

Major Cardiovascular Advances: Highlights from the 2019 American College of Cardiology Annual Scientific Session

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Abstract

The 69th American College of Cardiology Annual Scientific Session and Expo was held in New Orleans, Louisiana on March 16–18, 2019. For many years this meeting has gathered together an enormous number of participants, abstracts, oral presentations, poster presentations, educational sessions, late-breaking clinical trial results, and clinical practice guidelines under one roof. The authors have selected and summarized the key points from a number of key landmark trials, featured clinical research results and clinical practice guidelines that were presented during this year's meeting.

Keywords

American College of Cardiology, late-breaking clinical trials, clinical practice guidelines

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WRAP-IT

The Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) was a prospective multicenter study to determine the safety and efficacy of an absorbable surgical mesh envelope containing two antibiotics (minocycline and rifampin) in reducing infection incidence in patients with cardiac implantable electronic devices compared to standard care.¹ Approximately 7,000 patients were included in this trial. The primary composite endpoint was infection resulting in device removal or revision, long-term antibiotic therapy with infection recurrence, or mortality within 12 months after the implantation procedure.

During his presentation, Tarakji et al. announced that the primary endpoint had been met in 0.7% of the envelope group and 1.2% of the control group (HR 0.60; 95% CI [0.36–0.98]; $p=0.04$).¹ Given the high envelope price, a rationale would be helpful to determine which patient population with cardiac implantable electronic devices might benefit from the implantation of that envelope.

POET Long-term Follow-up

The original Partial Oral Treatment of Endocarditis (POET) trial was a multicenter randomized, non-inferiority trial comparing the efficacy of intravenous antibiotics with oral antibiotics in stable patients with infective endocarditis of the left side of the heart.² Overall, there was no difference between the two groups with regards to the composite

primary endpoint (all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen at 6 months). In their study, Bundgaard et al. reported that in the long-term POET follow-up, at a median of 3.5 years, the primary outcome had occurred in 26.4% of the oral antibiotics group compared with 38.2% of the intravenous antibiotics group ($p=0.01$).³ Interestingly, all-cause mortality at the end of follow-up was 16.4% in the oral antibiotics group versus 27.1% in the intravenous antibiotics group ($p<0.05$). The results of this trial might ultimately reduce hospital length of stay as well as peripherally inserted central catheter-related complications.

HoT-PE

The prospective, multicenter, single-arm Home Treatment of Pulmonary Embolism (HoT-PE) trial assessed the safety and efficacy of early discharge and out-of-hospital treatment with rivaroxaban 15 mg twice daily in 525 patients with low-risk pulmonary embolism.⁴ The majority of participants were Caucasian (98.5%) and the patients had an average age of 56.7 years. The primary outcome was recurrent symptomatic venous thromboembolism or death due to recurrent pulmonary embolism within 3 months. According to Konstantinides et al., of the 525 patients included in the interim analysis, three patients developed symptomatic non-fatal venous thromboembolism recurrence (0.6%; one-sided upper 99.6% CI [2.1%]), Major bleeding occurred in 6 (1.2%) patients. Of note, the median length of hospital stay was 34 hours, with 93.6% of the patients being discharged within 48 hours.⁴

These results support the initiation of rivaroxaban in the emergency department and the early discharge of low-risk pulmonary embolism patients without the need for parenteral anticoagulation or extended hospital stay.

PARTNER 3 and Evolut Transcatheter

The results from two studies on the safety and efficacy of transcatheter valves in low-risk patients with aortic stenosis were presented: the Safety and Effectiveness of the SAPIEN 2 Transcatheter Heart Valve in Low Risk Patients with Aortic Stenosis (PARTNER 3) and Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients study.

PARTNER 3 compared transfemoral transcatheter aortic valve replacement (TAVR) with surgery in 1,000 patients. Participants had severe aortic stenosis and a low risk of surgery, and were randomly assigned to undergo balloon-expandable TAVR or surgical aortic valve replacement in this multicenter study.⁵ The average age of participants in both groups was 73 years and the average Society of Thoracic Surgeons risk score was 1.9%. The primary endpoint included a composite of death from any cause, rehospitalization, and stroke at 1 year.

Mack et al. informed delegates that the PARTNER 3 results favored TAVR, with 8.5% of the TAVR group versus 15.1% of the surgical group experiencing the primary endpoint (absolute difference -6.6 percentage points; 95% CI [-10.8 to -2.5]; $p < 0.001$ for non-inferiority; HR 0.54; 95% CI [0.37-0.79]; $p = 0.001$ for superiority). Of note, Mack et al. also revealed that patients who underwent TAVR had statistically significantly lower rates of stroke, death, or stroke, and new-onset AF at 30 days.⁵

The Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients trial assessed the efficacy and safety of using TAVR with a self-expanding supraannular bioprosthesis versus surgical aortic-valve replacement in patients with severe aortic stenosis deemed to have a low risk for surgery.⁶ A total of 1,403 patients were enrolled, 65% were men, with an average age of 74 years. The primary endpoint was a composite outcome of death or disabling stroke at 24 months.

It was reported that the primary endpoint occurred in 5.3% of the TAVR group and 6.7% of the surgical aortic-valve replacement group. Popma et al. stated that this met the statistical significance margin for non-inferiority but not for superiority; TAVR was therefore the better treatment option in this patient group.⁶

Hopefully, the Centers for Medicare and Medicaid will provide coverage for this management modality in low-risk patients once the Food and Drug Administration approves its use in this patient population as a result of the positive outcomes of these two trials.⁵ According to Reardon et al., it might be reasonable to consider moving TAVR in low-risk patients with severe aortic stenosis to a class I guideline indication.⁷ The results of these two trials may alter the entire level of aortic stenosis management.⁷

MOMENTUM-3 Final Report

Mehra et al. presented the final report from the open-label Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3; NCT02224755). In this trial, approximately 1,000 patients with advanced heart failure from more

than 60 different sites were randomized to receive either the centrifugal-flow pump HeartMate 3 or the axial-flow pump HeartMate 2 between September 2014 and August 2016.⁸ The average age of patients was 59.5 years, and two-thirds were men. Almost half of these patients had heart failure as a result of an ischemic event. All patients had reduced ejection fraction. Destination therapy was intended for >50% of patients enrolled in both groups.

The composite primary endpoint of survival free from disabling stroke or reoperation to replace or remove a malfunctioning device at 2 years occurred in 76.9% of the HeartMate 3 group and 64.8% of the HeartMate 2 group, according to Mehra et al.⁸ Both the non-inferiority criterion and the superiority criterion were statistically significantly in favor of the HeartMate 3. The results of this study will improve quality of life for patients with advanced heart failure, as well as adding many years to their lifespan.

Hopeful Heart

In the Blended Collaborative Care for Heart Failure and Co-Morbid Depression (Hopeful Heart; NCT02044211) study, investigators randomized 500 patients with heart failure and depression to receive blended collaborative care for heart failure and depression or collaborative care for heart failure alone. At 12 months, the blended collaborative care for depression and heart failure significantly improved mental health-related quality of life and mood symptoms, according to Herbeck Belnap et al. However, blended collaborative care did not have an impact on the incidence of readmission or mortality. The results of this study reinforce the role of blended collaborative care in managing cardiac patients suffering from other comorbidities.⁹

CODIACS-QOL

In the COMparison of Depression Identification after Acute Coronary Syndrome: Quality of Life and cost outcomes (CODIACS-QOL; NCT01993017) trial, investigators randomized 1,500 patients with recent acute coronary syndrome (ACS) to receive either depression screening, depression screening and treatment, or no depression screening. At 18 months, this study failed to detect any statistical difference in quality-adjusted life-years from baseline between the three groups. It was therefore concluded that screening patients with recent ACS for depression was not beneficial.

PANACHE Trial

In the Trial to Study Neladenoson Bialanate Over 20 Weeks in Patients with Chronic Heart Failure with Preserved Ejection Fraction (PANACHE; NCT03098979), investigators randomized more than 300 patients with heart failure with preserved ejection fraction to receive either neladenoson (an adenosine A1 receptor agonist) or placebo. At 20 weeks, there was no significant difference between the groups in terms of the primary endpoint, which was change in 6-minute walking distance.

Apple Heart Study

Over 400,000 individuals with an Apple Watch and iPhone were enrolled in the Apple Heart Study to evaluate the ability of the optical sensor in the Apple Watch to identify pulse irregularity (AF) and make a subsequent clinical evaluation (NCT03335800). The average age of participants was 41 years, almost 60% were men, and 13% had a CHA₂DS₂-VASc score of >2.

Turakhia, who presented the results of this study, revealed that <1% (n=2,161) of those enrolled had received notification that they had an irregular rhythm. The majority of those who had received the notification were elderly and men. Following notification, 658 participants were sent a Food and Drug Administration-approved ECG patch analysis; AF was detected in 34% of these patches.¹⁰ For patients wearing both an ECG patch and their watch simultaneously, the positive predictive values for the tachogram and the notification were 0.71 (95% CI [0.69–0.74]) and 0.84 (95% CI [0.76–0.92]), respectively. Approximately 20% of these patients were found to have AF all of the time, and almost 90% had AF durations of at least 1 hour. Of the 2,161 individuals who received a notification, around 30% were started on a new medication, 30% were referred to a specialist, and the remaining individuals required additional investigation and testing.

The investigators concluded that the use of this technology was associated with a low proportion of notification. However, in those who were notified, the relatively high positive predictive values may support the ability to identify pulse irregularity correctly. Turakhia pointed out that the results of this study should not be the sole determinant of pulse irregularity, and that clinicians should continue to look for other risk factors, provide thorough physical examinations and take a good history.¹⁰

PIONEER-HF

In their study, Velazquez et al. reported the results of the Comparison of Sacubitril/Valsartan versus Enalapril on Effect on NT-proBNP in patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial.¹¹ The investigators randomized more than 800 patients with acute decompensated heart failure to receive either sacubitril/valsartan (target dose, 97 mg sacubitril with 103 mg valsartan twice daily) or enalapril (target dose, 10 mg twice daily).¹¹ The average age of individuals enrolled in this study was 61 years, and almost 70% were men. The median NT-proBNP at baseline was 4,800 pg/ml. At 8 weeks, the primary endpoint of time-averaged reduction in NT-proBNP was –46.7% for sacubitril/valsartan and –25.3% for enalapril (HR 0.71, 95% CI [0.63–0.81], p<0.001). There was also a significant reduction in rehospitalization for heart failure in patients receiving sacubitril/valsartan.

According to Velazquez et al., after being approved in patients with reduced ejection fraction, this trial might expand the use of sacubitril/valsartan to include patients with acute decompensated heart failure.¹¹

CLEAR WISDOM

Ballantyne et al. reported on the Evaluation of Long-Term Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk (CLEAR WISDOM; NCT02991118) trial.¹² Investigators enrolled more than 700 patients with documented atherosclerotic cardiovascular disease and/or heterozygous familial hypercholesterolemia to receive either bempedoic acid 180 mg or placebo once daily. They also enrolled patients with baseline LDL cholesterol \geq 2.6 mmol/l (100 mg/dl) at screening and \geq 1.8 mmol/l (70 mg/dl) following placebo run-in, while receiving maximally tolerated statin therapy.

At 52 weeks, bempedoic acid significantly reduced LDL cholesterol from baseline in comparison with placebo (–15.1% versus 2.4%, p<0.001). Despite this reduction, Ballantyne et al. reported that there was no difference in clinical outcomes between the groups.¹² This agent could

be beneficial, especially for those individuals with high LDL cholesterol despite statin or ezetimibe therapy who are unable to afford or receive proprotein convertase subtilisin/kexin type 9 inhibitors.

CREOLE

In the Comparison of Combination Therapies in Lowering Blood Pressure in Black Africans (CREOLE) trial, investigators randomized 728 patients with hypertension to receive a daily regimen of amlodipine 5 mg plus hydrochlorothiazide 12.5 mg or amlodipine 5 mg plus perindopril 4 mg or perindopril 4 mg plus hydrochlorothiazide 12.5 mg.¹³ The average age of individuals enrolled in this study was 51 years, and almost 65% were women. Investigators excluded patients with a history of cardiovascular disease and those with secondary hypertension.

In their study, Ojji et al. revealed that at 6 months the use of a combination of amlodipine with either hydrochlorothiazide or perindopril was superior in terms of change in 24-hour systolic blood pressure.¹³ The results of this trial therefore might provide further insight into potential hypertension treatment options for black patients.

INFINITY

In the Intensive Versus Standard Blood Pressure Lowering to Prevent Functional Decline in Older People (INFINITY; NCT01650402) trial, investigators randomized approximately 200 hypertensive patients with cerebrovascular disease to receive intensive (systolic blood pressure \leq 130 mmHg) or standard (systolic blood pressure 145 mmHg) ambulatory blood pressure lowering to assess the effect of blood pressure control on mobility and cognitive function.¹⁴

In his study, White announced that at 3 years there was a significant difference in the percentage change from baseline to end of study white matter hyperintensity (0.29% in the intensive group and 0.48% in the standard group; p=0.03).¹⁴ There was no significant difference in gait speed between the two groups during the study (p=0.91). White therefore concluded that intensive systolic blood pressure lowering was not associated with improved mobility or cognitive function. Notably, however, patients in the intensive group had significantly fewer non-fatal cardiovascular events compared to the standard group (4.1% versus 17%, respectively; p<0.01).¹⁴

TREAT

The Ticagrelor in Patients with ST Elevation Myocardial Infarction Treated with Pharmacological Thrombolysis (TREAT) trial compared the efficacy and safety of ticagrelor versus clopidogrel in patients with ST-segment elevation MI (STEMI) who were treated with fibrinolytic therapy.¹⁵

A total of 3,799 patients aged <75 years were randomized to receive either ticagrelor (180 mg loading dose followed by 90 mg twice daily) or clopidogrel (300–600 mg loading dose followed by 75 mg per day). The primary outcome was time to first major bleeding event (thrombolysis in MI). The secondary outcomes were a composite of cardiovascular mortality, MI or stroke, as a measure of efficacy, and bleeding events, which determined safety.

According to Berwanger et al., at 12 months there was a non-significant reduction in time to first major bleeding events in patients who

received ticagrelor (6.7%) compared with (7.3%) in patients who received clopidogrel.¹⁵ In terms of safety, there were no differences in the rates of major, fatal, and intracranial bleeding between ticagrelor and clopidogrel following fibrinolytic therapy in patients with STEMI. The results of this trial might expand the indications of ticagrelor to include individuals with STEMI treated with fibrinolytic therapy.

STOPDAPT-2 ACS and SMART-CHOICE

The results of two large trials examining the use of dual antiplatelet therapy (DAPT) in patients undergoing percutaneous coronary intervention (PCI) were presented on the last day of the American College of Cardiology (ACC) meeting. These trials were Short and Optimal Duration of Dual Antiplatelet Therapy-2 Study for Patients with Acute Coronary Syndrome (STOPDAPT-2 ACS; NCT03462498) and the Comparison Between P2Y₁₂ Antagonist Monotherapy and Dual Antiplatelet Therapy after DES (SMART-CHOICE; NCT02079194). Both trials compared the efficacy and safety of varying lengths of DAPT treatment.

The STOPDAPT-2 ACS trial was conducted to evaluate the efficacy and safety of 1 month of DAPT compared with 12 months of DAPT in patients undergoing PCI. The trial included 3,045 adult patients undergoing PCI with a cobalt chromium everolimus-eluting stent. Patients were randomized to receive either 1 month of DAPT followed by clopidogrel monotherapy for 5 years (n=1,523) or 12 months of DAPT followed by aspirin monotherapy for 5 years (n=1,522). The primary efficacy outcome was a composite of death, MI, stent thrombosis, stroke, and thrombolysis in MI major/minor bleeding at 1 year. Watanabe et al. reported that the use of DAPT for 1 month significantly reduced the chance of the primary outcome (2.4%) compared with 12 months of DAPT (3.7%).¹⁶

The SMART-CHOICE trial randomized 2,993 patients who had undergone PCI with a drug-eluting stent to receive DAPT for 3 months (n=1,495) or 12 months (n=1,498), and had a primary outcome was a composite of all-cause mortality, MI, or stroke. Hahn et al. announced that short-duration DAPT was non-inferior to a longer duration of DAPT in terms of the primary composite outcome (2.9% versus 2.5%, respectively). However, bleeding rates were significantly lower in those taking DAPT for 1 month (2%) compared with those taking DAPT for 12 months (3.4%).¹⁷

The results of STOPDAPT-2 ACS and SMART-CHOICE provide further evidence in favor of shorter-duration antiplatelet therapy in patients undergoing PCI.

AUGUSTUS

The Study of Apixaban in Patients with Atrial Fibrillation, not Caused by a Heart Valve Problem, Who are at Risk for Thrombosis (Blood Clots) due to having had a Recent Coronary Event, such as a Heart Attack or a Procedure to Open the Vessels of the Heart (AUGUSTUS) was conducted to evaluate the efficacy of antithrombotic therapy after ACS or PCI in patients with AF.¹⁸

A total of 4,614 patients with AF and a recent ACS or PCI and who were planning to take of a P2Y₁₂ inhibitor were enrolled. They were randomized to receive apixaban 5 mg twice daily (n=2,306) or vitamin K antagonist with an international normalized ratio goal of 2–3 (n=2,308) and to receive aspirin 81 mg daily (n=2,307) or matching placebo (n=2,307). The primary outcome was major or clinically relevant non-major bleeding.

The rates of the primary outcome reported by Lopes et al. were significantly lower in the apixaban group (10.5%) compared with the VKA group (14.7%).¹⁸ He also stated that bleeding events occurred in a significantly higher proportion of patients who had received aspirin (16.1%) compared with placebo (9%).

The results of this trial have highlighted an additional advantage of using direct oral anticoagulants over VKA. Despite the positive results of this trial, clinicians should be cautious not to extrapolate the results of AUGUSTUS with apixaban to other direct oral anticoagulants.

Primary Prevention Guidelines

The updated ACC/American Heart Association primary prevention of cardiovascular disease guidelines were launched at the ACC meeting. These emphasize the importance of adopting a healthy lifestyle, eating a healthy diet, engaging in physical activities, and smoking cessation, and for healthcare professionals to take a team-based care approach.¹⁹

For people with type 2 diabetes already on metformin and who have made lifestyle modifications, the new guidelines suggest initiating a sodium-glucose cotransporter-2 inhibitor or a glucagon-like peptide-1 receptor agonist. This is due to their effectiveness, in terms of improving glycemic control and reducing cardiovascular disease risk.

Given the lack of net benefit, the updated guidelines recommend against the use of low-dose aspirin for the primary prevention of atherosclerotic cardiovascular disease among adults >70 years of age or adults of any age who are at increased risk of bleeding. ■

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