Medicom International Conference Series in Cardiology

AHA Scientific Sessions 2019

American Heart Association

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PEER-REVIEWED CONFERENCE REPORT

Inclisiran Safely Halves LDL-Cholesterol

The ORION-10 trial safely demonstrated effect of the RNAi inclisiran in patients with atherosclerotic cardiovascular disease and elevated LDL with a follow-up of 18 months.

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ISCHEMIA Trial: Invasive Treatment not Better

Invasive therapy does not reduce the risk of major adverse cardiac events compared with optimal medical therapy/lifestyle modulation in patients with stable ischaemic heart disease and moderate-to-severe ischaemia.

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PARAGON-HF: Benefits for Women and Lower EF

Two new analyses of the PARAGON-HF trial show that among patients with heart failure with preserved EF, particularly women and patients with below-normal LVEF range benefitted from sacubitril/valsartan.

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Editor Prof. Marc P. Bonaca, University of Colorado, USA

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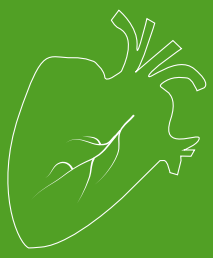

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Introduction

Dear Reader,

The American Heart Association Scientific Sessions 2019 saw many presentations of exciting and practice-changing trials, novel therapeutic approaches currently in development, guidelines updates, a deeper dive in existing management strategies, in addition to cutting-edge fundamental and translational science.

The ISCHEMIA trial, for example, was long anticipated and reported here that invasive treatment is not clearly the best management strategy for higher-risk patients with stable ischaemic heart disease, when compared with conservative medical therapies (like aspirin or statins) coupled with lifestyle advice, except perhaps for angina burden, which seemed to be better served by an invasive approach.

By contrast, the COLCOT trial reported that low-dose colchicine in patients with a recent MI was not only safe but can prevent major adverse CV events compared with placebo by a 28% margin. The wide accessibility of colchicine could make this trial a game changer.

These any many other highlights presented at the AHA 2019 are covered in peer-reviewed summaries in the following pages.

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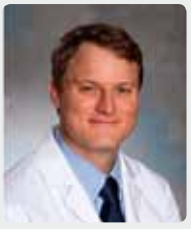


Prof. Marc Peter Bonaca

Editor Biography

Marc P. Bonaca, MD, MPH, is a Cardiologist and Vascular Medicine Specialist who serves as the Executive Director of CPC Clinical Research and CPC Community Health at the University of Colorado Anschutz Medical Campus. He is the Director of Vascular Research and an Associate Professor of Medicine at the University of Colorado School of Medicine and the inaugural holder of the William R. Hiatt Endowed Chair in Cardiovascular Research.

Dr Bonaca earned his medical degree from the University of Connecticut School of Medicine and his Masters in Public Health at Harvard University. He served as a Medical House Officer at Brigham and Women's Hospital and Harvard Medical School. After completion of his training he joined the faculty of the Cardiovascular Division and Vascular Medicine section of Brigham and Women's Hospital and Harvard Medical School and became an Investigator at the TIMI Study Group.

Dr Bonaca's research focus is on ischemic risk in patients with atherosclerotic vascular disease, risk prediction, and risk modification through the use of pharmacologic and biologic therapies. His key areas of interest include patients with peripheral artery disease, polyvascular disease and diabetes with a focus on the breadth of risk including ischemic limb outcomes, microvascular complications and major adverse cardiovascular events.

Conflict of Interest Statement:
Grant support to BWH from AstraZeneca, MedImmune, Merck, Pfizer.
Grant support to CPC from Amgen, AstraZeneca, Bayer, Janssen, NovoNordisk, Sanofi.

New Approaches to CVD Risk Reduction

Phase 3 BETonMACE trial did not meet its primary endpoint

The results of a placebo-controlled trial showed that apabetalone does not decrease cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke in diabetic patients with recent acute coronary syndrome (ACS).

Prof. Kausik K. Ray (Imperial College London, United Kingdom) presented the results of the phase 3, international, multicentre, randomised, double-blind, placebo-controlled BETonMACE trial. This study aimed to determine whether modulating epigenetics with the selective bromodomain and extra-terminal (BET) protein inhibitor apabetalone is safe and effective in reducing CV risk [1]. Patients with type 2 diabetes mellitus, ACS within the preceding 7-90 days, and low HDL-C (≤40 mg/dl for men and ≤45 mg/dl for women) were randomised to receive either apabetalone (100 mg orally, twice a day; n=1,212) or matched placebo (n=1,206) in addition to standard-of-care therapy, e.g. intensive or maximum-tolerated treatment with atorvastatin or rosuvastatin. The primary outcome of the study was the time to CV death, non-fatal MI, or non-fatal stroke. A key secondary outcome was time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for unstable angina or urgent/emergency coronary revascularisation.

Apabetalone changed HDL-C from baseline at 100 weeks by 16.2% versus 10.4% (P=0.001). Over a median follow-up of 26 months, the primary outcome occurred in 10.3% and 12.4% of patients treated with apabetalone versus placebo, respectively (HR 0.82; 95% CI 0.65-1.04; P=0.11). The rate of adverse events was similar across treatment groups, with 830 patients (68.5%) in the apabetalone arm and 820 (67.9%) in the placebo arm reporting at least 1 adverse event. However, discontinuation of treatment due to elevated liver function tests was more frequent in the apabetalone arm. The conclusion presented was that apabetalone has an adequate safety profile, and although HDL-C was significantly reduced from baseline at 100 weeks, no differences could be derived for patients with regard to CV death, non-fatal MI, or non-fatal stroke.

1. Ray KK, et al. Effect of BET Protein Inhibition With Apabetalone on Cardiovascular Outcomes in Patients With Acute Coronary Syndrome and Diabetes - Results of the BETonMACE Trial. LBS01, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

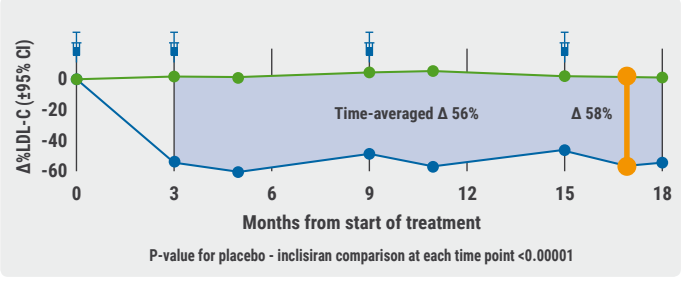
Inclisiran safely halves LDL-Cholesterol

Prof. R. Scott Wright (Mayo Clinic, Rochester, USA) presented the latest data from the phase 3, randomised, placebo-controlled, double-blinded ORION-10 trial, testing the effect of the small interfering RNA (siRNA) inclisiran in patients with atherosclerotic cardiovascular disease (ASCVD) and elevated low-density lipoprotein cholesterol (LDL-C) [1]. With a follow-up of 18 months, inclisiran halved LDL-C levels compared with placebo. The safety profile was favourable.

ORION-10 randomised 1,561 ASCVD patients with elevated LDL-C (≥70 mg/mL) who were already taking maximum tolerated statins to receive either 4 injections (at 0, 3, 9, and 15 months) of placebo or of 300 mg inclisiran with a follow-up of 18 months. The co-primary endpoints were percentage of LDL-C change from baseline at day 510 and the average percentage change from day 90 to day 540.

At the study end at day 510, LDL-C was 58% lower in the inclisiran arm versus the placebo arm, and the time-averaged reduction was similar at 56% reduction (both P<0.00001; see Figure). Treatment-emergent adverse event rates were similar between the placebo and inclisiran arms (75% vs 74%), as were the rates of serious adverse events (26.3% vs 22.4%), including those that led to drug discontinuation (2.2% vs 2.4%). There were only 20 instances of an injection site event (2.6%)—13 mild and 7 moderate; but these numbers fell after the protocol switched to a prefilled syringe midway through the study. There were no detected toxicities in liver or kidney function or in prespecified exploratory cardiovascular endpoint of CV death, fatal or non-fatal MI, or stroke.

Figure: Percentage change in LDL-C from baseline in ITT population [1]



CI, confidence interval; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol.

The invited discussant, Prof. Karol E. Watson (David Geffen School of Medicine at UCLA, USA) pointed out that although these data are very promising, it is still not clear how inclisiran affects HDL-C, triglycerides, and lipoprotein(a) levels. A further limitation in this study was that it did not use clinical events as a primary outcome. In conclusion, in patients with ASCVD on maximum tolerated statin therapy, inclisiran injections twice a year generated a significant and durable reduction in LDL-C while being well tolerated. The use of a siRNA is a novel approach to management of LDL-C.

1. Wright RS, et al. Safety and Efficacy of Inclisiran in Patients With ASCVD and Elevated LDL Cholesterol - Results From the Phase 3 ORION-10 Trial. LBS01, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

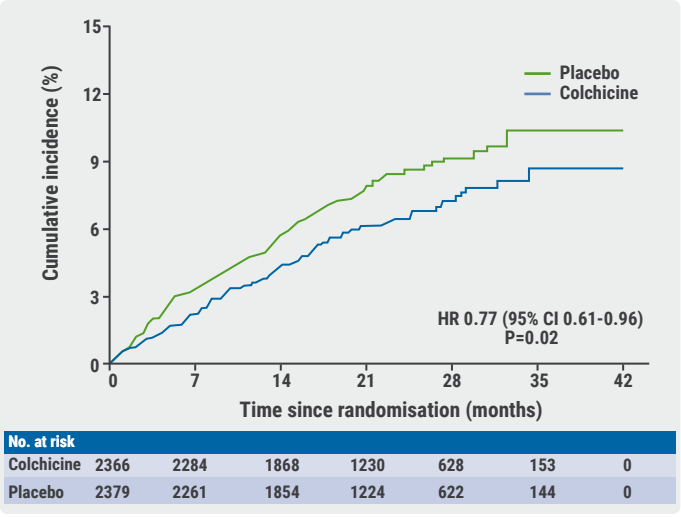
Colchicine prevents cardiovascular events

Low-dose colchicine in patients with a recent myocardial infarction (MI) can prevent major adverse cardiovascular (CV) events compared with placebo by a 28% margin. The benefit was primarily attributable to a lowered incidence of stroke or urgent hospitalisation for unstable angina leading to revascularisation in patients, according to the COLCOT trial presented by Prof. Jean-Claude Tardif (University of Montreal, Canada) [1].

Although the smaller LoDoCo trial previously showed that 0.5 mg colchicine reduced the risk of CV events in the setting of stable coronary artery disease, suggestive of a benefit, it was limited by the lack of a placebo comparator. To address the value of low-dose colchicine (0.5 mg once daily) in patients with a recent history of MI, the COLCOT trial randomised 4,745 patients (mean age 60.6 years; 19.2% female) in 12 countries to either colchicine or placebo. Patient characteristics in both groups were similar, with trial entry being a mean of 13.5 days post-MI in both groups.

The primary efficacy endpoint —a composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalisation for angina requiring revascularisation— was met; at a median follow-up of 22.6 months, the proportion of patients receiving colchicine who experienced a primary-endpoint event was significantly lower than those who received placebo (5.5% vs 7.1%; HR 0.77; 95% CI 0.61-0.96; P=0.02; see Figure). Analysing the individual components of the primary endpoint revealed no significant differences in CV death, resuscitated cardiac arrest, or MI between the 2 study arms. However, the secondary composite endpoint of CV death, cardiac arrest, MI, or stroke was not significantly altered by colchicine treatment (HR 0.85; 95% CI 0.66-1.10). The results were simultaneously published in the *New England Journal of Medicine* [2].

Figure: Primary efficacy endpoint (i.e. CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalisation for angina requiring revascularisation) in ITT population. Modified from [2]



No. at risk							
Colchicine	2366	2284	1868	1230	628	153	0
Placebo	2379	2261	1854	1224	622	144	0

Serious adverse events were equally common overall between the 2 study arms, though pneumonia was more common with colchicine than with placebo (0.9% vs 0.4%; P=0.03), as was nausea (1.8% vs 1.0%; P=0.02). Drug discontinuation did not differ between colchicine and placebo users. The relatively short median follow-up of 23 months precludes the ability to draw firm conclusions regarding the long-term safety and efficacy of colchicine. However, the broad access and affordability of colchicine, as well as renewed interest in treating inflammation for secondary prevention after MI, make this study particularly notable.

1. Tardif J-C, et al. The COLchicine Cardiovascular Outcomes Trial (COLCOT). LBS01, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
2. Tardif J-C, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019 [Epub ahead of print].

Interventional Management for Acute Coronary Syndrome

Drop aspirin after 3 months in non-STEMI ACS patients on dual antiplatelet therapy

In a sub-analysis of the TWILIGHT trial, which looked only at patients with acute coronary syndrome (ACS), researchers confirmed that dropping aspirin after 3 months of dual antiplatelet therapy (DAPT) with ticagrelor following percutaneous coronary intervention (PCI) lowers bleeding risk without increasing the rate of ischaemic events. The benefit observed with ticagrelor monotherapy was independent of risk levels or whether the patients had non-ST elevation myocardial infarction (NSTEMI) or unstable angina at presentation.

Prof. Usman Baber (Icahn School of Medicine at Mount Sinai, USA) provided the rationale behind this particular sub-analysis: "The basis for DAPT in ACS really comes from trials conducted almost 20 years ago showing that it is superior to aspirin," but he noted that "one of the challenges we have with the provision of antiplatelet therapy right now is that a lot of patients who should probably be getting potent agents are not getting them due to concerns of bleeding" [1].

Of the 4,614 ACS patients enrolled in TWILIGHT, 2,494 had unstable angina and 2,120 had NSTEMI. Patients were randomised to drop aspirin after 3 months and continue ticagrelor monotherapy (n=2,273) or to continue with DAPT (n=2,341). Patient characteristics were similar in both groups; the mean age was 64 years, 35% had diabetes, and 61% had multivessel disease. There were, however, more smokers in the continued DAPT arm of the trial (26.6% vs 23.3%; P=0.02).

The primary endpoint at 1 year was Bleeding Academic Research Consortium (BARC) 2, 3, or 5. The results showed that the primary endpoint was met: bleeding was significantly lower in the ticagrelor monotherapy group compared with the arm that continued DAPT (3.6% vs 7.6%; HR 0.47; 95% CI 0.36-0.61; P<0.001). The 2 arms appeared similar for the secondary endpoint of all-cause death, MI, or stroke at 1 year (4.3% vs 4.4%; HR 0.97; 95% CI 0.74-1.28; P=0.84). Neither risk factors at presentation nor whether the patients had presented with unstable angina or NSTEMI made a difference. Prespecified ischaemic endpoints between the 2 arms were similar, including cardiovascular death, all-cause death, any MI, stroke, and stent thrombosis.

1. Baber U, et al. Ticagrelor with aspirin or alone in high-risk patients after coronary intervention for acute coronary syndrome. LBS04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Immediate coronary angiography after cardiac arrest does not improve survival

Immediate coronary angiography after cardiac arrest did not improve survival at 1 year compared with delaying the procedure in resuscitated patients who had had out-of-hospital cardiac arrest (OHCA) without ST segment elevation (STE).

Dr Jorrit Lemkes (Amsterdam University Medical Center, the Netherlands) presented the 1-year follow-up data from the Coronary Angiography after Cardiac Arrest (COACT) trial [1], which was the first randomised trial in cardiac arrest patients without STE investigating whether immediate angiography could improve survival and major adverse cardiac events at 1 year, as opposed to a delayed invasive strategy. This open-label, multicentre trial enrolled 552 OHCA patients who were allocated to receive either immediate angiography (n=264) or delayed angiography (n=258).

Survival at 90 days was the primary endpoint. Secondary endpoints included survival at 90 days with good cerebral performance or moderate disability, thrombolysis in myocardial infarction major bleeding, recurrence of ventricular tachycardia, occurrence of acute kidney injury and need for renal-replacement therapy, time-to-target temperature, duration of inotropic/catecholamine support, duration of mechanical ventilation, myocardial injury, and markers of shock.

The results did not indicate significant improvement with immediate angiography; 1-year survival outcomes were 61.4% of patients in the immediate angiography group and

64.0% of patients in the delayed group (OR 0.90; 95% CI 0.63-1.28). Additionally, no significant differences were observed in the rates of myocardial infarction, revascularisation, hospitalisation due to heart failure, or implantable cardioverter defibrillator (ICD) shocks between the 2 treatment groups at 1 year. These results do not support a strategy of immediate angiography with intent to revascularise for patients with resuscitated OHCA without STE.

1. Lemkes J, et al. One Year Outcomes of Coronary Angiography After Cardiac Arrest. LBS04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Complete revascularisation for obstructive non-culprit lesions with vulnerable plaque

Dr Natalia Pinilla-Echeverri (McMaster University, Canada) presented new results from a sub-study of the COMPLETE trial analysing the optical coherence tomography (OCT) data from participants. This data determined that 47% of the patients in that trial had obstructive non-culprit lesions with vulnerable plaque, which may contribute to the improved outcomes observed with complete versus culprit lesion-only revascularisation in the main trial [1].

The results of the COMPLETE trial published in September 2019 showed that patients with ST segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease who underwent complete revascularisation benefitted from a lower risk for cardiovascular (CV) death or new myocardial infarction (MI) [2]. However, as Dr Pinilla-Echeverri explained during her presentation, "whether the benefit of routine non-culprit lesion percutaneous coronary intervention might be associated with vulnerable plaque morphology is unclear."

Using OCT to image thin-cap fibroatheromas, the researchers identified vulnerable plaques in 93 patients (mean age 61 years; 83% male). Among obstructive lesions, 35.4% were identified as containing thin-cap fibroatheroma, while only 23.2% of non-obstructive lesions had thin-cap fibroatheroma (P=0.022). Although the lengths and lumen areas of obstructive versus non-obstructive thin-cap fibroatheromas were similar, significant differences were observed in the lesion lipid content and features of plaque vulnerability.

Overall, nearly half (47.3%) of patients undergoing OCT in this analysis had an obstructive non-culprit lesion with vulnerable plaque. The researchers concluded that these findings may help explain the benefit of routine percutaneous coronary intervention of obstructive non-culprit lesions in patients with STEMI and multivessel disease. Further research is required to determine the best strategy post-PCI for the STEMI patients with only non-culprit obstructive lesions and without vulnerable plaque morphology as determined by OCT.

1. Pinilla-Echeverri N, et al. OCT COMPLETE: Non-culprit Lesion Plaque Morphology in Patients with ST-segment Elevation Myocardial Infarction: Substudy from the Complete Trial using Optical Coherence Tomography (OCT). LBS04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
2. Mehta SR, et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. N Engl J Med. 2019 Oct 10;381(15):1411-1421.

Colchicine: no difference in peri-procedural cardiovascular events 30 days post-PCI

Dr Binita Shah (NYU School of Medicine, USA) presented the 30-day follow-up data of 400 subjects who underwent percutaneous coronary intervention (PCI) in the double-blind, single-site COLCHINE-PCI trial [1].

COLCHICINE-PCI studied pre-procedural use of colchicine in patients with ischaemic heart disease or acute coronary syndrome undergoing PCI. The primary endpoint — myocardial injury, as determined by troponin I concentration— was not different between the 2 arms. In total, 118 subjects assigned to the colchicine arm (57.3%) versus 122 patients in the placebo arm (64.2%) experienced a primary outcome event (P=0.19). Furthermore, no statistically significant distinctions were observed between the colchicine arm versus the placebo arm for any of the secondary endpoints, i.e. peri-procedural myocardial injury using CKMB and the SCAI definition of clinically relevant myocardial infarction after coronary revascularisation or the occurrence of major adverse cardiac events (MACE) with composite of the earliest occurrence of death from any cause, non-fatal myocardial infarction (defined by the Universal Definition), or target vessel revascularisation (bypass surgery or repeat PCI of the target vessel) at 30 days. No differences were observed in all-cause mortality (P=0.49).

In a pre-specified inflammatory marker sub-study with 280 subjects, there was no significant difference for the primary biomarker outcome of soluble interleukin (IL)-6 levels from baseline to 1 hour post-PCI, when comparing the colchicine (n=141) with the placebo (n=139) group. However, at 24 hours post-PCI, IL-6 (76% vs 338%; P=0.02) and high-sensitivity C-reactive protein (7% vs 57%; P=0.001) were both significantly reduced in the colchicine group compared with the placebo group.

In summary, while colchicine appears to attenuate inflammatory cytokine increases during the first 24 hours after PCI, there was no significant difference in peri-procedural myocardial injury or major adverse cardiovascular events at 30 days post-PCI.

1. Shah B, et al. Effects of Acute Colchicine Administration Prior to Percutaneous Coronary Intervention: The COLCHICINE-PCI Randomized Trial. LBS04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Intra-aortic balloon pump better than Impella: new observational data

New data demonstrates that the use of the Impella device is associated with worse outcomes in cardiogenic shock and high-risk percutaneous coronary intervention (PCI) patients when compared with an intra-aortic balloon pump (IABP).

Presented by Dr Sanket S. Dhruva (University of California, San Francisco, USA), this observational study identified 28,304 matched patients with acute myocardial infarction with cardiogenic shock (AMICS) undergoing PCI from the National Cardiovascular Data Registry (NCDR) for the period between October 2015 and December 2017 [1]. The mean age was 65 years, 33% were female, 81.3% had had a STEMI, and 43.3% had had cardiac arrest. Dr Dhruva noted that use of the Impella rose from 3.5% to 8.7% in AMICS patients during the study period.

Within this large cohort, researchers identified 1,680 propensity-matched pairs who received Impella versus IABP. Results showed that the use of the Impella device was associated with significantly higher rates of in-hospital mortality and major bleeding "regardless of timing of device placement" as compared with IABP. In-hospital mortality was 45.0% with Impella and 34.1% with IABP. Major bleeding affected 31.3% and 16.0% of the Impella and IABP patients, respectively.

Dr Dhruva concluded, "These data provide important insights into the performance of mechanical circulatory support devices in routine clinical practice, and outcomes in randomised controlled trial settings may differ. Better evidence and guidance are needed regarding the optimal management of patients with AMICS as well as the role of mechanical circulatory support devices in general, and Impella in particular."

1. Dhruva SS, et al. Comparative effectiveness and costs of Impella versus intra-aortic balloon pump in the United States. LBS04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Results for the Ischemia Trials: To Intervene or Not to Intervene

ISCHEMIA trial: Invasive treatment only better for angina burden

Invasive therapy does not reduce the risk of major adverse cardiac events compared with optimal medical therapy in patients with stable ischaemic heart disease and moderate-to-severe ischaemia. However, quality-of-life data in patients with angina did indicate significant pain improvement in the invasive arm of the study.

As the largest study of its kind, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) was one of the most anticipated results at the congress. The investigators randomly assigned 5,179 patients with coronary artery disease at 320 sites in 37 countries to receive 1 of 2 treatment strategies: either 'invasive' therapy including early stent implants or bypass surgery, or 'conservative' therapy, where patients received only medication (e.g. aspirin, statins) and lifestyle advice.

Prof. Judith Hochman (New York University School of Medicine, USA) presented the results, reporting that over a median follow-up of 3.3 years, there were no differences between the 2 groups in the risk for the primary composite endpoint of time to cardiovascular death, myocardial infarction (MI), or hospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest (HR 0.93; 95% CI 0.80-1.08; P=0.34) [1].

However, the data was slightly more complex, Dr Hochman pointed out, because the curves crossed at 2 years follow-up. At 6 months, the absolute rates favoured the conservative therapy by 1.9%. Yet, at 4 years, the data favoured the patients who had received early angiography prior to percutaneous coronary intervention (PCI) or bypass surgery by 2.2% (13.3% vs 15.5%, respectively). Prof. Hochman underscored that it is unclear what longer follow-up may reveal.

There was no difference between the invasive and conservative strategies in the key secondary endpoints of cardiovascular death or MI (11.7% vs 13.9%; HR 0.90; 95% CI 0.77-1.06; P=0.21) or in all-cause death (6.5% vs 6.4%; HR 1.05; 95% CI 0.83-1.1).

In a parallel quality-of-life study, presented in the same session by Dr John Spertus (Saint Luke's Mid America Heart institute, USA), data showed that revascularisation provided greater relief from angina symptoms than conservative therapy, with 50% of the patients at 1 year reporting no angina symptoms at all, as opposed to just 20% of those in the conservative therapy arm [2].

Although the overall interpretation of this trial was of a neutral outcome, the results suggest that invasive therapy for stable ischaemic heart disease patients needs to be carefully considered in the context of angina burden and background medical therapy, and that optimal coronary revascularisation can be achieved with low procedural complications.

1. Hochman JS, et al. International Study of Comparative Health Effectiveness With Medical and Invasive Approaches: Primary Report of Clinical Outcomes. LBS02, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
2. Spertus JA, et al. International Study of Comparative Health Effectiveness With Medical and Invasive Approaches: Primary Report of Quality of Life Outcomes. LBS02, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Controversies in Contemporary Management of Aortic Stenosis

Full GALILEO results: Why did rivaroxaban fail after TAVR?

The full results of the prematurely terminated GALILEO trial confirm that oral anticoagulation with rivaroxaban was associated with worse clinical outcomes compared with antiplatelet therapy in patients after successful transcatheter aortic valve replacement (TAVR). However, the GALILEO-4D CT sub-study showed that rivaroxaban prevents some leaflet thickening and leaflet motion, indicative of a specific benefit. Both studies were simultaneously published in the *New England Journal of Medicine* [1,2].

Prof. George Dangas (Icahn School of Medicine at Mount Sinai, USA) pointed out that although current guidelines recommend dual antiplatelet therapy after TAVR, the evidence base for the optimal treatment strategy for patients who have had TAVR is weak [3]. Earlier observational studies provided some evidence that oral anticoagulation could lower the incidence of sub-clinical leaflet thrombosis, which in turn may prevent post-TAVR cerebrovascular lesions, but high-level evidence has been lacking.

GALILEO was an open-label trial designed to test rivaroxaban for a primary composite efficacy outcome of death or thromboembolic events in patients within a week of successful TAVR. Investigators randomised 1,644 patients (mean age 80.6 years; 49.5% female) without an established indication for oral anticoagulation to either rivaroxaban-based treatment (10 mg daily plus aspirin 75-100 mg daily for 3 months, then maintenance with rivaroxaban alone) or antiplatelet treatment arm (aspirin plus clopidogrel 75 mg daily for 3 months, then maintenance with aspirin alone).

The rate of death or thromboembolic events was higher with rivaroxaban-based therapy than with antiplatelet therapy (12.7% vs 9.5%; HR 1.35; 95% CI 1.01-1.81). The individual endpoint of death was significantly increased in the rivaroxaban treatment arm as well (7.7% vs 4.6%; HR 1.69; 95% CI 1.13-2.53). Consequently, the trial was halted prematurely.

Although serious bleeding was somewhat more frequent in the rivaroxaban arm of the trial, Prof. Dangas presented the data that underlying causes of the observed mortality could not be explained by bleeding and remain uncertain and perhaps related to non-cardiovascular causes. VARC-2 major, disabling, or life-threatening bleeding was only borderline significantly increased (5.6% vs 3.8%; HR 1.50; 95% CI 0.95-2.37), while there were no significant differences in VARC-2 major, TIMI major/minor, ISTH major, and BARC type 2, 3, or 5 bleeding events.

In contrast, presenting a pre-planned sub-study of the 4-dimensional CT data derived from 231 patients in GALILEO, dubbed GALILEO-4D, Prof. Ole De Backer (Copenhagen University Hospital, Denmark) showed data that rivaroxaban significantly reduced subclinical leaflet thickening [4]. Leaflet thickening was noted in 12.4% patients from the rivaroxaban-based strategy arm versus 32.4% of the patients treated with a clopidogrel-based strategy (P<0.05). Furthermore, the percentage of patients with ≥1 prosthetic leaflet with reduced leaflet motion was reduced by rivaroxaban: 2.1% with rivaroxaban-based strategy versus 10.9% with clopidogrel-based strategy (P=0.014).

In conclusion, although leaflet improvements were observed, using a rivaroxaban-based antithrombotic strategy post-TAVR increased mortality in addition to moderately increasing bleeding risk. Thus, novel regimens for antithrombotic management following TAVR remain an area of open research.

1. Dangas GD, et al. A Controlled Trial of Rivaroxaban After Transcatheter Aortic-Valve Replacement. N Engl J Med 2019; Nov 16 [Epub ahead of print].
2. De Backer O. Reduced Leaflet Motion After Transcatheter Aortic-Valve Replacement. N Engl J Med 2019; Nov 16 [Epub ahead of print].
3. Dangas GD, et al. Global Comparison of a Rivaroxaban-Based Antithrombotic Strategy versus an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) Trial: Primary Results. Session LBS03, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
4. De Backer O, et al. Randomized Clinical Trial Comparing a Rivaroxaban-Based Strategy With an Antiplatelet-Based Strategy for the Prevention of Subclinical Leaflet Thrombosis in Transcatheter Aortic Valves (GALILEO-4D). Session LBS03, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Balloon-expandable better than self-expanding transcatheter heart valves

Dr Eric Van Belle (CHU Lille, France) presented the FRANCE-TAVI nationwide registry study, which attempted to determine the impact of transcatheter heart valve (THV) design (balloon-expandable [BE] or self-expanding [SE]) on the risk of paravalvular regurgitation (PVR), intrahospital mortality, and 2-year mortality [1]. The authors concluded that BE-THV had fewer complications.

In this registry-based, multicentre, prospective, open, non-randomised study, 12,141 patients with native aortic stenosis received either BE-THV (n=8,038) or SE-THV (n=4,103). Follow-up was available for all patients (median 20 months, interquartile range 14-30). Co-primary outcomes of this study were the occurrence of ≥moderate PVR and/or in-hospital mortality, as well as 2-year all-cause mortality.

For the presented matched-propensity analyses, 25 clinical, anatomical, and procedural variables, coupled with the date of the procedure (within 3 months) were used to score patients either treated with BE-THV (n=3,910) or SE-THV (n=3,910). The results showed that ≥moderate PVR and/or in-hospital mortality was higher in patients who received SE-THV (19.8%) compared with BE-THV (11.9%; relative risk [RR] 1.68; 95% CI 1.46-1.91; P<0.0001). The individual components of the composite outcome were both also higher in SE-THV patients: ≥moderate PVR (15.5% vs 8.3%; RR 1.90; 95% CI 1.63-2.22; P<0.0001) and in-hospital mortality (5.6% vs 4.2%; RR 1.34; 95% CI 1.07-1.66; P=0.01). All-cause mortality at 2 years was higher in patients treated with SE-THV than in patients treated with BE-THV (29.8% vs 26.6%; HR 1.17; 95% CI 1.06-1.29; P=0.003). The authors concluded that use of SE-THV was associated with a higher risk of PVR and higher in-hospital and 2-year mortality as compared with BE-THV.

1. Van Belle E, et al. Balloon-Expandable versus Self-Expandable TAVR on Paravalvular Regurgitation and 2-Year Mortality: A Propensity-Matched Comparison From the FRANCE-TAVI Registry. LBS04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

RECOVERY: Benefit of early surgery in asymptomatic severe aortic stenosis

Results of the RECOVERY trial demonstrate that early pre-emptive aortic valve replacement (AVR) is better for asymptomatic patients with severe aortic stenosis (AS) than conservative management for the outcomes of operative or cardiovascular death, as well as death from any cause [1].

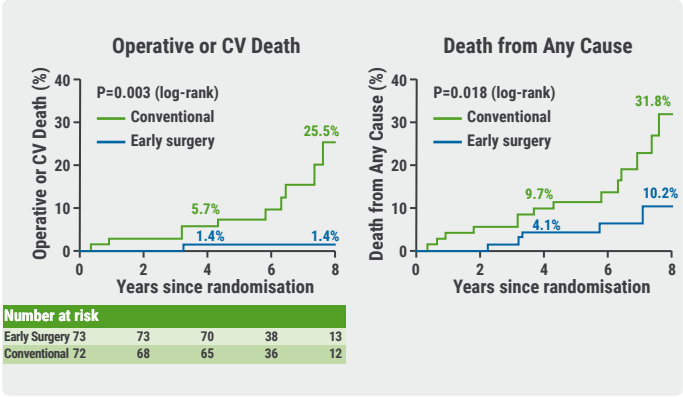
It has been unclear to date as to whether the risk of death outweighs the risk of AVR-related death in asymptomatic AS patients, and the ESC2017 guidelines currently recommend watchful observance. However, there has never been a randomised trial to support this approach. Prof. Duk-Hyun Kang (Asan Medical Center, South Korea) presented the 8-year follow-up results of The Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis (RECOVERY) study. RECOVERY was

a prospective, multicentre, open-label, randomised trial in which asymptomatic patients with severe AS were randomly assigned to early surgery (n=73) or to conventional treatment (n=72). The primary endpoint of the trial was a composite of peri-operative mortality or cardiovascular death. The major secondary endpoint was death from any cause.

Patients randomised to early surgery received AVR within 2 months (n=69 intention-to-treat), while patients in the conventional treatment arm were treated according to the current guidelines (n=52 intention-to-treat). Patients who were assigned to conventional care were referred for AVR if they became symptomatic, had a left ventricle ejection fraction <0.50, or an increase in peak aortic velocity >0.5 m/s per year.

In the pre-emptive surgery group, the rate of peri-operative death was 1.4% at both 4 and 8 years of follow-up compared with 5.7% at 4 years and 25.5% at 8 years in the conventional treatment arm (P=0.003; see Figure). The rate of all-cause mortality was also higher in the conventional treatment arm

Figure: Primary and secondary endpoints of the RECOVERY trial [1]



compared with the early surgery group (9.7% vs 4.1% at 4 years and 31.8% vs 10.2% at 8 years, respectively; P=0.018; see Figure). The evidence from this trial strongly supports early AVR intervention for asymptomatic patients with severe aortic stenosis.

1. Kang D-H, et al. RECOVERY: Early Surgery versus Conventional Management for Asymptomatic Severe Aortic Stenosis. LBS04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Guidelines: Updates and Controversies

New guidelines on the prevention of cardiovascular conditions

A collaboration between the American College of Cardiology (ACC) and the American Heart Association (AHA) released the 2019 Primary Prevention of Cardiovascular Disease guideline [1].

Co-chair of the guideline committee Prof. Roger S. Blumenthal (Johns Hopkins University, USA) provided a summarised update including new key points on patient diet, tobacco use, and risk factor management for physicians [2]. One notable change in the recommendations is to limit aspirin use in the primary prevention of cardiovascular disease and stroke (see Table).

The ACC-AHA committee made a series of recommendations which they systematically scored using a 5-point grading scale based on clinical benefits versus risks; coupled with the highest for level of evidence available. Some of the key recommendations are:

1. Employ a team-based care approach for the control of risk factors associated with atherosclerotic cardiovascular disease (ASCVD) utilising shared decision-making with the patient.
2. Improve glycaemic control in adults with type 2 diabetes (T2DM), achieve weight loss if needed, and improve other ASCVD risk factors. T2DM patients should get at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity.
3. T2DM patients 40-75 years old should receive moderate-intensity statin therapy, regardless of estimated 10-year ASCVD risk.
4. It is "reasonable" to prescribe either sodium-glucose co-transporter 2 (SGLT-2) inhibitors or glucagon-like peptide-1 receptor agonist to reduce CVD risk in adults with T2DM and additional ASCVD risk factors, who may require glucose-lowering treatment despite initial lifestyle modifications and metformin.

5. In adults with intermediate (≥7.5% to <20%) 10-year ASCVD risk, a moderate-intensity statin is recommended.
6. In adults with hypertension, including those requiring antihypertensive medications, nonpharmacological interventions should include weight loss, a heart-healthy diet (focused on fruits, vegetables, legumes, nuts, whole grains, and fish), sodium reduction, dietary potassium supplementation, increased physical activity with a structured exercise programme, and limited alcohol.
7. Recent evidence has shown that daily aspirin confers a bleeding risk that outweighs its benefit in primary stroke and CV risk prevention for most adults. For secondary prevention, the new guidelines still recommend aspirin for who have experienced a prior stroke, acute myocardial infarction, angina, coronary revascularisation, or carotid revascularisation.

   However, low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among those adults 40-70 years old at higher risk of ASCVD risk but not at increased bleeding risk (see Table).

Table: 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease – Recommendations for aspirin use. Modified from [1]

Recommendations	Class	Level of evidence
Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.	IIb	A
Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 of age.	III: Harm	B-R
Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.	III: Harm	C-LD

1. Arnett DK, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140(11).
2. Blumenthal RS, et al. 2019 AHA/ACC Prevention Guidelines. QU.SMP.505, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Trials in Electrophysiology and Left Ventricular Function

RENAL-AF trial: Apixaban similar to warfarin

The RENAL-AF trial showed that apixaban 5 mg twice daily results in similar rates of bleeding and stroke as warfarin among patients with end-stage renal disease on haemodialysis [1].

This randomised controlled trial assessed the safety and efficacy of apixaban as a means for stroke prophylaxis among patients with atrial fibrillation (AF) and end-stage renal disease on haemodialysis, but it was terminated early due to slow enrolment. Dr Sean Pokorney (Duke Clinical Research Institute, USA) presented the interim trial results, which included data on 154 patients with AF and end-stage renal disease who received renal replacement therapy by haemodialysis and who were candidates for oral anticoagulants. Patients were randomised to either apixaban 5 mg twice daily (n=82; 29% received 2.5 mg twice daily) or warfarin (n=72). The mean age of patients in both arms was 69 years; 35% were female. Nearly 20% of the patients had suffered a prior stroke.

The primary outcome was clinically relevant non-major bleeding, which occurred in 31.5% of patients receiving apixaban versus 25.5% receiving warfarin (P>0.05). Secondary outcomes were intracranial bleeding rates (1.2% apixaban vs 1.4% warfarin), gastrointestinal bleeding (2.4% apixaban vs 8.3% warfarin), ISTH major bleeding (8.5% apixaban vs 9.7% warfarin), stroke (2.4% apixaban vs 2.8% warfarin), and cardiovascular death (11% apixaban vs 5.6% warfarin).

In conclusion, the results of this trial indicate that apixaban 5 mg twice daily results in similar rates of bleeding and stroke compared with warfarin among patients with end-stage renal disease on haemodialysis. Unique to this trial is the fact that 44.9% of the patients included in RENAL-AF were of African-American descent, making this the only oral anticoagulant trial with a significant minority cohort. Ongoing pharmacokinetic analyses may provide new data that could help guide apixaban dose selection in this high-risk population.

1. Pokorney SD, et al. Apixaban versus warfarin for strike prevention in patients with end stage renal disease on hemodialysis and atrial fibrillation: results of a randomized clinical trial assessing safety. FS.AOS.04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Apple Heart Study: Not just for atrial fibrillation

The Apple Heart Study, a prospective, single-group, open-label, site-free, pragmatic study, demonstrated that wearable technology (Apple Watch) is a feasible means of detecting not only atrial fibrillation (AF) but also other types of arrhythmias in the general population.

Prof. Marco Perez (Stanford University, USA) presented new findings from this study, showing that the pulse sensor paired with a mobile app identified important arrhythmias apart from AF with a high positive predictive value [1]. The study had two co-primary endpoints: (1) AF >30 seconds as validated by ECG patch monitoring, and (2) simultaneous ECG patch-validated AF and irregular patient tachogram. Key secondary outcomes were simultaneous AF on ECG patch monitoring while the pulse notification algorithm detected an irregular pulse, and post-study healthcare provider intervention within 3 months after an irregular pulse notification.

The study, published in the *New England Journal of Medicine* [2], showed that an irregular pulse was detected in 0.52% of the 419,297 participants between November 2017 and February 2019. Participants were required to own an Apple Watch and iPhone and to install the study app that used an irregular pulse notification algorithm. If the pulse algorithm registered an irregular tachogram, sampling frequency was increased. If 5 out of 6 tachograms within a subsequent 48-hour period were irregular, a notification was sent to the participant, who would be recommended to contact a study physician by video consultation. As a result, 658 participants (0.16% of total) received an ECG patch by mail to wear for up to 7 days, of which 450 were returned for analysis (23% women; 40% >65 years).

Of the 450 participants who returned ECG patches, 18 patients had heart rates >200 bpm, 1 had a pulse pause of >6 seconds, and 1 had ventricular tachycardia for >6 seconds. In this study, 153 (34%) of the returned ECG patches confirmed AF. Among participants who were notified of an irregular pulse, the positive predictive value was 0.84 (95% CI 0.76-0.92) for observing AF on the ECG simultaneously with a subsequent irregular pulse notification. Among 297 participants who were shown to not have AF, 74 (25%) did have premature atrial contraction burden between 1-15%, and 4 (1.3%) participants had a burden of >15%. High-grade atrioventricular block episodes were identified in 3 patients that were linked to transient sinus slowing that lasted <4 seconds. In addition, 2 individuals were identified with premature ventricular contractions of >15%, and 11 participants (3.7%) had an episode of ventricular tachycardia for >8 heartbeats. The investigators concluded that the wearable technology had adequate sensitivity to detect AF as well as rarer arrhythmias in the general population and that this approach could potentially identify asymptomatic individuals at significant risk and direct them to specialised care.

1. Perez MV, et al. Apple Watch App Identifies Clinically Important Arrhythmias Other Than Atrial Fibrillation: Results From the Apple Heart Study. FS.AOS.04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
2. Perez MV, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. N Engl J Med 2019;381:1909-1917.

Early apixaban safe as secondary prevention of stroke from AF

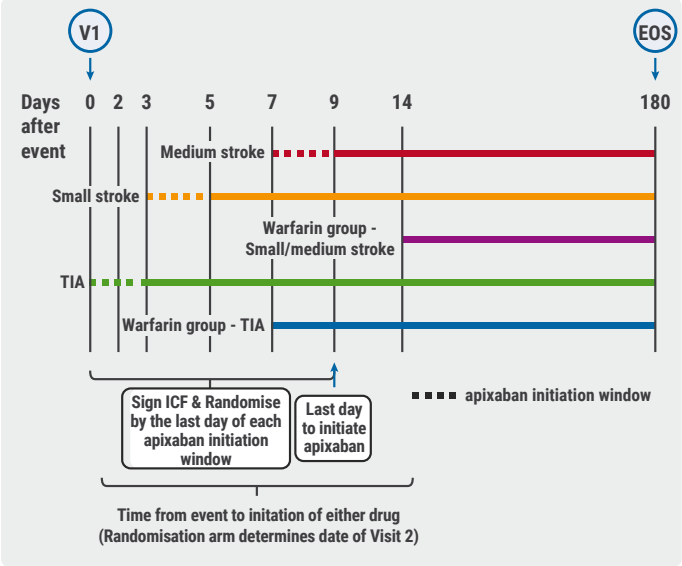
Dr Arthur Labovitz (University of South Florida, USA) presented the initial results of the pilot, open-label, parallel-group, multicentre, randomised controlled Apixaban for Early Prevention of Recurrent Embolic Stroke and Hemorrhagic Transformation (AREST) trial [1].

The study intended to determine the optimal timing of anticoagulation initiation after atrial fibrillation (AF)-induced acute ischaemic stroke (AIS), which is associated with larger infarct volumes. Previous landmark randomised trials have all waited weeks or months to begin anticoagulation after a stroke, but this trial aimed to establish the clinical value of early intervention. To that end, the safety and efficacy of early anticoagulation were evaluated based on stroke size, secondary prevention of ischaemic stroke, and risks of subsequent haemorrhagic transformation.

Patients were randomised 1:1 to receive early apixaban (n=41) at day 0–3 for transient ischaemic attack (TIA), day 3–5 for small-sized AIS (<1.5 cm), and day 7–9 for medium-sized AIS

(≥1.5 cm but less than a full cortical territory), or warfarin (n=47) at 1 week post-TIA or 2 weeks after a small or medium stroke (see Figure). Patients with large AIS were excluded. Enrolment was suspended prematurely after a 2019 guideline update recommended direct oral anticoagulants over warfarin in AF, excepting valvular disease.

Figure: Study schedule for the AREST study (V1 = visit 1, time 0; EOS = end of study, day 180) [2]



The primary study outcome was a composite of recurrent ischaemic stroke, TIA, or fatal stroke. Key secondary outcomes were intracranial haemorrhage, haemorrhagic transformation of ischaemic stroke, cerebral microbleeds, neurologic disability (e.g. modified Rankin Scores [mRS], National Institutes of Health Stroke Scale [NIHSS], Stroke Specific Quality of Life scale [SS-QOL]), and cardiac biomarkers (e.g. AF burden, transthoracic echo/transoesophageal echo abnormalities).
At 180 days of follow up, although not statistically significant, early intervention with apixaban resulted in empirically fewer recurrent ischaemic strokes, TIAs, or fatal strokes (19.5% vs 27.7%; P=0.46). Early apixaban use was not associated with increased risk of intracranial bleeding or any of the other secondary outcomes. Dr Labovitz concluded that the early use of apixaban is safe in this patient population and may potentially be associated with improved outcomes, although further studies are warranted.

1. Labovitz AJ, et al. Apixaban for early prevention of recurrent embolic stroke and hemorrhagic transformation in patients with atrial fibrillation: results of the AREST trial. FS.AOS.04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
2. Rose DZ, et al. Protocol for AREST: Apixaban for Early Prevention of Recurrent Embolic Stroke and Hemorrhagic Transformation—A Randomized Controlled Trial of Early Anticoagulation After Acute Ischemic Stroke in Atrial Fibrillation. Front Neurol. 2019;10:975.

Carvedilol does not improve exercise performance in Fontan patients

Dr Ryan Butts (University of Texas Southwestern, Dallas, USA) presented the results of a double-blind, placebo-controlled, cross-over trial of carvedilol in single-ventricle patients with Fontan physiology [1]. The rationale behind the trial was that beta-blockers may ameliorate the increased circulating catecholamines in these patients and, consequently, improve their exercise performance; however, no difference was observed between the 2 arms.

The study enrolled 26 single-ventricle patients between 10-35 years old with a previous Fontan operation who were able to complete a maximal exercise test (respiratory exchange ratio [RER] >1.0). Two 12-week treatment arms were separated by a period of 6 weeks for drug washout. Exercise testing was performed at the beginning and end of each treatment arm. Study drug was increased to a goal maximum dose (0.2-0.3 mg/kg/dose twice daily). The primary study outcome was an improvement in peak oxygen consumption/kg (pVO_2) from the baseline measurement.

Out of the 26 participants, 23 were able to complete the study. In the carvedilol arm, 4 subjects were unable to reach the maximum dose, as compared with a single participant in the placebo arm (P=0.14). The primary outcome was not met; the mean change in pVO_2 between treatments was not different (-2.1 mL/kg/min in the carvedilol arm vs -1.42 in the placebo arm; P=0.28). The peak heart rate decreased in subjects taking carvedilol (P<0.01) leading to a subsequent increase in peak oxygen pulse (P<0.01). No differences were reported for ventilatory efficiency (slope of VE/VCO_2 curves), oxygen uptake efficiency, or maximum work performed. Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels increased with carvedilol (mean +23.77 pg/mL) compared with the placebo arm (mean -5.37 pg/mL; P=0.03).

No serious adverse events were observed in the carvedilol arm. Dr Butts concluded that carvedilol had a safe tolerability profile in the majority of subjects with Fontan physiology, despite not being associated with improved exercise performance. Furthermore, carvedilol was associated with mildly increased levels of NT-proBNP. In brief, this study suggests that there is no indication for carvedilol in healthy Fontan patients. The role of potential carvedilol therapy in Fontan patients with heart failure may warrant additional research.

1. Butts RJ, et al. Carvedilol Does Not Improve Exercise Performance in Fontan Patients: Results of a Cross Over Trial. FS.AOS.04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Testosterone gel increases left ventricular mass

Dr Elizabeth Hutchins (UCLA, USA) reported the first-ever, double-blind, randomised controlled trial to measure the effect of testosterone therapy on left ventricular (LV) mass in humans. The multicentre, placebo-controlled Testosterone Cardiovascular Trial reported that treating hypogonadism in older men with testosterone gel boosted their LV mass by 3.5% within 1 year [1].

Dr Hutchins presented new findings on the effect of treatment with 1% topical testosterone gel (AndroGel) on body surface area–indexed LV mass. Men over the age of 65 with low serum testosterone (n=123) were randomised to apply either testosterone gel or placebo. Coronary CT angiography was performed at baseline, and again after 1 year. The study cohort was complex and had significant comorbidities; >80% of the men were above age 75, half were obese, >65% had hypertension, and 30% had diabetes.

Serum testosterone was measured every 3 months in all participants. Testosterone levels in the men assigned to the testosterone gel arm rapidly normalised and remained stable in the normal range for the full 12-month study period, whereas the placebo-treated participants continued to manifest low testosterone levels throughout the study period.

In the testosterone gel arm, participants' LV mass indexed to body surface area rose by 3.5%, from an average of 71.5 g/m^2 at baseline to 74.8 g/m^2 at 1 year (P=0.033), whereas no changes were detected in the LV mass of the placebo group. No changes were observed in the left or right atrial or ventricular chamber volumes in either arm.

Given evidence from animal and observational human studies that increased LV mass can be associated with increased mortality, Dr Hutchins concluded that topical testosterone application should be prescribed to patients cautiously and after careful consideration.

1. Hutchins E, et al. Randomized controlled trial of testosterone treatment on left ventricular mass in older men with low testosterone. FS.AOS.04, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

New Frontiers in Lipid Therapy

Icosapent ethyl plus statins reduces total plaque volume

The pre-specified, interim, 9-month follow-up analysis from the EVAPORATE trial suggests that icosapent ethyl 4 g/day did not reduce low attenuation plaque volume compared with placebo, although it did reduce total plaque volume, as assessed by coronary CT angiography.

Prof. Matthew J. Budoff (UCLA, USA) presented the early results from EVAPORATE, which aimed to assess the efficacy of icosapent ethyl in addition to statin therapy in reducing plaque burden among patients with known angiographic coronary artery disease [1].

Patients between 30-85 years of age with persistently high triglycerides (135-499 mg/dL) were randomised 1:1 to either icosapent ethyl 4 g/day (n=40) or placebo (n=40). In each arm, 30% had a family history of coronary artery disease. The primary outcome was the percentage change in low attenuation plaque volume.

At 9 months follow-up, the primary outcome was not met; the icosapent ethyl arm had 94% change in low attenuation plaque volume, whereas participants in the placebo arm had a mean 74% change (P=0.47). No differences were observed either for the secondary outcome of change in fibrofatty plaque volume: 25% versus 87% (P=0.65). However, the other secondary outcome of total plaque volume was significantly reduced by 26% in the icosapent ethyl arm versus 15% in the placebo arm (P=0.0004).

In conclusion, the results of this trial at 9 months indicate that icosapent ethyl 4 g/day does not reduce low attenuation plaque volume compared with placebo but does reduce total plaque volume, as assessed by coronary CT angiography. The planned total duration of follow-up is 18 months, which may yet alter these preliminary data analysed at 9 months.

1. Budoff MJ, et al. EVAPORATE- Effect of icosapent ethyl on progression of coronary atherosclerosis in patients on statin therapy with elevated triglycerides. LBS06, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

ORION-9: Inclisiran RNAi halves LDL in familial hypercholesterolaemia patients

The phase 3 ORION-9 trial data demonstrated that the novel lipid-lowering drug inclisiran halved low-density lipoprotein (LDL) levels in patients with familial hypercholesterolaemia (FH) [1].

Prof. Frederick Raal (University of the Witwatersrand, South Africa) presented the placebo-controlled 18-month follow-up data of 482 patients with diagnosed FH (half had genetic variants of the LDL receptor, 5% had apolipoprotein B variants, 1 patient had a *PCSK9* gain-of-function variant, 7% had 2 different gene variants, and 24% had no detected gene variant). All subjects had LDL levels higher than 100 mg/dL (mean 150 mg/dL), and almost all were already taking maximum tolerated doses of statins (90% of patients; 80% were on high-intensity statin treatment) with or without ezetimibe (50% of patients). Participants were randomly assigned to receive subcutaneous injections of inclisiran 300 mg or placebo at day 1 and day 30, thereafter every 6 months for 18 months.

The primary outcome at both prespecified time points (day 510, and time average day 90-540) was LDL reduction. The primary endpoint was met at both timepoints: the absolute mean reduction in LDL in the inclisiran arm was 71 mg/dL at day 510 (50% reduction compared with placebo; P<0.0001) and 63 mg/dL over the time average period (45% reduction compared with placebo; P<0.0001).

The novel mode of action of inclisiran is that it works to interfere with translation of the PCSK9 protein and is selectively taken up by the liver, resulting in an exceptionally long duration of action, requiring dosing only twice yearly. As such, Prof. Raal concluded, "inclisiran shows potential to address the unmet need of high-risk FH patients."

1. Raal F, et al. Safety and efficacy of inclisiran in patients with heterozygous familial hypercholesterolemia. LBS06, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

New RNAi therapies to reduce triglycerides: 2 studies show favourable results

According to preliminary data from 2 new therapies utilising RNA interference (RNAi) to reduce cellular levels of proteins involved in lipoprotein metabolism (apolipoprotein C-III [*APOC3*] or angiopoietin-like protein 3 [*ANGPTL3*]), plasma triglycerides and cholesterol levels were reduced in healthy volunteers for prolonged periods of time. Furthermore, in the case of the *APOC3*-silencing therapy, these reductions were coupled with an increase in high-density lipoprotein cholesterol (HDL-C).

Presenting the phase 1 and 2 study targeting *APOC3*, Prof. Christie Ballantyne (Baylor College of Medicine, USA) focused on the safety and tolerability of the RNAi therapy given as a single dose or 2 monthly doses [1]. Likewise, presenting the phase 1 and 2 study targeting *ANGPTL3*, Prof. Gerald Watts (University of Western Australia, Australia) showed the durability of that RNAi [2].

Invited discussant for both presentations, Prof. Daniel J. Rader (University of Pennsylvania, USA), compared the 2 studies head-to-head. The dose ranges were 10-100 mg for *APOC3* silencing and 35-300 mg for *ANGPTL3* silencing, which resulted in a maximum reduction in serum APOC3 protein levels of 94% versus 83% for ANGPTL3 protein levels. At the highest doses, silencing *APOC3* reduced triglyceride levels by 64%, whereas silencing the *ANGPTL3* gene did so by 66%. In both cases, these reductions were durable for at least 16 weeks. Silencing of *APOC3* and *ANGPTL3* decreased the mean maximum low-density lipoprotein (LDL) levels by 30% and 25%, respectively. One point of difference was that silencing *APOC3* was associated with an HDL-C increase of 52%, whereas *ANGPTL3* silencing decreased HDL levels by up to 16%. It is unclear what this discrepancy may indicate.

No serious adverse events were reported for either study. Although rare in frequency, reactions at the injection site did occur but were all mild. It remains to be investigated how these RNAi therapies compare to antibody- and antisense oligonucleotide-based methods that target the same proteins.

Prof. Radar concluded: "We are in a brave new world of RNAi therapeutics, a very interesting technology that is similar to but mechanistically different than antisense oligonucleotides." Here, the process is 'catalytic,' in that "the same molecule can go around and destroy multiple aspects of the RNAs in a way that provides substantial longevity in terms of their duration of effect."

1. Ballantyne C, et al. RNA interference targeting apolipoprotein C-III results in deep and prolonged reductions in plasma triglycerides. LBS06, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
2. Watts GF, et al. RNA interference targeting hepatic angiopoietin-like protein 3 results in prolonged reductions in plasma triglycerides and LDL-C in human subjects. LBS06, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

Targeting LDL-C <70 mg/dL is better than 100 mg/dL after stroke

A large trial evaluated the reduction in cardiovascular (CV) events by targeting low-density lipoprotein cholesterol (LDL-C) <70 mg/dL after atherothrombotic ischaemic stroke compared with a target of LDL-C 100 ± 10 mg/dL, concluding that treating to target LDL-c <70 mg/dL confers a lower risk of recurrent ischaemic events.

The Treat Stroke to Target trial 3.5-year follow-up data were presented by Prof. Pierre Amarenco (Xavier Bichat Medical School and Denis Diderot University, France) [1]. This open-label trial randomised patients who had had an atherothrombotic ischaemic stroke in the past 3 months or a transient ischaemic attack (TIA) in the past 15 days (n=2,860) to either a LDL-C target of <70 mg/dL or a target of 100 mg/dL (±10 mg/dL) using statins and/or other lipid lowering therapy (e.g. ezetimibe).

The primary endpoint was a composite of ischaemic stroke, myocardial infarction (MI), new symptoms requiring urgent coronary or carotid revascularisation, and death. The primary endpoint occurred in 8.5% patients in the arm targeting <70 mg/dL versus 10.9% of patients in the target 100 mg/dL arm (adjusted HR 0.78; 95% CI 0.61-0.98; P=0.036; see Table). A large number of secondary endpoints were also evaluated (see Table).

The authors concluded that after an atherothrombotic ischaemic stroke, targeting LDL-C <70 mg/dL lowered the risk for CV events more than the 100±10 mg/dL target. The results were recently published in full in the *New England Journal of Medicine* [2].

Table: Primary and secondary endpoint results comparing the 2 LDL-C targets of the Treat Stroke to Target trial

	LDL-C <70 md/dL (n=1,430)	LDL-C 100 mg/dL (n=1,430)	HR (95% CI)	P-value
Primary endpoint n (%)				
Major cardiovascular event, i.e. Death from cardiovascular causes Nonfatal cerebral infarction or stroke of undetermined origin Nonfatal acute coronary revascularisation Urgent coronary revascularisation Urgent carotid revascularisation	121 (8.5)	156 (10.9)	0.78 (0.61-0.98)	P=0.036
Secondary endpoints n (%)				
Myocardial infarction or urgent coronary revascularisation	20 (1.4)	31 (2.2)	0.64 (0.37-1.13)	P=0.12*
Cerebral infarction or urgent revascularisation of carotid or cerebral artery	88 (6.2)	109 (7.6)	0.81 (0.61-1.07)	-
Cerebral infarction or TIA	120 (8.4)	139 (9.7)	0.87 (0.68-1.11)	-
Any revascularisation procedure (i.e. coronary, carotid, or peripheral artery)	94 (6.6)	99 (6.9)	0.93 (0.70-1.24)	-
Death due to cardiovascular cause	22 (1.5)	32 (2.2)	0.69 (0.40-1.18)	-
Death due to any cause	88 (6.2)	93 (6.5)	0.97 (0.73-1.30)	-
Cerebral infarction or intracranial haemorrhage	103 (7.2)	126 (8.8)	0.82 (0.63-1.07)	-
Intracranial haemorrhage	18 (1.3)	13 (0.9)	1.38 (0.68-2.82)	-
Newly diagnosed diabetes	103 (7.2)	82 (5.7)	1.27 (0.95-1.70)	-
Primary outcome or intracranial haemorrhage	133 (9.3)	165 (11.5)	0.80 (0.63-1.00)	-

* P values for additional secondary endpoints were not calculated, as there was no significant between-group difference for the first endpoint on hierarchical testing

HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischaemic attack.

1. Amerenco P, et al. Treat stroke to target- Benefit of a target LDL cholesterol less than 70 mg/dl after ischemic stroke due to atherosclerosis. LBS06, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
2. Amarenco P, et al. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. N Engl J Med 2020 Jan 2;382(1):9.

Challenges in Heart Failure Management

FUEL trial: Udenafil improves some exercise measurements in Fontan

In The Fontan Udenafil Exercise Longitudinal Trial (FUEL), udenafil treatment was not associated with an improvement in oxygen consumption at peak exercise in patients with Fontan physiology; however, multiple measures of exercise performance at the ventilatory anaerobic threshold did show marked improvements.

Dr David Goldberg (Children's Hospital of Philadelphia, USA) presented the 30-centre phase 3 clinical trial that attempted to address a problem resulting from the Fontan physiology, which can lead to deterioration of cardiovascular efficiency associated with a decline in exercise performance [1]. The researchers hypothesised that udenafil may improve exercise performance. The primacy efficacy endpoint of this study was a between-group difference in the change in oxygen consumption (VO_2) from baseline to 26 weeks at peak exercise. Key secondary endpoints included myocardial performance index, exercise measures at ventilatory equivalents of CO_2 at anaerobic threshold, brain natriuretic peptide, and reactive hyperaemia index.

Between 2017 and 2019, adolescents with Fontan physiology (n=400) were randomised to either udenafil 87.5 mg twice daily or placebo. The mean age was 15.5 ±2 years, and 60% of participants were male. All 400 participants were included in the primary analysis with imputation of the 26-week endpoint for 21 participants with missing data (i.e. 11 randomised to udenafil and 10 to placebo).

The primary efficacy endpoint was not met: peak oxygen consumption was not significantly changed, increasing by 44 ±245 mL/min (2.8%) in the udenafil arm and declining by 3.7 ±228 mL/min (-0.2%) in the placebo arm (P=0.071). However, improvements in the udenafil group versus the placebo group were evident in some of the secondary endpoints, including mean oxygen consumption (+33 ±185 [3.2%] vs -9 ±193 [-0.9%] mL/min, respectively; P=0.012), ventilatory equivalents of CO_2 (-0.8 vs -0.06, respectively; P=0.014), and work rate (+3.8 vs +0.34 Watts, respectively; P=0.021). No differences were observed in the other secondary endpoints.

In conclusion, although the primary endpoint was not met, some benefits from udenafil treatment were observed in the secondary efficacy endpoints in patients with Fontan physiology, which may warrant further investigation.

1. Goldberg DJ et al. Longitudinal results from the Pediatric Heart Network: effect of udenafil on exercise performance after Fontan. LBS.05, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.

DAPA-HF: Dapagliflozin also good for heart failure patients without diabetes, of any age, or any health status

In heart failure patients with reduced ejection fraction (HFrEF), dapagliflozin in addition to standard therapy reduced the risk of worsening cardiovascular (CV) events and CV death while simultaneously improving symptoms. This benefit was seen in patients both with and without type 2 diabetes mellitus (T2DM), across all age groups, and without association to the health status of the patient at enrolment.

The main results of DAPA-HF trial were presented by Prof. John J. McMurray (Cardiovascular Research Centre, Scotland) [1]. The goal of this phase 3, randomised, double-blinded trial was to evaluate 10 mg/day dapagliflozin (a sodium-glucose cotransporter 2 [SGLT2] inhibitor) + standard therapy versus placebo + standard therapy in HFrEF patients. Specifically, investigators wanted to determine whether adverse outcomes could be prevented in non-diabetic patients in addition to patients with T2DM. The results were recently published in the *New England Journal of Medicine* [2]. Two additional prespecified sub-analyses, looking at age and health status, were also presented at the AHA Scientific Sessions [3,4].

The primary outcome was the composite of CV death, hospitalisation for heart failure, or urgent heart failure visit. Key secondary outcomes were separate evaluation of CV death, hospitalisation for heart failure, and worsening of renal function.

In total, 4,744 HFrEF patients with and without T2DM were enrolled with a median follow-up of 18.2 months. Primary outcome events occurred in 16.3% of the dapagliflozin group compared with 21.2% of the placebo group (P<0.001), which translated to a reduction of 26% for the combined endpoint of CV death and worsening of heart failure, alongside standard of care (see Table).

Table: Relative benefit of dapagliflozin as compared with placebo in patients with and without type 2 diabetes mellitus

Dapagliflozin vs placebo	T2DM HR (95% CI)	No T2DM HR (95% CI)
Composite outcome	0.75 (0.63–0.90)	0.73 (0.60–0.88)
Cardiovascular death	0.79 (0.63-1.01)	0.85 (0.66-1.10)
Worsening heart failure	0.77 (0.61-0.95)	0.62 (0.48-0.80)

HR, hazard ratio; T2DM, type 2 diabetes mellitus.

The DAPA-HF cohort included 2,139 patients with T2DM (45%) and 2,605 without T2DM. Those with T2DM had a 21% reduction in CV death with dapagliflozin versus placebo, while the reduction was 15% in patients without diabetes. The relative benefit was reversed in worsening of heart failure: among patients with T2DM, there was a 23% reduction in events versus placebo, while there was a 38% reduction in heart failure events among those without diabetes.

Prof. Felipe A. Martinez (National University of Córdoba, Spain) presented a sub-analysis aimed to examine the effects of age on response to dapagliflozin versus placebo in the DAPA-HF cohort, which spanned the ages of 22-94 years [3]. The benefits of dapagliflozin were evident across all age groups when compared with placebo: 636 patients were <55 years old (13.4%; HR 0.87; 95% CI 0.60-1.28); 1,242 were ages 55-64 (26.2%; HR 0.71;95% CI 0.55-0.93); 1,717 were ages 65-74 (36.2 %; HR 0.76; 95% CI 0.61-0.95); and 1,149 were >75 years (24.2%; HR 0.68; 95% CI 0.53-0.88). The interaction between age and response was not significant ($P_{interaction}$=0.76). Results showed that the rate of the primary outcome –a composite of an episode of worsening heart failure or CV death– in each age group in the placebo group was 13.6%, 15.7%, 15.1%, and 18.0%, respectively, versus the dapagliflozin group: 11.8%, 11.4%, 11.4%, and 12.6, respectively [5]. Prof. Martinez said that "dapagliflozin was well tolerated, with no significant difference between dapagliflozin and placebo in any age group," and that the effects were consistent "both in terms of efficacy and safety." The investigators concluded that dapagliflozin has substantial clinical benefits in older as well as younger patients.

In a separate analysis of the DAPA-HF cohort, presented by Prof. Mikhail N. Kosiborod (Saint Luke's Mid America Heart Institute, USA), dapagliflozin was compared with placebo based on health status as determined by the Kansas City Cardiomyopathy Questionnaire (KCCQ) [4,6]. Data was available for 4,443 patients. Results showed that dapagliflozin versus placebo was associated with a 2.3-point increase in KCCQ overall summary score from baseline to 8 months (P<0.0001). However, dapagliflozin benefits were consistent across all tertiles of KCCQ total symptom scores: lowest tertile (HR 0.70; 95% CI 0.57-0.86), middle tertile (HR 0.77; 95% CI 0.61-0.98), and highest tertile (HR 0.62; 95% CI 0.46-0.83), with no significant association with any of the 3 tertiles individually ($P_{heterogeneity}$=0.52).

In conclusion, dapagliflozin was beneficial for symptomatic HFrEF patients and was associated with a reduction in CV deaths and heart failure events and improvement in symptoms. Age, diabetes, and baseline health status did not influence the benefit of dapagliflozin. There were no safety signals of concern. These trials will likely change the practice of treating patients with HFrEF with dapagliflozin.

1. McMurray JJ, et al. The dapagliflozin and prevention of adverse-outcomes in heart failure trial (DAPA-HF): results in non-diabetic patients. LBS.05, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
2. McMurray JJ, et al. DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008.
3. Martinez FA, et al. DAPA-HF- Effect of treatment based on age in the dapagliflozin and prevention of adverse-outcomes in heart failure. LBS.05, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
4. Kosiborod MN, et al. DAPA-HF- Effect of treatment measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) in the dapagliflozin and prevention of adverse-outcomes in heart failure. LBS.05, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
5. Martinez FA, et al. Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to Age. Circulation. 2020;141:100–111.
6. Kosiborod MN, et al. Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction: Results From the DAPA-HF Trial. Circulation. 2020 Jan 14;141(2):90-99.

PARAGON-HF: Benefits for women and lower ejection fraction

Two new analyses of the PARAGON-HF trial show that, in patients with heart failure with preserved ejection fraction (HFpEF) receiving sacubitril/valsartan compared with valsartan alone, women in particular had fewer hospitalisations due to HF [1]. In addition, patients with chronic HF and a left ventricular ejection fraction (LVEF) below the normal range also benefited [2].

The main results of PARAGON-HF were reported late last year; sacubitril/valsartan did not reduce the primary outcome of hospitalisation for cardiovascular (CV)-related death and HF in patients with HFpEF (EF >45%). The recent subgroup analyses of the trial examined the same primary outcome by gender and LVEF to detect any benefit for sacubitril/valsartan.

In the analysis based on gender, 2,479 women (mean age 74 years; mean LVEF 59%) and 2,317 men (mean age 72 years;

mean LVEF 56%) from the PARAGON-HF cohort were analysed separately. The results indicated that sacubitril/valsartan was associated with a reduction in the primary outcome in women (relative risk [RR] 0.73; 95% CI 0.59-0.90) but not men (RR 1.03; 95% CI 0.84-1.25; $P_{interaction}$=0.017); this was mainly driven by reductions in total HF hospitalisations (RR in women 0.67; 95% CI 0.53-0.85; RR in men 1.07; 95% CI 0.85-1.34; $P_{interaction}$=0.0046). There was no difference in CV mortality in women (HR 1.02; 95% CI 0.76-1.36) or men (HR 0.90; 95% CI 0.7-1.17; $P_{interaction}$=0.5763). No gender-based differences in quality of life, NYHA class, or renal function were observed.

In the second analysis, researchers assessed data in which patients from both the PARAGON-HF and PARADIGM-HF trials were stratified by EF. "We have recently completed the PARAGON-HF trial, and that allows us to take the data from both the PARAGON and the PARADIGM trials, which are the 2 large outcomes trials with sacubitril/valsartan and pool them in a prespecified pooled analysis," Prof. Scott D. Solomon (Harvard Medical School, USA) explained. "This allows for examination of the effect of sacubitril/valsartan across the full spectrum of ejection fraction."

PARADIGM-HF's design was sufficiently similar to PARAGON-HF to allow cross-study data pooling. This pooled analysis included 13,195 patients from both trials whose EFs were then stratified into the following EF groups:

- <22.5% (n=1,269; mean age 61 years; 19% women);
- 22.5-32.5% (n=3,987; mean age 63 years; 21% women);
- 32.5-42.5% (n=3,143; mean age 66 years; 24% women);
- 42.5-52.5% (n=1,427; mean age 71 years; 40% women);
- 52.5-62.5% (n=2,166; mean age 73 years; 54% women); and
- >62.5% (n=1,202; mean age 74 years; 63% women).

The study researchers assessed the primary endpoints for PARADIGM-HF (a composite of CV death or HF hospitalisation) and PARAGON-HF (a composite of total HF hospitalisations or CV death).

Sacubitril/valsartan was superior to renin-angiotensin system inhibition for CV death (HR 0.84; 95% CI 0.76-0.92), all-cause mortality (HR 0.88; 95% CI 0.81-0.96), HF hospitalisation (HR 0.84; 95% CI 0.77-0.91), and first CV death or HF hospitalisation (HR 0.84; 95% CI 0.78-0.9). However, the treatment effect of sacubitril/valsartan was greatest in patients with LVEF below the normal range ($P_{interaction}$=0.02), though the CV death benefit of sacubitril/valsartan was diminished in patients in the lower EF range.

The incidence of non-CV death was similar across all EF categories, although the proportion of patients with non-CV death when considered among total deaths was higher in patients at the highest end of the EF spectrum.

Invited discussant Prof. Lynne W. Stevenson (Vanderbilt University Medical Center, USA) summarised: "It appears that sacubitril/valsartan has impact to decrease hospitalisations for congestion across EF whether it is reduced or preserved, but perhaps disease progression and cardiac mortality present better targets if you have a low EF than if you have a preserved EF. It is particularly important that we understand the patients who benefit and how they benefit for all of the new therapies we are considering both for this and for dapagliflozin."

1. McMurray J, et al. PARAGON-HF - Effects of sacubitril/valsartan in women compared to me with heart failure and preserved ejection fraction. LBS.05, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.
2. Solomon S, et al. PARAGON-HF -Secondary analysis- Effect of sacubitril/valsartan across the spectrum of ejection fraction in heart failure. LBS.05, AHA Scientific Sessions 2019, 14-18 November, Philadelphia, USA.