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Reviews

Review of Interventional Late Breaking Trials From AHA Scientific Sessions 2020 Virtual Meeting

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Contents

1. Introduction ............................................................... 71
2. Primary prevention ........................................................... 72
   2.1. Effect of high-dose omega-3 fatty acids vs. corn oil on major adverse cardiovascular events in patients with high cardiovascular risk . . . 72
   2.2. Statin vs placebo vs no treatment: N-of-1 trial of patient symptoms: The SAMSON trial ................................................................. 72
   2.3. The efficacy and safety of evinacumab in patients with refractory hypercholesterolemia ................................................................. 73
3. Coronary ................................................................ 73
   3.1. Coronary OCT and cardiac MRI to determine underlying causes of MINOCA in women ................................................................. 73
   3.2. Novel healing-targeted DES with synchronized antiproliferative drug delivery to target smooth muscle cell proliferation after DES implantation in coronary artery disease ................................................................. 73
   3.3. One-month dual antiplatelet therapy followed by aspirin monotherapy after drug-eluting stent implantation: Randomized One-Month DAPT trial ................................................................. 74
   3.4. Early coronary CT angiography in patients with suspected or provisionally diagnosed acute coronary syndrome: The RAPID CTCA trial .... 74
4. COVID-19 ................................................................ 75
4.1. Findings from the AHA COVID-19 CVD registry ................................................................. 75
Funding ............................................................................. 76
Declaration of competing interest. ................................................................. 76
References ............................................................................. 76

1. Introduction

In 2020, the coronavirus disease 2019 (COVID-19) pandemic prompted every major cardiology conference to cancel or go virtual since March 2020, including the American Heart Association’s (AHA) annual Scientific Sessions. The virtual meetings have allowed more people than ever to participate in a robust online experience. In this article, we give a brief overview of selected late-breaking clinical trials

Abbreviations: ACS, acute coronary syndromes; AHA, American Heart Association; Apo-B, apolipoprotein B; BMI, body mass index; CA, carboxylic acids; CCS, chronic coronary syndromes; CI, confidence interval; CMR, cardiac magnetic resonance imaging; COVID-19, coronavirus disease 2019; CTCA, computed tomography coronary angiography; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DHA, docosahexaenoic acid; DP-DES, durable-polymer-based DES; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; HT-DES, healing targeted Supreme DES; ID, ischemia-driven; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary artery disease; NHANES, National Health and Nutrition Examination Survey; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; STEMI, ST-elevation myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularization; TV, target vessel; UA, unstable angina.

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presented at the AHA Scientific Sessions 2020 Virtual Meeting that carry significant clinical implications.

2. Primary prevention

2.1. Effect of high-dose omega-3 fatty acids vs. corn oil on major adverse cardiovascular events in patients with high cardiovascular risk

Presenter: Dr. Michael Lincoff

Key Points: A new fish oil medication (omega-3 carboxylic acids [CA]) did not reduce the risk of cardiac events as compared to placebo in those patients with existing heart disease or who were at high risk of heart disease due to other medical conditions, according to results from the STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) trial.

Considerable research efforts have been expended on the potential for omega-3 fatty acids to lower cardiovascular risk. Previous observational studies have demonstrated that dietary consumption of either fatty fish or omega-3 fatty acids can lower prospective risk of cardiovascular events. Furthermore, additional studies have suggested that red blood cell concentrations of either eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) are inversely correlated with cardiovascular risk. Finally, biomarker studies have demonstrated that omega-3 fatty acids exert favorable effects on lipoprotein metabolism and inflammatory, oxidative, thrombotic, and arrhythmogenic factors implicated in cardiovascular disease.

All that being said, it remains uncertain whether omega-3 fatty acids reduce cardiovascular risk or prevent heart disease in the general population. A CA formulation of EPA and DHA (omega-3 CA, brand name Epanova) has been previously documented to have favorable effects on lipid and inflammatory markers. It is administered as a free fatty acid not requiring hydrolysis by pancreatic lipase during intestinal absorption, eliminating the need for co-administration with a high-fat diet and resulting in greater bioavailability compared with standard omega-3 ethyl ester formulations.

The investigators of the STRENGTH trial assessed the effects of omega-3 CA on cardiovascular outcomes. A. Michael Lincoff, MD, of Cleveland Clinic, presented the results of the STRENGTH trial, which were simultaneously published online in JAMA [1,2]. STRENGTH was a double-blind, randomized, multicenter, international trial comparing omega-3 CA (4 g daily, n = 6539) with a matching corn oil placebo (n = 6539) in statin-treated participants with high cardiovascular risk, hypertriglyceridemia (triglyceride levels ≥180 mg/dL and < 500 mg/dL and low levels of high-density lipoprotein cholesterol (LDL-C) < 42 mg/dL for men or < 47 mg/dL for women). The primary efficacy measure was a composite of cardiovascular, death, non-fatal myocardial infarction (MI), non-fatal stroke, coronary revascularization, and hospitalization for unstable angina (UA). Changes in lipid and inflammatory biomarkers, as well as safety and tolerability, were evaluated.

The study began in 2014 and was stopped slightly early, in January 2020, after an independent Data and Safety Monitoring Board recommended for futility because preliminary results of the study deemed it unlikely to prove the benefit of omega-3 CA medication. Over a median follow-up time of approximately 3 years, 1580 patients experienced at least one cardiac event. There were no significant differences in the number of patients experiencing cardiac events between the two treatment groups. Additionally, atrial fibrillation (AF) occurred more frequently among patients taking the omega-3 CA medication than in those receiving the control corn oil.

The neutral results of the omega-3 CA medication in STRENGTH are in contrast with the favorable results of icosapent ethyl shown in the REDUCE-IT trial, first presented at the AHA Scientific Sessions 2018 and published in The New England Journal of Medicine in January 2019, which showed that the risk of ischemic events, including cardiovascular-related death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo [3]. Icosapent ethyl is a highly purified EPA omega-3 acid in ethyl ester form.

One question Lincoff raised regarding the diverging results between STRENGTH and REDUCE-IT was the nature of the placebo in each trial. He said that mineral oil, the placebo in REDUCE-IT, raised that study's patients' triglyceride levels by a mean of 2.2%, low-density lipoprotein cholesterol (LDL-C) levels by a mean of 10.2%, apolipoprotein B (Apo-B) by 7.8%, and high-sensitivity C-reactive protein (hsCRP) by 32%. By contrast, the corn oil placebo in STRENGTH lowered this study's patients' triglyceride levels by a mean of 0.9%, LDL-C by 1.1%, Apo-B by 1.0% and hsCRP by 6.3%.

The STRENGTH trial was funded by AstraZeneca, manufacturer of the omega-3 CA.

2.2. Statin vs placebo vs no treatment: N-of-1 trial of patient symptoms: The SAMSON trial

Presenter: Dr. James P. Howard

Key Points: Patients really do feel side effects from statins, which can prompt them to stop taking the cholesterol-lowering medication. But this study shows that patients experienced nearly as many symptoms while taking a placebo as they did while taking statins.

Many people who start taking statins eventually abandon them because of side effects, with usage rates among those prescribed dropping to 62% after 1 year and 47% after 2 years. About 1 in 10 people prescribed statins report symptoms, most commonly muscle pain. Yet patients in the statin arm of placebo-controlled trials tend to more faithfully adhere to their statin regimen and show no more symptoms than patients in the placebo arm.

James P. Howard, PhD, of Imperial College London, presented the results of the SAMSON (Self-Assessment Method for Statin Side-effects Or Nocebo) trial, which were simultaneously published online as a research letter in The New England Journal of Medicine [4,5]. Investigators in the SAMSON trial used a three-arm, double-blinded, n-of-1 design to investigate whether symptoms were induced by statin or placebo tablets. The investigators hypothesized that more than 50% of patients' symptom burden is “nocebo” rather than pharmacological and that, at 6 months, the majority of participants would either be taking statins or would have declined statins for reasons other than perceived side effects.

The study recruited 60 participants in London between June 2016 and March 2019 who had previously stopped taking statins because of side effects. The subjects received 12 1-month medication bottles in a random sequence: four contained 20 mg of atorvastatin, four contained placebo, and four were empty. Participants reported the intensity of their symptoms daily via a smartphone app on a scale of 0 (no symptoms) to 100 (“worst imaginable”). If symptoms became intolerable, the subjects could stop taking tablets that month. One key inclusion criterion was that study participants needed to have reported feeling symptoms within 2 weeks that were so bad they stopped the medication. This would make it more likely that they might feel those symptoms again within a 1-month time period in the study. The primary endpoint was the “nocebo ratio,” that is, the ratio of symptom intensity induced by statin tablets that was also induced by taking a placebo.

The nocebo ratio in the study was 0.90, meaning that 90% of the symptom burden stemming from taking statins was also prompted by placebo. Mean symptom intensity was 6.3 during no-tablet months (95% confidence interval [CI], 2.8–9.8), 12.1 during placebo months (95% CI, 8.6–15.6; p = 0.0005 vs. no-tablet months) and 12.8 during statin months (95% CI, 9.3–16.3; p = 0.0005 vs. no-tablet months and p = 0.499 vs. placebo months). Six months after the trial, 30 patients (50%) had successfully resumed taking statins, four planned to, and one could not be contacted. The remaining 25 refused to restart.

Howard concluded that patients must be taken seriously when they report side effects of medications because they really feel them but that...
exploring these side effects can make all the difference. The novel n-of-1 trial design comprising active treatment, placebo, and no treatment can help patients explore the etiology of their symptoms.

The SAMSON study was funded by the British Heart Foundation, the United Kingdom’s (U.K.) cardiovascular charity.

2.3. The efficacy and safety of evinacumab in patients with refractory hypercholesterolemia

Presenter: Dr. Robert S. Rosenson

Key Points: Evinacumab, whether administered intravenously or subcutaneously, significantly reduced LDL-C, by greater than 50% at the highest dose levels, as compared to placebo, and the drug was generally well-tolerated.

Patients who have hypercholesterolemia that persists despite maximally tolerated statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and other lipid-lowering therapies have increased risk of atherosclerotic cardiovascular disease. The investigators assessed the safety and efficacy of intravenous and subcutaneous evinacumab, an angiopoietin-like protein 3 inhibitor, in these patients.

Robert S. Rosenson, MD, of the Icahn School of Medicine at Mount Sinai, New York, presented the results, which were simultaneously published online in The New England Journal of Medicine [6,7]. The double-blind phase 2 trial randomized 272 patients to the following groups: subcutaneous evinacumab (450 mg weekly, 40 patients; 300 mg weekly, 43 patients; 300 mg every 2 weeks, 39 patients) or placebo (41 patients); or intravenous evinacumab (15 mg/kg of body weight every 4 weeks, 39 patients; 5 mg/kg every 4 weeks, 36 patients) or placebo (34 patients). The primary endpoint was percentage of LDL-C reduction at 16 weeks.

Mean baseline LDL-C levels were similar among the intravenous treatment groups: 15 mg/kg monthly dose LDL-C level, 143.1 mg/dL; 5 mg/kg monthly dose, 146.0 mg/dL; placebo, 144.5 mg/dL. At week 16, patients in the evinacumab groups saw reduced LDL-C levels. The difference in the least-squares mean was −50.5% (p < 0.0001) for the 15 mg/kg group and −24.2% (p < 0.0109) in the 5 mg/kg group. The placebo group saw virtually no change in LDL-C level at week 16 (+0.6%). In the subcutaneous treatment groups, mean baseline LDL-C levels were 146.3 mg/dL for the 450 mg weekly dosage group, 159.1 mg/dL for the 300 mg weekly group, 136.2 mg/dL for the 300 mg every 2 weeks group, and 157.8 mg/dL for the placebo group. At week 16, the baseline-adjusted least-squares mean differences were −56.0% (450 mg weekly), −52.9% (300 mg weekly) and −38.5% (300 mg every 2 weeks; all groups, p < 0.0001). The placebo group saw an increase in LDL-C level (+8.8%).

The investigators reported that most patients receiving either subcutaneous or intravenous evinacumab experienced adverse events at higher rates than those receiving the respective placebos. Adverse events in the subcutaneous groups that occurred more commonly in the evinacumab vs. placebo groups were urinary tract infection (evinacumab 11% vs. placebo 8%), injection-site erythema (6% vs. 3%), arthralgia (5% vs. 3%) and myalgia (5% vs. 0%). Adverse events in the intravenous groups that occurred more commonly in the evinacumab vs. placebo groups were abdominal pain (evinacumab 6% vs. placebo 0%), back pain (7% vs. 6%), dizziness (7% vs. 0%), fatigue (7% vs. 6%), arm or leg pain (7% vs. 6%), nausea (7% vs. 0%) and nasopharyngitis (12% vs. 6%). However, few adverse events were serious, and there were no clinically significant differences between the treatment and placebo groups in both subcutaneous and intravenous administrations.

Only one event that resulted in stoppage of treatment in the subcutaneous group was related to the trial drug: dyspnea, in the evinacumab 300 mg every 2 weeks dosage group, and was fully resolved. One patient who received 300 mg of evinacumab weekly died of heart failure or cardiogenic shock, and one in the 300 mg every 2 weeks group died of sudden cardiac death. These patients had underlying heart disease, and their deaths were not considered to be related to evinacumab. In the intravenous groups, there was one serious adverse event that led to treatment stoppage and was related to the trial drug, anaphylactic reaction, which occurred with the second dose of 15 mg/kg of evinacumab. The reaction was resolved with oral diphenhydramine the same day. No adverse events resulting in death were reported in the intravenous groups.

Study limitations included the small sample size and short treatment duration. Also, the study group was not as racially diverse as the study investigators intended, meaning that robust safety of evinacumab could not be established.

The study was funded by Regeneron Pharmaceuticals, the manufacturer of evinacumab.

3. Coronary

3.1. Coronary OCT and cardiac MRI to determine underlying causes of MINOCA in women

Presenter: Dr. Harmony Reynolds

Key Points: Using both optical coherence tomography (OCT) and cardiac magnetic resonance (CMR) imaging outperformed using only one of those modalities in identifying MI with non-obstructive coronary artery disease (MINOCA) in women.

Harmony R. Reynolds, MD, of the New York University Grossman School of Medicine, presented the results of the HARP (Women’s Heart Attack Research Program)-MINOCA study [8]. She was the first author on a paper reporting the results that was simultaneously published online in Circulation [9]. Between 6% and 15% of MIs occur with non-obstructive coronary artery disease; the rate of MINOCA is about 3 times higher in women than in men. Moreover, Reynolds said, the 4-year risk of a major adverse cardiovascular event (MACE) after MINOCA is 24%, and the mortality rate within 5 years of MINOCA is 11%.

The prospective, observational study enrolled 301 women at 16 sites in North America. Of these, 170 were diagnosed with MINOCA, 145 of them had evaluable OCT images, and 116 underwent CMR. OCT identified a definite or possible culprit lesion in 46.2% of the 145 OCT-imaged patients. The culprit was most commonly a ruptured plaque, intra-plaque cavity, or layered plaque. CMR was abnormal in 74.1% of the 116 patients imaged through that modality. CMR showed an ischemic pattern (infarction or myocardial edema in a coronary territory) in 53.4% of patients undergoing CMR and a non-ischemic pattern (myocarditis, takotsubo syndrome, or non-ischemic cardiomyopathy) in 20.7%. Clinicians were able to identify a cause of MINOCA in 84.5% (98/116) of the women who underwent both OCT and CMR (95% CI, 76.3% to 90.3%). This rate was significantly higher than in patients who underwent OCT alone (51/116 = 44.0%; 95% CI, 34.9% to 53.5%; p < 0.001) or CMR alone (86/116 = 74.1%, 95% CI, 65.0% to 81.6%; p = 0.001).

Reynolds concluded that the study shows the mechanisms of MINOCA are similar to MI with obstructive coronary artery disease, specifically atherothrombosis with a possible contribution of coronary artery spasm.

The study’s limitations included that the sample size was relatively small and there were very few ST-elevation myocardial infarction (STEMI) cases. Myocardial edema is a single coronary territory that is considered evidence of ischemic injury, but it does not rule out regional myocarditis. There was no spasm testing, no control group, and not all of the women had three-vessel OCT and CMR. Finally, the study was limited to women, meaning there was no comparison with men.

The study was funded by the AHA through a grant from the Go Red for Women Strategically Focused Research Network.

3.2. Novel healing-targeted DES with synchronized antiproliferative drug delivery to target smooth muscle cell proliferation after DES implantation in coronary artery disease

Presenter: Dr. Alexandra Lansky
Key Points: A novel biodegradable-polymer-coated drug-eluting stent (DES) was found to be as safe and effective as the contemporary polymer-based DES in patients with acute coronary syndromes (ACS) and chronic coronary syndromes (CCS) undergoing percutaneous coronary intervention (PCI).

Current DES carry late failure rates that range between 2% and 3% per year. This is mostly secondary to delayed healing as a result of chronic inflammation associated with their polymer coatings. SINOMED, a technology company based in China, developed a novel stent that is made of cobalt chromium, is as thin as some current polymer-based DES (80 μm) and has biodegradable coating that facilitates rapid drug delivery and polymer degradation.

Alexandra Lansky, MD, of the Yale School of Medicine, presented the results of the PIONEER III trial [10]. In the PIONEER III trial, patients with acute or chronic coronary artery disease who had up to three de novo native lesions in up to two major vessels were randomized in a 2:1 fashion to undergo intervention with either the novel healing targeted Supreme DES (HT-DES, SINOMED) or contemporary polymer-based DES (DP-DES, Xience [Abbott] or Promus [Boston Scientific]). The primary endpoint was target lesion failure (TLF), a composite of cardiac death, target vessel (TV) MI and ischemic-driven (ID) target lesion revascularization (TLR) at 12 months. Secondary safety endpoints included death, MI, and Academic Research Consortium-defined stent thrombosis. An efficacy endpoint included device and lesion success, TLR, and vessel revascularization.

A total of 1629 ACS or CCS patients were randomized at 74 sites in North America, Europe, and Japan. The patients’ average age was 64 ± 10 years. 25.4% were women, 30.4% had diabetes, 72.7% had hypertension, and 28.8% had prior PCI. The most common clinical presentation was stable angina (49.4%) followed by non-ST-elevation myocardial infarction ACS (20.9%), unstable angina (20.4%), and silent ischemia (9.3%). Most treated lesions were complex (AHA/American College of Cardiology type B2 or C: 66.2%), with a mean of 1.2 ± 0.5 treated lesions per patient with 1.3 ± 0.6 stents (range: 0–5). Approximately half of the lesions were located in the left anterior descending artery (44.8%), 25.4% were in the left circumflex artery, and 29.7% were in the right coronary artery. Most cases (80.4%) were performed via radial access.

The primary endpoint occurred in 5.3% of the HT-DES group and 5.0% of the DP-DES group (hazard ratio [HR], 1.05; 95% CI, 0.67–1.66; p = 0.82), meaning that the primary non-inferiority endpoint was met. The secondary endpoint of ID-TLR was numerically higher in the HT-DES group than in the DP-DES group (2.3% vs. 1%, p = 0.06), while the rates of TV-MI, CV death and that of the composite secondary endpoints were not significantly different between the groups. There was no significant difference between the groups for stent thrombosis. However, late stent thrombosis did show a numerical difference, with 0.1% in the HT-DES group and 0.4% in the DP-DES group (p = 0.22). Finally, there were no significant differences in TLF at 1 year by subgroups.

Lansky concluded by saying that HT-DES was as safe and effective as DP-DES in patients undergoing PCI for ACS and CCS. Whether the findings of a numerically higher rate of CV death, TV-MI, and late stent thrombosis favoring HT-DES translate into significant clinical benefits in the longer-term will be assessed at 5-year follow-up, she said.

3.3. One-month dual antiplatelet therapy followed by aspirin monotherapy after drug-eluting stent implantation: Randomized One-Month DAPT trial

Presenter: Dr. Myeong-Ki Hong

Key Points: A short, 1-month treatment combining antiplatelet medication and aspirin followed by an aspirin-only regimen was as effective as a 6- to 12-month course of dual treatment at preventing death, MI, stroke, bleeding, or revascularization.

Myeong-Ki Hong, MD, PhD, of Severance Cardiovascular Hospital, Seoul, South Korea, presented the findings of the One-Month DAPT trial [11]. Currently, dual antiplatelet therapy (DAPT) is recommended for 6 to 12 months after DES implantation. However, it is necessary to determine the appropriate minimal duration of DAPT followed by aspirin monotherapy to minimize unnecessarily long DAPT, Hong said. The One-Month DAPT trial investigators hypothesized that 1 month of DAPT followed by aspirin monotherapy would be noninferior to 6 to 12 months of DAPT in terms of the composite endpoints of cardiovascular events or major bleeding at 1 year after DES implantation.

In the trial, patients who were considered for revascularization with DES were enrolled in 23 centers in South Korea. Between December 2015 and September 2019, a total of 3020 patients were randomized to receive either 1-month DAPT followed by aspirin monotherapy after receiving BioFreedom, a polymer-free Biolimus A9-coated stent (1-month DAPT group, n = 1507), or 6 to 12 months of DAPT followed by aspirin monotherapy after implantation with BioMatrix (biodegradable-polymer, Biolimus A9-coated) or Ultimaster (biodegradable-polymer, sirolimus-eluting) stents (6–12 months DAPT group, n = 1513).

The primary endpoint was a 1-year composite of cardiac death, non-fatal MI, TV revascularization, cerebrovascular accident, or major bleeding. The estimated event rate for patients in the 6–12 month DAPT group was 6.2%. A 3% noninferiority margin was prespecified, giving the study 90% power with a one-sided alpha error rate of 2.5% and allowing for at least 10% loss to follow-up, which required a sample size of 3020 patients. Noninferiority could be declared if the upper limit of the one-sided 97.5% CI for the difference in primary endpoint incidences between the groups was less than 3%.

Of the 3020 patients who were randomized, 1507 were assigned to the 1-month group and 1513 were assigned to the 6–12 month group. At baseline, the groups were well-matched. Patients in both groups had a mean age of 67 years, and 69% were men. About 60% of study patients presented with stable angina. About 17% of patients in the 1-month group did not adhere to the DAPT regimen. A total of 2969 patients completed 1-year follow-up. An analysis found no significant difference in the number of cardiac events between the two groups: The 1-month group had a 5.9% composite event rate compared to 6.5% in the 6–12 month treatment group. Each component of the primary endpoint, including major bleeding, was not significantly different between the two groups.

The absolute difference between groups at 1 year was −0.7%, and the upper limit of the one-sided 97.5% CI was 1.33 (HR, 0.90; 95% CI, 0.68–1.20; p < 0.001 for noninferiority, p = 0.475 for superiority). The shorter DAPT regimen also met noninferiority under a 1-month landmark analysis (HR, 0.91; 95% CI, 0.66–1.26; absolute difference −0.5%; upper limit of 97.5% CI, 1.31; p < 0.001 for noninferiority, p = 0.571 for superiority).

Hong noted that the One-Month DAPT study was the first randomized trial to compare 1-year clinical outcomes of 1-month DAPT followed by aspirin monotherapy to the currently recommended 6- to 12-month regimen in patients with coronary artery disease who have received stents.

This study was funded by DIO, Cardinal Health Korea, and Terumo Corp. (manufacturer of the Ultimaster stent). Biosensors International manufactures the BioFreedom and BioMatrix stents.

3.4. Early coronary CT angiography in patients with suspected or provisionally diagnosed acute coronary syndrome: The RAPID CTCA trial

Presenter: Dr. Alasdair Gray

Key Points: Early computed tomography coronary angiography (CTCA) in intermediate- or high-risk patients presenting to the emergency department with suspected or provisionally diagnosed ACS did not impact overall treatment or prevention of ACS but was associated with a modest increase in length of stay and healthcare costs.

Emergency department visits for chest pain continue to be a global health concern. Routine evaluation for ACS includes history, physical examination, electrocardiogram, and serial troponin testing. Adjunct CTCA has been studied in low-risk patients, but data on intermediate- and high-risk patients are lacking.
Alasdair Gray, MD, of the University of Edinburgh, United Kingdom, presented the results of the prospective, randomized, open blinded end-point parallel group clinical trial of early CTCA in the management of intermediate- and high-risk patients presenting to the emergency department with suspected or provisionally diagnosed with ACS [12]. Patients were considered intermediate- or high-risk if they had at least one of the following: prior history of coronary artery disease, troponin elevation >99th percentile and an abnormal electrocardiogram. In this trial, patients were randomized to CTCA or standard of care. The primary outcome of interest was all-cause mortality or a type 1 or 4b MI at 1 year.

The study included 1748 patients across 37 sites in the United Kingdom from 2015 through 2019, of whom 877 were randomized to CTCA and standard of care, with the remaining 871 receiving the standard of care only. The patients’ mean age was 62 years, and 64% were men. In the CTCA group, a CTCA was performed in 87% of patients (767) a median of 4.2 h from randomization, with >90% achieving diagnostic quality. The mean effective radiation dose was 3.1 mSv, with half of patients having non-obstructive coronary artery disease. With regard to the primary outcome of all-cause mortality or subsequent MI, there was no statistically significant difference (adjusted HR, 0.91; 95% CI, 0.62, 1.35; p = 0.65). There were no significant differences in any of the individual key secondary outcomes relating to all-cause mortality, coronary heart disease, cardiovascular death, or non-fatal MI. Furthermore, there were no differences in overall ACS treatment or preventative therapies between the two groups.

Diagnostic certainty did increase in the CTCA group (7.1 to 8.5 using a scale from 1 to 10, with 10 being the most certain) and there was an increase in participant satisfaction (from 79.7% to 83.3%). Despite this, median length of stay was the same in both groups, (2.2 vs. 2.0 days) and mean healthcare costs ($9494 vs. $8776) favored the standard-of-care group.

The RAPID CTCA trial was funded by the National Institute for Health Research Health Technology Assessment Programme.

4. COVID-19

4.1. Findings from the AHA COVID-19 CVD registry

Presenter: Dr. James De Lemos

Key Points: Clear public messages should warn of higher risk for obese COVID-19 patients, while more must be done to tackle the endemic issue of systemic racism in the United States (US), researchers said, stressing that both obese and minority patients have fared worse, according to the AHA COVID-19 Cardiovascular Disease Registry.

These calls were based on findings reported in three new analyses of the registry for hospitalized COVID-19 patients [13]. The results were presented by UT Southwestern Medical Center's James De Lemos, MD, PhD. The latest analyses cover data running from the registry's inception on April 3 through July 31, 2020, for which clean data were available in approximately 9000 patients. As of November 9, 2020, the study included 109 hospitals across 35 US states, with more than 22,500 patient records.

The COVID-19 pandemic has driven severe outcomes in some patients, killing more than 1.3 million at the time of reporting at AHA, according to the World Health Organization. Although experts have been rushing to fill in the data blanks throughout 2020 on the novel coronavirus and its effects, it is believed that patients with cardiovascular disease and cardiovascular risk factors were likely at greater risk of severe outcomes. Multiple cardiovascular and thrombotic complications have been reported among those hospitalized, authors of the overarching registry report noted.

The aim of the registry is to provide generalizable insights on patients hospitalized with the disease and to understand its impact on the heart. It was rapidly deployed, leveraging the existing AHA “Get With The Guidelines” platform. Patient data cover detailed patient demographics, cardiovascular risk factors, and existing prevalent cardiovascular disease, alongside other medical comorbidities. The researchers are also collecting “granular data” on over 200 data fields per patient, including deep information on laboratory tests and biomarkers.

The obesity findings came from the registry study on the association of body mass index (BMI) with death, mechanical ventilation, and cardiovascular outcomes in COVID-19, led by Nicholas Hendren, MD. The researchers compared distribution of BMI in the registry with an adjusted U.S. population sample from National Health and Nutrition Examination Survey (NHANES), finding that patients admitted to hospital with COVID-19 are notably more obese than the US population. In particular, there was a higher prevalence of Class III (severe) obesity, at 11% in the AHA registry compared to 7% in the general population as recorded by NHANES.

The differences were magnified among people younger than 50 years, an age group in which obesity is dramatically over-represented in hospitalized COVID-19. In particular, the probability of BMI greater than 40 kg/m² in the AHA registry was double that of the overall population younger than 50. There were “striking differences” in age between hospitalized patients of a normal weight and the severely obese, who were almost 20 years younger, he added. The interaction between BMI and age can also clearly be seen for in-hospital death rates and mechanical ventilation (as a function of BMI). The relationship is attenuated and not significant among middle-aged and older adults. Severely obese people are at a mechanical disadvantage when it comes to pulmonary morbidity and the virus’s purported effects on the renin–angiotensin system, which is already dramatically upregulated for obesity.

The findings have important public health implications as the pandemic surges. This calls for “clear public health messaging for younger obese individuals who may have received the false message that they are at low risk for severe COVID infection,” De Lemos said. In addition, severely obese individuals, including young people, should be considered at higher risk for infection and, therefore, could warrant prioritization for vaccination.

Data from the AHA COVID-19 CVD Registry also highlighted the endemic national issue of systemic racism, with Black and Hispanic people making up the majority (58%) of hospitalized cases in the corresponding analyses of around 8000 individuals. In the study of racial and ethnic differences in presentation and outcomes for patients hospitalized with COVID-19, the investigators compared those enrolled in the AHA registry with census-tracked data from the hospitals where those patients were admitted.

The percentage of Black and Hispanic people hospitalized with COVID-19 in the AHA registry, 58%, is a much larger proportion than in the communities where the hospitalizations occur. Black and Hispanic patients admitted to the hospital were younger than White patients by 9 and 12 years, respectively, while the probability of patients being uninsured or self-payers was significantly higher than in White people (non-Hispanic White 2.5%, non-Hispanic Black 4.5%, Hispanic all races 12.8%). Obesity, diabetes, and hypertension were more prevalent in Black and Hispanic people. Black patients were also over-represented in the obesity study, in the group with Class III severe obesity, making up 40% of the total.

Nevertheless, once in the hospital, race and ethnicity were not independently associated with worse outcomes, although Black and Hispanic patients did clearly face disproportionate mortality and morbidity because of higher rates of hospitalization. The figures show an issue with disparities in care upstream of the hospitalization event.

In the overall analysis of data from the AHA COVID-19 CVD Registry, researchers were surprised to find that in-hospital cardiovascular complications were less common than originally thought. Overall, in-hospital mortality across the survey was frequent, with 16.7% of patients dying in the hospital and a further 2.8% referred for hospice, although the overwhelming majority of these outcomes (72%) were caused by
respiratory complications. Cardiac complications accounted for 10% of deaths, while 18% were linked to other causes. A composite cardiovascular outcome of cardiovascular death, MI, stroke, heart failure, and shock occurred in just over 8% of individuals. The individual endpoint of MI occurred in 4% of individuals, while stroke, heart failure, and cardiogenic or mixed shock each occurred in less than 2%. Myocarditis, which has emerged as an important potential risk even in younger people and athletes, was uncommon, occurring in only 0.3% of hospitalized COVID-19 patients. Atrial fibrillation was the most common cardiovascular complication, with a rate of around 8%, while deep vein thrombosis and pulmonary embolism were only seen in under 4%, a significantly lower proportion than had been reported in single-center studies and those with active surveillance for these endpoints. Although cardiac complication numbers were better than expected, given the scale of the pandemic, with 70,000 U.S. people hospitalized with the illness, the absolute number of cardiac complications remains high.

Panelists aired their hopes that the new collaborative and rapid methods used to devise the registry during an “unprecedented” situation could be used more widely in future studies. It was recognized early on that usual methods, which often have a dwell time of around 12–18 months, would not serve the needs of the clinical community in the pandemic setting. AHA researchers, therefore, devised a disruptive and democratized process for the research leveraging the organization’s Precision Medicine Platform, a secure cloud-based environment that has allowed dozens of teams of investigators to work in parallel on the same curated and de-identified data set in a “learn-as-we-go” approach. The advantage shortened time to discover and dissemination of results to allow for presentation of three abstracts. This was completed in less than 6 months from the registry launch at lower cost and higher yield for knowledge acquisition from a much larger group of investigators than may have otherwise been possible.

Although he conceded that there still remain challenges to this approach, including maintaining scientific rigor despite less central control of the research process, De Lemos and other experts were hopeful of positive downstream effects.

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Declaration of competing interest

Ron Waksman – Advisory Board: Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd.; Consultant: Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd.; Grant Support: AstraZeneca, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance.

All other authors – None.

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