset less than 7 days) may warrant further investigation.

Evinacumab for Patients with Severe Hypertriglyceridemia and Pancreatitis

Study Overview

Severe hypertriglyceridemia (sHTG) is defined as triglycerides greater than 500 mg/dL and occurs in 1% of the US adult population [21]. Elevated fasting plasma triglyceride (TG) levels are associated with an increased risk for future atherosclerotic cardiovascular disease (ASCVD) and pancreatitis, with the risk of pancreatitis progressively increasing with TG levels [22, 23]. sHTG likely accounts for 1 to 10 percent of cases of acute pancreatitis [24].

Lipoprotein lipase (LPL) is a key rate-limiting enzyme involved in the metabolism and breakdown of triglyceride and triglyceride-rich lipoproteins (TGRL). ANGLPTL3 is a hepatic protein that inhibits LPL and endothelial lipase and results in delayed clearance and increased plasma levels of TG, TGRL, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Carriers of loss of function mutation in ANGPTL3 demonstrate significantly lower levels of triglycerides and LDL-C as well as lower risk for future atherosclerotic cardiovascular events compared to non-carriers [25].

Evinacumab is a first in line fully human monoclonal antibody that works by binding to and blocking ANGPTL3. In

phase 1 clinical trials, evinacumab was well tolerated and demonstrated significant dose-dependent reductions in TG levels [26, 27]. Results of a phase II study evaluating efficacy and safety of evinacumab in patients with sHTG and history of one or more hospitalizations for acute pancreatitis were presented as a late-breaking clinical trial at the American College of Cardiology (ACC) 70th Annual Scientific Session 2021.

In a double-blind, placebo-controlled phase 2 trial, 51 patients were initially assigned to three cohorts based on genotype and medical history at screening: (1) patients with familial chylomicronemia syndrome and bi-allelic mutation in genes APOA5, APOC2, GPIHBP1, LMF1, or LPL (n=17); (2) patients with multifactorial chylomicronemia syndrome (MCS) and heterozygous mutation in LPL pathway mutations (n=15); and (3) patients with MCS and no LPL pathway mutations (n=19). These patients were then randomized in a 2:1 fashion to receive either evinacumab 15mg/kg or placebo. The median baseline fasting TG levels were 3,141 mg/dl, 1,238 mg/dl, and 1,917 mg/dl in the three cohorts, respectively. At the end of the 12-week placebo-controlled double-blind period, the median triglyceride level dropped by more than 800 mg/dL (57%) in patients taking evinacumab, compared with an overall increase of 50 mg/dL (1.8%) in participants taking a placebo. The median change in TG levels was -64.8% compared to +9.4% in placebo for cohort 2 and -81.7% compared to +80.9% in placebo in cohort 3. While in cohort 1, there was no significant reduction in triglyceride levels. Substantial reductions in non-HDL-C, apo-CIII, and apoB-48 levels were also observed.

The number of treatment-emergent adverse events was similar in the evinacumab and placebo group. During the 12-week, double-blind treatment period, five patients reported acute pancreatitis: 9.6% in the evinacumab group (n=3/35) vs 12.5% in the placebo group (n=2/16).

Clinical Implications

Despite lifestyle modification, dietary restrictions and use of currently approved TG-lowering patients with sHTG have inadequately controlled TG levels. The trial has important clinical implications for this population as evinacumab showed substantial reductions in TG levels in patients with sHTG and may be a promising therapeutic option. Moreover, the study also demonstrates the importance of genetic testing in patients with sHTG to determine which patients are most likely to respond to evinacumab. The magnitude of reduction in TG levels was dependent on a participant's genetic profile, with individuals with two LPL pathway gene mutations demonstrating no benefit, whereas patients with a single mutation or no mutations in the LPL pathway genes demonstrate clinically meaningful triglyceride reductions. Finally, while the trial was not designed to determine the effect on the occurrence of acute pancreatitis, a lower number of recurrent acute pancreatitis events were seen in the

evinacumab arm compared to placebo. This has important implications on improving quality of life and reducing healthcare costs as patients with sHTG are vulnerable to recurrent episodes of acute pancreatitis. A future study is currently underway evaluating the effects of evinacumab on the reduction of pancreatitis. Furthermore, as a phase 2 trial, the study was limited by its small sample size. Larger clinical outcome clinical trials are needed to elucidate the benefit of evinacumab in a broader population of patients with elevated levels of TG and LDL-C.

Achieved Levels of Omega-3 Fatty Acid Levels and Major Cardiovascular Outcomes

Study Overview

Recently, two large double-blind randomized controlled trials evaluating the use of high-dose omega-3 fatty acids in high-risk patients have demonstrated contradictory results. In Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT), the use of purified formulation of eicosapentaenoic acid (EPA) compared with a mineral oil placebo in patients with ASCVD or high risk for ASCVD and elevated TG levels demonstrated a significant reduction in major adverse cardiovascular events [28], whereas in Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial, use of a mixture of EPA and docosahexaenoic acid (DHA) administered at 4 g/day did not show significant benefit in cardiovascular outcomes [29]. Several theories have been proposed to explain these disparate results including potential adverse effects of mineral oil, higher EPA levels achieved in REDUCE-IT, or positive results of EPA offset by potential harmful effects of DHA in STRENGTH. The results of secondary analysis of STRENGTH were presented at ACC 2021 assessing the association of achieved levels of EPA and DHA with cardiovascular outcomes to address the latter two concerns [1][30].

In the current secondary analysis of STRENGTH, omega-3 fatty acid levels were available at baseline and 12 months in 10,382 patients. The median (IQR) for plasma EPA was 89 (46–131) $\mu\text{g/mL}$, and the median (IQR) DHA level was 91 (71–114) $\mu\text{g/mL}$ at 12 months in the active therapy arm. The highest tertile of EPA and DHA achieved were 151 $\mu\text{g/mL}$ and 118 $\mu\text{g/mL}$, respectively. Compared to corn oil, the highest tertile of achieved EPA in the active therapy arm did not show any significant difference in major cardiovascular events (HR 0.98, 95% CI 0.82–1.16).

Clinical Implications

This post hoc analysis of STRENGTH demonstrates two important findings. First, the achievement of higher levels in

EPA levels was not associated with cardiovascular benefit. Second, higher levels of achieved DHA levels were not associated with net harm or benefit in cardiovascular outcomes. Taken together, this analysis does not provide evidence that achieved levels of EPA or DHA are associated with a significant difference in cardiovascular outcomes. Other alternative explanations for the observed differences in outcomes between both trials that remain unexplored include chemical composition and pharmacological differences between carboxylic acid formulation used in STRENGTH vs ethyl ester in REDUCE-IT or choice of the comparator used (mineral oil vs corn oil).

However, the results of this secondary analysis have important limitations. Post hoc analyses of a randomized clinical trial are exploratory and hypothesis-generating as they lack the rigor of randomization. Performing a stratified analysis by tertiles may have reduced statistical power to detect a significant difference in clinical outcomes. Furthermore, as this analysis is performed post-randomization, despite the use of multivariable analysis, baseline characteristics of tertiles are not balanced, and there is potential for residual confounding. Finally, the median levels of EPA achieved in STRENGTH were much lower than REDUCE-IT (median 144 $\mu\text{g/mL}$ vs 89 $\mu\text{g/mL}$), and there was a modest correlation between achieved levels and change in EPA and DHA levels which has implications on the strength of association with clinical events and makes it difficult to extrapolate these results to patients studied in other clinical trials.

Worldwide ST-Elevation Myocardial Infarction Care: 1-Year Results of the American College of Cardiology Global Heart Attack Treatment Initiative (GHATI)

Study Overview

Acute myocardial infarction (AMI) remains as one of the leading causes of cardiovascular mortality and morbidity. Significant improvements pertaining to the care of patients presenting with myocardial infarction have been made over the last decade in western nations including the USA and several European nations. However, with rising global burden of cardiovascular disease, similar improvements in AMI care have lagged in developing nations. Furthermore, there is a significant lack of real-world data from developing nations which has limited evaluation of gaps in care and interventions to bridge these gaps. It was in light of this that the American College of Cardiology (ACC), along with its assembly of international governors, launched the Global Heart Attack Treatment Initiative (GHATI) in early 2019 [31]. The primary objective of the GHATI workforce was to evaluate, improve,

and implement best practices and evidenced-based AMI care in low- and middle-income developing nations.

GHATI tracked patients presenting with ST-elevation myocardial infarction (STEMI) to eighteen medical centers across thirteen low- and middle-income nations and four continents. Data elements derived as part of this quality improvement initiative were those set forth by the ACC Chest Pain-MI registry. The participating institutions were required to prospectively report these data points and AMI performance metrics on a quarterly basis spanning from October 2019 through September 2020. The GHATI workgroup aimed to evaluate compliance with AMI guidelines and change in adherence to these guidelines over the study period.

At the conclusion of the first year, a total of 1,073 STEMI patients were reported by the GHATI investigators. Females comprised a small proportion of the overall patient population, 18.7%, and roughly one-third of all patients were observed to be smokers. Rates of cardiogenic shock prior to arrival were reported to be 9.5% and 6.1% of patients experienced cardiac arrest prior to intervention. Over the course of the study period, there was a decrease in mean transportation time to the hospital by roughly 26 min. Similarly, first medical contact (FMC) to device time reduced by 31% over the study year ($p=0.05$). Overall use of reperfusion therapy increased by 12%, while the adherence to guideline-directed medical therapy (GDMT, defined as use of statin therapy, beta blockers, aspirin, P2Y12 inhibitor, and ACE inhibitor in patients with left ventricular dysfunction) remained high although did not vary significantly over the study period. These measures translated in patient outcomes as the proportion of patients with cardiac arrest upon arrival decreased by 4.6% over the study year.

Clinical Implications

The 1-year data from GHATI suggest two key findings. First, a quality improvement initiative and reporting such as GHATI may hold promise in not only identifying barriers to optimal STEMI care but also improving STEMI care and patient outcomes in these low- to middle-income nations. Second, the current 1-year data suggests that physicians in these nations are well versed with STEMI guidelines and demonstrate a high level of adherence to them. However, it may be systemic factors such as transport time to hospital, availability of emergency response teams, and coordination of care within healthcare systems which require further close evaluation and optimization.

The current report is not without its inherent limitations. The reported results are part of a quality improvement initiative and do not reflect findings of a randomized controlled trial. Therefore, changes in observed patient-centered outcomes may not be attributed to reported changes in systemic factors over the study years. Additionally, the current report is

limited by its small cohort and short follow-up which limits the significance of observed trends. Finally, a lack of standardized electronic medical record at some institutions may hinder accurate long-term outcomes assessment.

Despite its limitations, the GHATI workgroup has introduced a concept of quality improvement in institutions which were previously not accustomed to track and report quality metrics. This measure in itself may provide a culture of change and encourage healthcare professionals to provide more accountable and guideline-directed medical care. Positive trends demonstrated by GHATI not only provide momentum for continuation of this program but also provide a platform for further expansion to other nations and individual institutions with the common goal of optimizing global cardiovascular care.

Effect of Genotype-Guided Oral P2y12 Inhibitors vs Conventional Clopidogrel on Long-Term Ischemic Outcomes After Percutaneous Coronary Intervention: the TAILOR-PCI Randomized Clinical Trial Follow-Up Study

Study Overview

Prior data has suggested a higher incidence of ischemic events among clopidogrel-treated carriers of CYP2C19 loss of function (LOF) alleles as compared to patients who are non-carriers of CYP2C19 mutation [32]. The LOF of CYP2C19 hinders transformation of clopidogrel (prodrug) to its active metabolite thereby reducing levels of active drug and increasing platelet aggregation and subsequent ischemic events. TAILOR-PCI was an open label, multicenter, randomized clinical trial which was designed to evaluate ischemic events among patients undergoing percutaneous coronary intervention (PCI) who are carriers of CYP2C19 LOF variant gene. The trial was structured to examine whether genotype-guided use of oral platelet adenosine diphosphate (P2Y12) inhibitors as compared to non-genotype-guided strategy leads to a reduction in recurrent ischemic events [4].

A total of 2,652 and 2,650 patients were randomized to genotype-guided strategy versus non-genotype guided strategy, respectively. In the genotype-guided arm, CYP2C19 LOF carriers were prescribed ticagrelor, while non-carriers were prescribed clopidogrel. In the non-genotype-guided arm, all patients received clopidogrel.

The primary analysis cohort of this trial included consisted of a total of 1,849 patients with CYP2C19 LOF allele (903 patients in genotype-guided strategy arm and 946 patients in non-genotype-guided strategy arm). Patients included in this trial were those undergoing PCI for stable ischemic heart disease (16%) or acute coronary syndromes (84%). Patients were

excluded from primary analysis if PCI was unsuccessful, CYP2C19 genotype was previously known, or there was planned revascularization of any vessel within 30 days. Primary endpoints of this analysis, adjudicated by a centralized, blinded committee, included a composite of cardiovascular death, myocardial infarction, stroke, definite or probable stent thrombosis, and severe recurrent ischemia. Safety endpoints included major or minor bleeding based on TIMI definitions. At 1-year follow-up, the investigators failed to demonstrate statistically significant improvement in primary endpoint between the two strategies (HR 0.66, 95% CI 0.43–1.02).

In the current extended follow-up study of TAILOR-PCI, the investigators studied the same 1,849 patients as enrolled in the original trial. In addition to having a median follow-up period extended to ~39 months, sensitivity analyses were conducted to understand impact on multiple events per subject as well as time dependent analysis of genotype-guided strategy. As in the main trial, there were no statistically significant differences in primary endpoint (HR 0.95, 95% CI 0.70–1.29) and safety endpoint (HR 1.10, 95% CI 0.60–2.04) between the two strategies even at extended follow-up. These outcomes were similar among the pre-specified subgroups. In the post hoc analysis, the investigators demonstrated benefit of genotype-guided therapy within the first 90 days after PCI (HR 0.21, $p=0.001$) and with regard to time to multiple recurrent ischemic events at 12 months (HR 0.60, $p=0.011$).

Clinical Implications

The initial TAILOR-PCI trial with its 12-month follow-up as well now with its extended follow-up study have both failed to demonstrate benefit of genotype-guided P2Y12 strategy over non-genotype-guided strategy among patients (carriers of CYP2C19 LOF allele) undergoing PCI for stable ischemic heart disease or acute coronary syndromes. Although the results did not reach statistical significance, given the modest reduction in hazards ratio, the clinical significance of genotype testing may warrant further evaluation as the field of precision medicine continues to advance.

The post hoc analysis of this trial also suggested that the net benefit associated with genotype-guided strategy may be most evident within the first 3 months after PCI. Additionally, the data suggests benefit with genotype-guided strategy when time to multiple recurrent ischemic events is considered. Though these results generate various speculations as to the reasons behind such observations, given the post hoc nature of this analysis, lack of benefit across subgroups, and observational nature of the extended follow-up study, these findings in its current state may not be practice changing.

For precision medicine such as genotype-guided P2Y12 strategy to be incorporated in routine real-world practice, pharmacoeconomics of such strategy should also be carefully

considered. Current data from TAILOR-PCI serves as a steppingstone for future trials to build on. However, without further randomized trials demonstrating a net clinical benefit of genotype-guided P2Y12 strategy and without pharmacoeconomic analyses showing a favorable incremental cost-effectiveness ratio, the use of such strategy may only be used sparingly and on a case-by-case basis among post-PCI patients.

Aspirin Dosing: a Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness—the ADAPTABLE trial

Study Overview

The appropriate dosing of aspirin to prevent adverse cardiac events in patients with established atherosclerotic coronary artery disease (ASCVD) has been a topic of debate. ADAPTABLE trial was a randomized, parallel, open label, multi-centric trial designed to assess the safety and efficacy of aspirin 325mg compared with 81mg among patients with ASCVD [33]. Patients were included if they had established ASCVD (prior myocardial infarction, revascularization procedure, prior angiogram with more than 75% obstruction) plus one additional risk factor (smoking, age ≥ 65 years, creatinine ≥ 1.5 mg/dl, cerebrovascular disease, smoking, heart failure, uncontrolled hypertension, diabetes mellitus, known triple vessel CAD). Those with aspirin allergy, concomitant anticoagulant use, gastrointestinal bleeding in the preceding 12 months, and those who were pregnant or nursing were excluded. The primary efficacy outcome was a composite of death from any cause, hospitalization for myocardial infarction, or hospitalization for stroke. The primary safety outcome was hospitalization for major bleeding. All outcomes were assessed in a time-to-event analysis.

A total of 15,076 patients were included (mean age 68 years, 31% women) and followed for a duration of 26.2 months. The primary efficacy outcome at 12 months occurred in 7.3% of patients in the aspirin 81mg group compared with 7.5% of the aspirin 325 mg group ($p=0.75$) with a HR 1.02 and 95% CI 0.91 to 1.14. The primary safety outcome at 12 months occurred in 0.6% of the aspirin 81mg group compared with 0.6% of the aspirin 325 mg group ($p=0.41$) with a HR 1.18 and 95% CI 0.79 to 1.77. Dose switching was more frequent in the aspirin 325 mg group compared with aspirin 81 mg group (41.6% vs 7.1% , $P < 0.05$).

Clinical Implications

The ADAPTABLE trial failed to show that aspirin 325 mg was superior to 81 mg in preventing adverse cardiac events in ASCVD patients. Interestingly, the aspirin use pattern prior to

the study was 81 mg (85%), 162 mg (2.5%), and 325 mg (12.3%). Further, only 38% of the trial population had diabetes mellitus. Importantly, the trial showed that aspirin 325 mg was as safe as aspirin 81 mg. However, the finding of higher rates of dose switching in the 325 mg group points toward a patient and provider preference to use low-dose aspirin. The trial was limited by its open label nature, high proportion of patients taking 81 mg prior to randomization (who may have consequently preferred to switch back to the lower dose after being randomized to the 325 mg arm), and an underrepresentation of women as well as minority ethnic groups, which may limit the external validity of these findings. However, the trial does provide valuable evidence to clinicians who are often faced with the appropriate dose conundrum when prescribing aspirin in clinical practice.

Rehabilitation Therapy in Older Acute Heart Failure Patients—the REHAB-HF

Study Overview

Elderly patients with acute decompensated heart failure have high rates of physical frailty and frequent readmissions. The REHAB-HF trial was a multicenter, randomized, controlled trial designed to compare the efficacy of a tailored cardiac rehabilitation program vs standard of care in elderly frail patients who were hospitalized with acute decompensated heart failure [3••]. The main intervention was a tailored cardiac rehabilitation program designed to improve strength, endurance, balance, and mobility that was carried out in an outpatient setting 3 times/week for 12 weeks followed by a course of self-directed home-based exercise. Patients were included if they were deemed to have adequate clinical stability to allow participation in study assessment and intervention and were able to walk at least 4 m at enrollment (with or without assist device). Patients who had a life expectancy < 1 year had advanced chronic kidney disease (including dialysis patients), functional impairment from stroke or dementia, were hospitalized with acute myocardial infarction, and were planned for a surgery at a later date, and those who had left ventricular assist devices were excluded from the trial. The primary outcome of interest was the change in score on Short Physical Performance Battery (SPPB score, range 0–12) at 3 months. Secondary outcome of interest was the 6-month rate of rehospitalization for any cause.

A total of 349 patients were included (mean age 73 years, 52% women) and followed for a period of at least 3 months. The mean duration of hospitalization prior to enrollment was 4.5 days, and close to 97% of the population was either frail or prefrail by modified Fried score. The change in SPPB score at 3 months was 8.3 vs 6.9 for the intervention arm compared with the control arm ($p < 0.001$). The secondary outcome of all-cause rehospitalization at 6 months was comparable (1.18 vs 1.28/patient, $p=0.32$). Other key outcomes such as change in 6-min walk

distance, gait speed, Kansas City Cardiomyopathy Questionnaire, and the composite of all-cause hospitalization or mortality at 6 months were similar in the two arms.

Clinical Implications

The REHAB-HF trial showed that a tailored cardiac rehabilitation program resulted in a greater improvement in physical function compared with usual care in elderly, frail patients who were hospitalized for acute decompensated heart failure. The trial had a good retention rate of 82% in the intervention arm and provides evidence for clinically meaningful improvements in functional status in such a patient population, despite an absence of a reduction in rehospitalizations and mortality.

Conclusion

The clinical trials and studies discussed above, which were presented at the ACC Scientific Sessions 2021, represent the ongoing advancements made in the field of CVD prevention, heart failure, and precision medicine that highlight potential avenues for future research efforts. We highlight some promising novel therapies for the management of heart failure and cardiometabolic disease (such as diabetes and lipid disorders) and also provide new insights and possible solutions to routine challenges faced in the field of prevention.

Compliance with Ethical Standards

Conflict of Interest Salim Virani: Research support: Department of Veterans Affairs, World Heart Federation, Tahir and Joona Family; Honorarium: American College of Cardiology (Associate Editor for Innovations, acc.org).

The other authors declare that they have no conflict of interest.

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.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Nissen SE, Lincoff AM, Wolski K, Ballantyne CM, Kastelein JJP, Ridker PM, Ray KK, McGuire DK, Mozaffarian D, Koenig W, Davidson MH, Garcia M, Katona BG, Himmelmann A, Loss LE, Poole M, Menon V, Nicholls SJ Association between achieved ω -3 fatty acid levels and major adverse cardiovascular outcomes in patients with high cardiovascular risk: a secondary analysis of the STRENGTH trial. *JAMA Cardiol.* (2021) <https://doi.org/10.1001/jamacardio.2021.1157>
2. Jones WS, Mulder H, Wruck LM, et al. Comparative effectiveness of aspirin dosing in cardiovascular disease. *N Engl J Med.* 2021;2021. <https://doi.org/10.1056/NEJMoa2102137> **In a randomized trial of over 15,000 participants with established coronary artery disease randomized to receive either aspirin 81mg or aspirin 325mg, there was no difference in the rate of adverse cardiac events or major bleeding. However, there was significant dose switching in the group assigned to receive aspirin 325 mg.**
3. Kitzman DW, Whellan DJ, Duncan P, et al. Physical rehabilitation for older patients hospitalized for heart failure. *N Engl J Med.* 2021;2021. <https://doi.org/10.1056/NEJMoa2026141> **In 349 older patients who were hospitalized for acute decompensated heart failure randomized to either routine care or an early, transitional, tailored, progressive rehabilitation intervention that included multiple physical-function domains, there was a greater improvement in physical function in the group that received rehabilitation than usual care. While there was no difference in all-cause mortality or rate of readmission, the improvement in functional status was clinically meaningful.**
4. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, et al. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA.* 2020;324:761–71.
5. Hussain A, Al Rifai M, Mahtta D, Liu J, Jain V, Virani SS. Highlights from studies presented at the American Heart Association Scientific Session 2020: navigating new roads in prevention. *Curr Atheroscler Rep.* 2020;23:1–9.
6. Jia X, Al Rifai M, Hussain A, Martin S, Agarwala A, Virani SS. Highlights from studies in cardiovascular disease prevention presented at the digital 2020 European Society of Cardiology Congress: prevention is alive and well. *Curr Atheroscler Rep.* 2020;22:72.
7. Jia X, Al Rifai M, Liu J, Agarwala A, Gulati M, Virani SS. Highlights of Studies in cardiovascular disease prevention presented at the 2020 American College of Cardiology Annual Scientific Session. *Curr Atheroscler Rep.* 2020;22:32.
8. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med.* 2021;384:129–39 **In a randomized trial of 10,584 heart failure patients with diabetes and chronic kidney disease, sotagliflozin (compared with placebo) was associated with a significant risk reduction in the composite end point of cardiac death and hospitalizations/urgent care visits for heart failure.**
9. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med.* 2021;384:117–28 **In a randomized trial of 1,222 patients with diabetes who were hospitalized for worsening heart failure, sotagliflozin (compared with placebo) was associated with a significant risk reduction in the composite end point of cardiac death and hospitalizations/urgent care visits for heart failure.**
10. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey de Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation.* 2017;136:e137–61.
11. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional variation in patients and outcomes in the treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial. *Circulation.* 2015;131:34–42.
12. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction | *NEJM.* <https://www.nejm.org/doi/full/10.1056/NEJMoa1908655>. Accessed 22 May 2021, 2019

13. Williams DM, Evans M. Dapagliflozin for heart failure with preserved ejection fraction: will the DELIVER study deliver? *Diabetes Ther.* 2020;11:2207–19.
14. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved trial. *Eur J Heart Fail.* 2019;21:1279–87.
15. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18:844–7.
16. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145–7.
17. Jia X, Virani SS. Statins in COVID-19 infection: a rehash of old themes or truly a new hope? *Journal of Clinical Lipidology.* 2021;15:399–401. <https://doi.org/10.1016/j.jacl.2021.04.002>.
18. Simvastatin in the acute respiratory distress syndrome | NEJM. <https://www.nejm.org/doi/full/10.1056/nejmoa1403285>. Accessed 22 May 2021, 2014
19. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med.* 2018;6:691–8.
20. Gupta A, Madhavan MV, Poterucha TJ, DeFilippis EM, Hennessey JA, Redfors B, et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. *Nat Commun.* 2021;12:1325.
21. Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Hypertriglyceridemia and its pharmacologic treatment among US adults. *Arch Intern Med.* 2009;169:572–8.
22. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation.* 2007;115:450–8.
23. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA.* 2007;298:299–308.
24. Valdivielso P, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. *Eur J Intern Med.* 2014;25:689–94.
25. Stitzel NO, Khara AV, Wang X, Bierhals AJ, Vourakis AC, Sperry AE, et al. ANGPTL3 deficiency and protection against coronary artery disease. *J Am Coll Cardiol.* 2017;69:2054–63.
26. Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med.* 2017;377:211–21.
27. Ahmad Z, Banerjee P, Hamon S, Chan KC, Bouzelmat A, Sasiela WJ, et al. Inhibition of angiotensin-like protein 3 with a monoclonal antibody reduces triglycerides in hypertriglyceridemia. *Circulation.* 2019;140:470–86.
28. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med.* 2019;380:11–22.
29. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: The STRENGTH randomized clinical trial. *JAMA.* 2020;324:2268–80.
30. Virani SS, Nambi V, Ballantyne CM. Has the 'strength' of fish oil therapy been 'reduced'? Reconciling the results of REDUCE-IT and STRENGTH. *European Heart Journal - Cardiovascular Pharmacotherapy.* 2021;7:e7–8.
31. Levenson B, Herrera C, Wilson BH. New ACC global heart attack treatment initiative: improving STEMI Care worldwide. *J Am Coll Cardiol.* 2020;75:1605–8.
32. Mega JL, Simon T, Collet J-P, Anderson JL, Antman EM, Bliden K, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA.* 2010;304:1821–30.
33. Jones WS, Mulder H, Wruck LM, et al (2021) Comparative effectiveness of aspirin dosing in cardiovascular disease. *New England Journal of Medicine* 0:null

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.