Medicom International Conference Series in Cardiology

70th ACC Scientific Session

American College of Cardiology

15-17 MAY 2021

PEER-REVIEWED CONFERENCE REPORT

NODE-301 Trial: Positive After All?

Significant improvement in symptoms related to paroxysmal supraventricular tachycardia (PSVT) is resurrecting etripamil as a self-administered nasal spray a year after it failed to meet the primary endpoint.

read more on PAGE 3

RAFT-AF Trial

Rhythm control with catheter ablation and rate control with drugs and/or pacemaker performed similarly in patients with high-burden atrial fibrillation and heart failure for time to death or HF progression.

read more on PAGE 4

Reigniting the Omega-3 Debate

New data from the STRENGTH trial showed no benefit of a high-dose combined omega-3 fatty acid product in patients, in contrast to the previously reported REDUCE-IT trial.

read more on PAGE 15

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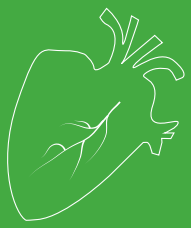
Editor Prof. Marc P. Bonaca, University of Colorado, USA

Contents



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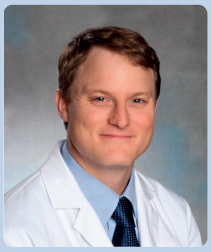
Letter from the Editor



Prof. Marc P. Bonaca

Dear colleagues,

We thank you for your interest in this edition of Medicom's Conference Reports focused on the 2021 American College of Cardiology (ACC) Annual Scientific Sessions. This year's ACC meeting was rich with late-breaking presentations and cutting-edge science.

Topics ranging from heart failure, vascular medicine, electrophysiology, and COVID 19 are covered. Late-breaking trials including PARADISE MI, DARE, REHAB-HF presented their primary results and are described in the following concise summaries. Important clinical trial updates including the total burden of vascular events in VOYAGER PAD and sex and outcomes from TWILIGHT are also presented.

We hope you find the following pages to be informative, concise, and balanced as our editorial team constantly strives to produce the highest quality summaries. Most of all, we hope you and your families are safe and healthy, we thank you for your contributions through this difficult time, and we hope to see you in person at upcoming events.

Sincerely,

Marc Bonaca

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
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Cardiology in COVID-19 times

Interview with ACC president
Dr Dipti Itchhaporia, MD, FACC,
conducted by Dr Kelly Schoonderwoerd

Dr Itchhaporia is the programme director of disease management at the Jeffrey M. Carlton Heart and Vascular Institute in California, USA, where she leads the congestive heart failure management programme and the anticoagulation clinic. She is also an associate professor at the University of California School of Medicine.

What was new or different in the way that the ACC scientific session was organised this year?

ACC.21 underscored the resilience of the global cardiovascular community and our ability to continue to conduct research, learn, and provide life-saving care to patients no matter the circumstances. ACC.21 was a robust meeting with 6 simultaneous "live" channels with over 100 presentations over 3 days, over 300 on-demand sessions featuring over 3,000 abstracts, and the ability to engage through live presenter chat and virtual networking sessions. And although nothing can replace the excitement and camaraderie that happens at an in-person conference, the shift to virtual allowed even those who may be unable to attend in person, to participate.

This year's theme was "Reimagine Global Heart Health." Can you expand on some areas that require reimagining?

A key response to the pandemic has been the large-scale deployment of telemedicine as a substitute for in-person care throughout the USA, and worldwide. Telehealth has quickly become a viable option for continuing to treat and manage patients.

Health equity is also part of how we are reimagining heart health. We need to recognise socioeconomic determinants of health and how they contribute to heart disease as the number one killer worldwide.

The ACC.2021 presented an extensive programme; which presentations do you consider to be particularly pivotal or ground-breaking?

ACC.21 featured several sessions addressing the COVID-19 pandemic and lessons learned to date, as well as several important sessions looking at health equity and social determinants of health in the context of patient care. We had an impressive line-up of Late-Breaking Clinical Trials and Featured Clinical Research. Two noteworthy ones were the ADAPTABLE trial and the ATLANTIS trial.

Your area of interest includes medical and lifestyle interventions; which presentations at the conference were especially relevant to the goal of prevention?

One that stood out for me was the Lancet Commission Report on the Global Burden of CV disease in women; it put forth 10 recommendations that provide an important framework and tangible actions that need to happen if we hope to save the lives of women around the globe.

What solutions would you like to see implemented towards health equity / improving access to care for underserved patients?

We have developed the ACC Presidential Health Equity Task Force to help actualise our health equity goals by focusing on 5 key areas:

1. improving access to care;
2. reducing systemic and structural barriers that cause health disparities;
3. addressing social, economic, educational, and environmental conditions that influence cardiovascular health;
4. leveraging established tools for change (e.g. education, public policy) and emerging new social technologies; and
5. strengthening partnerships with effective leadership organisations (e.g. the Association of Black Cardiologists, American Board of Internal Medicine, and the American Medical Association).

Given your focus on emerging risk factors, are there any conditions that you forecast will be occurring with greater frequency in the upcoming years?

Clinician wellness is a key area of focus now and in the future. The COVID-19 pandemic has exacerbated the pre-existing problem of clinician burnout. I predict that digital transformation will improve our lives.

Do you see a changing or expanding role for cardiologists, post-COVID?

COVID has reminded us that better health lowers risk for other diseases; therefore, our message of prevention of cardiac risk factors is more important than ever. Post-COVID, cardiologists will continue to implement telehealth in the management of heart disease across the continuum of care. It will be interesting to look back in 10 years to see how telehealth has transformed medicine and patient care.

Electrophysiology

Favourable outcomes with transcatheter atrial appendage occlusion

Real-world data from the National Cardiovascular Data Registry (NCDR) left atrial appendage occlusion (LAAO) registry showed a decrease in thromboembolic events 1 year after receiving a WATCHMAN implant [1]. These 1-year clinical outcomes suggest a favourable alternative to anticoagulants for patients with non-valvular atrial fibrillation who are unable to take oral anticoagulants.

The WATCHMAN device is a permanent device that is implanted into the left atrial appendage to prevent clot formation. It is used as an alternative to oral anticoagulant therapy for stroke prevention in atrial fibrillation for patients in whom oral anticoagulants are contraindicated. It was approved by the FDA in 2015 based upon favourable data from the PROTECT AF (n=463 implants) and PREVAIL (n=269 implants) trials [2,3]. It has also been approved for Medicare/Medicaid coverage in the US, but the eligibility criteria to qualify for reimbursement differ from the inclusion criteria used in the PROTECT AF and PREVAIL trials. Therefore, there was a need to monitor the clinical outcomes achieved under these different criteria and to assess long-term safety and effectiveness data.

Dr Matthew Price (Scripps Clinic, CA, USA) shared the results of the US national LAAO Registry, which examined the rates of thromboembolic and bleeding events at 1-year follow up in 36,681 patients who received a WATCHMAN device in 2016, 2017, and 2018. Kaplan-Meier estimated endpoints examined were the 1-year rates of ischaemic stroke (1.5%; 95% CI 1.4–1.7), major bleeding (6.2%; 95% CI 6.0–6.5), and mortality (8.5%; 95% CI 8.2–8.8). There was a 77% risk reduction in ischaemic stroke with LAAO compared with the expected rate as predicted by congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score.

Dr Price concluded that these data support the early-to-mid-term clinical effectiveness of transcatheter LAAO as it is currently being employed in the US.

1. Price M. One-year Clinical Outcomes Following Watchman Transcatheter Left Atrial Appendage Occlusion for Stroke Prevention in Patients with Atrial Fibrillation: A Report from The NCDR LAAO Registry. ACC 2021 Scientific Session, 15–17 May.
2. Reddy VY, et al. JAMA. 2014;312(19):1988–1998.
3. Holmes DR, et al. J. Am. Coll. Cardiol. 2014;64(1):1–12.

Etripamil nasal spray significantly improves PSVT-related symptoms

Etripamil, a novel, L-type calcium channel blocker, significantly improved symptoms of paroxysmal supraventricular tachycardia (PSVT) and reduced the need for emergency interventions in the phase 3 trial NODE-301. Users reported higher levels of satisfaction and effectiveness than with a placebo [1].

Dr Bruce Stambler (Piedmont Heart Institute, GA, USA) reiterated the results of the phase 3 NODE-301 trial (NCT03464019), which were previously shared at the 2020 Heart Rhythm Society meeting. The multicentre NODE-301 study evaluated etripamil's ability to terminate episodes of PSVT effectively and safely.

Participants with a history of ECG-documented PSVT were randomised in a 2:1 fashion to self-administer either intranasal etripamil (n=107) or placebo (n=49) during an episode of PSVT. The study population had a median age of 55 years and had a high burden and frequency of PSVT episodes over the past year, ranging from 7.4 episodes in the etripamil group to 11.3 in the placebo group. NODE-301 failed to meet its primary efficacy endpoint of superiority of a single, 70 mg dose of etripamil over placebo for a conversion of an episode of PVST over 5 hours (HR 1.09; 95% CI 0.73–1.62; P=0.12). A post-hoc secondary analysis was also performed, which considered the known pharmacology of etripamil with a rapid onset of action (within 5-10 minutes) and short duration of action (30-45 minutes). This analysis demonstrated a clinically meaningful early treatment effect with etripamil as compared with placebo; etripamil was significantly more effective than placebo at converting PSVT over the first 45 minutes after administration of the nasal spray (HR 1.67; 95% CI 1.03–2.7; P=0.02). Etripamil had an acceptable and favourable safety profile.

At ACC 2021, Dr Stambler discussed the secondary clinical endpoints of the NODE-301 trial, namely:

- the relief of PSVT-specific symptoms (such as heart palpitations, rapid pulse, chest pain, anxiety, shortness of breath, dizziness, and fainting);
- patient-reported satisfaction as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM-9);
- the need for any emergency interventions; and
- the need for any additional rescue medication therapy.

Etripamil was more effective than placebo at relieving PSVT specific symptoms. TSQM-9 scores for global satisfaction with treatment and treatment effectiveness were both significantly higher in the etripamil group than in the placebo group. In the etripamil group, 14% of participants sought additional medical therapy compared with 26.5% in the placebo group; most commonly, this consisted of intravenous adenosine administered in the emergency room. During the 5-hour observation period after administration of etripamil, 28 participants sought additional rescue medication intervention; 25 of these presented to the emergency room, and 5 self-administered oral rescue medications for PSVT. The time to emergency room intervention was longer in the etripamil group than in the placebo group (116±14 vs 79±10 minutes; P<0.05).

The researchers concluded that further development of etripamil nasal spray for the treatment of PSVT is supported by these favourable data.

1. Stambler BS. Etripamil Nasal Spray Relieves Symptoms and Reduces Emergency Room Interventions in Patients with Paroxysmal Supraventricular Tachycardia (PSVT). ACC 2021 Scientific Session, 15–17 May.

Ablation-based rhythm control as effective as rate control in AF and HF

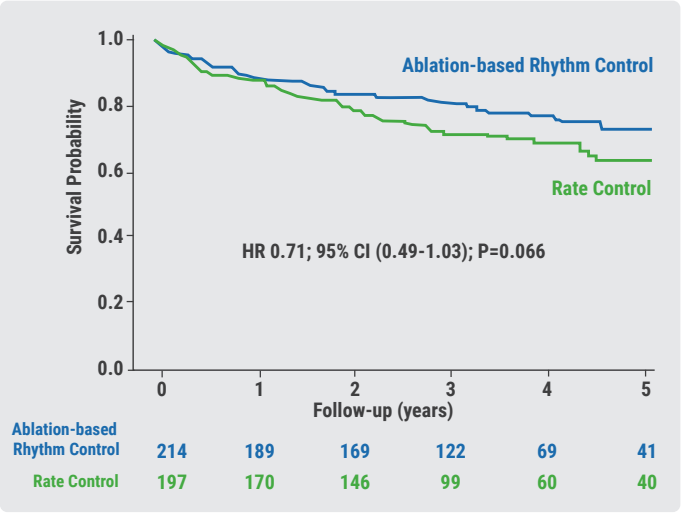
In patients with both atrial fibrillation (AF) and heart failure (HF), ablation-based rhythm control did not significantly reduce all-cause mortality or HF events when compared with rate control [1].

While catheter ablation offers an alternative to achieving rhythm control and resolving AF, no long-term studies have yet examined its effect on mortality and hospitalisations for HF. To address this gap, the RAFT-AF trial (NCT01420393) used a prospective, randomised, open-label, blinded endpoint (PROBE) design to compare catheter ablation-based AF rhythm control with rate control in participants diagnosed with both HF (stratified for reduced left ventricular ejection fraction [LVEF] of ≤45% or a preserved LVEF of >45%) and AF on the composite endpoint of all-cause mortality or HF events. An HF event was defined as admission to a healthcare facility for >24 hours, a significant worsening of HF requiring intervention, or receiving a previously unplanned intravenous diuretic and increased therapy for chronic HF.

Prof. Anthony Tang (University of Ottawa, Canada) shared the results of RAFT-AF. Participants with both HF and AF (n=411) were randomised to receive either ablation-based AF rhythm control (n=214) or rate control (n=197). Median follow-up period was 37.4 months.

From the 214 patients in the ablation-based rhythm control group, 50 (23.4%) participants reached the primary outcome compared with 64 (32.5%) participants in the rate control group. Although numerically fewer events were present in the ablation group, the difference was not statistically significant (HR 0.71; 95% CI 0.49–1.03; P=0.066) (see Figure).

Figure: Kaplan-Meier curves for the primary outcome of death and HF events in the RAFT-AF study [1]



Secondary outcomes included the Minnesota Living with Heart Failure questionnaire and the Atrial Fibrillation Effects on Quality of Life (AFEQT) scores. Changes from baseline in both scores were improved in both groups, but after adjusting for time and competing cause of death, a greater improvement was observed in the rhythm-control group than in the rate control group. All secondary outcome measures consistently showed the greatest improvement with rhythm control in the subgroup of patients with LVEF ≤45%. Adverse events occurred equally in the 2 groups: 99 patients (50.3%) in the rate control group and 102 patients (47.7%) in the rhythm-control group experienced a serious adverse events.

The safety profiles between these two treatment approaches were similar; approximately 50% from each treatment group experienced one or more serious adverse event. The researchers concluded that while the results demonstrated no statistically significant effect of ablation-based rhythm control over rate-based control in patients with AF and HF as a whole, there did appear to be some trends towards benefit in the LVEF ≤45% subgroup, which would require confirmation in subsequent studies.

1. Tang A. A randomised ablation-based atrial fibrillation rhythm control versus rate control trial in patients with heart failure and high burden atrial fibrillation (RAFT-AF). ACC 2021 Scientific Session, 15–17 May.

Finerenone reduces the risk of AF onset in patients with CKD and diabetes

An analysis of the FIDELIO-DKD trial demonstrated that finerenone decreased new-onset atrial fibrillation or flutter (AFF) in patients who have type 2 diabetes (T2D) and chronic kidney disease (CKD) irrespective of AFF history at baseline [1,2].

T2D and CKD are both promoters of AFF via structural and/or electrical remodelling, which is triggered by activation of mineralocorticoid receptors. Finerenone is a novel, non-steroidal, selective mineralocorticoid receptor antagonist with anti-inflammatory and anti-fibrotic effects.

Prof. Gerasimos Filippatos (Attikon University Hospital, Greece) presented a prespecified analysis of the FIDELIO-DKD trial (NCT02540993) [1]. The analysis examined the cardiorenal effects and impact of finerenone on new-onset AFF in participants with T2D and CKD. The multicentre, double-blinded, phase 3 FIDELIO-DKD trial randomised 5,674 participants to receive either finerenone or a placebo. Of the 5,674 participants, 461 (8.1%) had AFF at baseline, while 5,213 (91.9%) did not. Of the 5,213 participants with no pre-existing AFF, 2,593 (49.7%) received finerenone, and 2,620 (50.3%) participants received a placebo.

The primary endpoint was a composite of kidney failure, a sustained decrease of ≥40% in renal function, or renal death. The key secondary outcome was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure. Both endpoints were analysed by AFF history.

New-onset AFF occurred in 82 (3.2%) patients in the finerenone arm, and 117 (4.5%) patients in the placebo arm, yielding an incidence rate per 100 patient-years of 1.20 and 1.72, respectively, with a hazard ratio of 0.71 (95% CI 0.53–0.94; P=0.0164) and an absolute risk reduction of 1.3%. Prof. Filippatos noted that the following baseline characteristics seemed to have no impact on the protective effects of finerenone: age, sex, kidney characteristics, baseline serum potassium levels, systolic blood pressure, body mass index, glycated haemoglobin (HbA1c), nor use of glucose-lowering therapies. Baseline AFF did not appear to have a statistically significant impact on the effect of finerenone in either primary or secondary endpoints (P for interaction 0.16 and 0.85, respectively) [2].

One of the limitations of this study is that electrocardiograms were performed only once per year, raising the possibility that asymptomatic AFF may have been missed [3].

1. Fillipatos G. Finerenone And New Onset of Atrial Fibrillation or Flutter in Patients with Chronic Kidney Disease and Type 2 Diabetes. Abstract 411–16, ACC 2021 Scientific Session, 15–17 May.
2. Fillipatos G, et al. J. Am. Coll. Cardiol. 2021, May 17. DOI: 10.1016/j.jacc.2021.04.079.
3. Naccarelli GV, et al. J. Am. Coll. Cardiol. 2021, May 17. DOI: 10.1016/j.jacc.2021.04.080.

Heart Failure and Cardiomyopathy

PARADISE-MI: Sacubitril/valsartan not superior to ramipril in reducing HF events

Sacubitril/valsartan did not reduce the rate of cardiovascular (CV) death, heart failure (HF) hospitalisation, or HF in outpatients after acute myocardial infarction (MI) when compared with ramipril according to initial findings of the phase 3 PARADISE-MI trial [1].

Patients who have experienced MI are known to be at risk for subsequently developing HF. PARADISE-MI (NCT02924727) aimed to evaluate the efficacy and safety of sacubitril/valsartan, a first-in-class angiotensin receptor neprilysin inhibitor, compared with ramipril, an angiotensin-converting enzyme (ACE) inhibitor, in preventing the development of HF and CV death following MI [2].

PARADISE-MI was a multicentre, randomised, double-blind, active-controlled, parallel-group, phase 3 study, in which 5,669 patients with left ventricular systolic dysfunction and/or pulmonary congestion, but without prior history of chronic HF, were randomised to receive either sacubitril/valsartan (target dose of 97/103 mg twice daily; n=2,830) or ramipril (target dose of 5 mg twice daily; n=2,831) within 1 week of experiencing MI. The primary outcome was time to first

occurrence of the composite endpoint of CV death or HF requiring either hospitalisation or outpatient care. Prof. Marc Pfeffer (Brigham and Women's Hospital, USA) presented the preliminary results of the trial [1].

After a median follow-up period of 23 months, 338 (11.9%) patients in the sacubitril/valsartan arm and 373 (13.2%) in the ramipril arm had reached the primary endpoint, yielding a hazard ratio of 0.88 (95% CI 0.73–1.05; P=0.16). The safety profile between the 2 drugs was comparable, with 2,352 (83.1%) of patients in the sacubitril/valsartan arm and 2,325 (82.1%) of patients in the ramipril arm reporting adverse events. The top 2 adverse events experienced by those taking sacubitril/valsartan were hypotension (28.4%) and renal impairment (11.7%). The top 2 adverse events in the ramipril arm were hypotension (22.0%) and cough (13.1%).

Prof. Pfeffer concluded that sacubitril/valsartan showed a trend towards incremental benefit but did not significantly lower the rate of CV death, hospitalisation for HF, or outpatient HF requiring treatment when compared with ramipril. Both drugs were safe and well-tolerated.

1. Pfeffer MA. Prospective ARNI versus ACE inhibitor trial to determine superiority in decreasing heart failure events after myocardial infarction (PARADISE-MI). ACC 2021 Scientific Session, 15–17 May.
2. Eur J Heart Fail. 2021;Apr 12.DOI: 10.1002/ejhf.2191.

Mavacamten significantly improves QoL of patients with hypertrophic cardiomyopathy

Mavacamten improved the physical and social function and quality of life in patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM) compared with placebo, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ). Prof. John Spertus (Saint Luke's Mid America Heart Institute, MO, USA) presented a health status analysis of the previously published phase 3 EXPLORER-HCM trial results [1–3].

Current guideline-recommended pharmacological management of HCM mainly consists of β-blockers or calcium channel blockers. Mavacamten is a first-in-class myosin inhibitor that directly addresses the pathophysiological mechanism underlying HCM. The EXPLORER-HCM (NCT03470545) trial was a phase 3 randomised, double-blind, placebo-controlled study that compared mavacamten (n=123) with placebo (n=128) in patients with obstructive HCM [2].

Participants (mean age 59 years; 46% women; 5% with diabetes) received a once-daily dose of either mavacamten (starting dose of 5 mg with a 2-step dose titration) or placebo for 30 weeks followed by an 8-week washout period, for a total intervention of 38 weeks. The KCCQ was administered at baseline and again at weeks 6, 12, 18, 30 (end of treatment), and 38 (end of study) [2,3]. The KCCQ assess symptoms, physical function, social function, and quality of life. Scores range from 0 (i.e. poor score) to 100 (i.e. favourable score).
At week 30, 36% of participants in the mavacamten arm had achieved clinically meaningful improvements in their KCCQ score, as compared with only 15% of participants in the placebo arm. A greater proportion (23%) of patients in the placebo arm showed either no change or a deterioration in their KCCQ score, as compared with only 9% in the mavacamten arm. This benefit was no longer apparent at week 38 (i.e. following the washout period).

Prof. Spertus concluded that mavacamten represents a new potential strategy for improving symptoms, activities of daily living, and patient satisfaction.

1. Spertus JA. Health Status Benefits of Mavacamten In Patients with Symptomatic Obstructive Hypertrophic Cardiomyopathy: Results from the EXPLORER-HCM Randomised Clinical Trial. ACC 2021 Scientific Session, 15–17 May.
2. Olivotto I, et al. Lancet. 2020;396(10253):759–769.
3. Spertus JA, et al. Lancet. 2021;May 15. DOI: 1016/S0140-6736(21)00763-7.

Older adults with heart failure benefit from rehabilitation programme

In the REHAB-HF trial, older patients who experienced acute decompensated heart failure (HF) and participated in a physical rehabilitation programme achieved improvements in physical function, Kansas City Cardiomyopathy Questionnaire (KCCQ), and depression scores [1,2].

Older patients with acute decompensated HF are often physically frail, have a poor quality of life, and are frequently rehospitalised. Current guidelines fail to address physical functioning in older patients with acute decompensated HF. Accordingly, the REHAB-HF trial (NCT02196038) aimed to investigate the effects of a tailored, progressive rehabilitation programme in older adults who had been hospitalised for acute decompensated HF. Dr Dalane Kitzman (Wake Forest School of Medicine, NC, USA) presented the results.

The trial randomised 349 patients to either participate in the rehabilitation programme (n=175) or to receive usual care (n=174). The rehabilitation programme consisted of 36 sessions delivered over 12 weeks and encompassed

endurance, mobility, strength, and balance training. The primary outcome was a change in short physical performance battery (SPPB) score, which was assessed at baseline and upon programme completion. The SPPB tests standing balance, walking, and strength.

At 3 months, the least-squares mean score on the SPPB score was 8.3 in the rehabilitation group and 6.9 in the usual care group. This yielded a mean between-group difference of 1.5 (95% CI 0.9–2.0; P<0.001).

The secondary outcome was all-cause rehospitalisation within 6 months. The rehospitalisation rate at 6 months was not significantly different between the 2 groups, with 1.18 in the rehabilitation group and 1.28 in the usual care group (rate ratio 0.93; 95% CI 0.66–1.19).

Authors of a *New England Journal of Medicine* Editorial editors declared that "the results presented by Kitzman and colleagues provide a compelling argument for the adoption of exercise rehabilitation as standard care, even for elderly, frail patients with acute heart failure" [3].

1. Kitzman DW. A Novel Physical Rehabilitation Intervention for Older Patients with Acute Decompensated Heart Failure: The REHAB-HF Trial. ACC Scientific Session, 15–17 May 2021.
2. Kitzman DW, et al. N Engl J Med 2021;May 16. DOI: 10.1056/NEJMoa2026141.
3. Anker SD, Coats AJS. N Engl J Med Editorial 2021;May 16. DOI: 10.1056/NEJMe2106140.

Quality improvement intervention fails to improve care for patients with heart failure

A quality improvement intervention initiative designed to provide clinician education and feedback to enhance the quality of care failed to meaningfully improve outcomes for patients with heart failure (HF) over usual quality improvement processes in the CONNECT-HF trial [1].

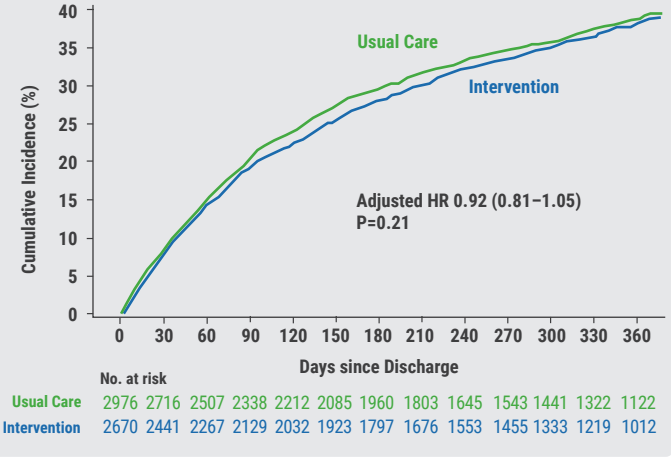
Outcomes in patients with heart failure with reduced ejection fraction (HFrEF) are suboptimal; patients with HFrEF experience a high symptom burden and high rates of rehospitalisation and death. These poor outcomes are due in part to poor implementation of guideline-directed medical therapy (GDMT).

In an attempt to provide data to inform best practices in hospitals and post-discharge quality improvement initiatives, a pragmatic, prospective, cluster-randomised trial was designed to compare the effectiveness of a customised, multifaceted, health system-level quality improvement programme with usual care on HF outcomes. The CONNECT-HF trial (NCT03035474), presented by Prof. Adam DeVore (Duke University School of Medicine, NC, USA) enrolled 161 hospitals across the USA who treated ≥50 patients with acute HF annually to either participate in a quality improvement programme (n=82) or proceed as per usual care pathways. These hospitals had treated a total of 5,647 patients for HF; after hospital randomisation, 2,675 of these patients were in the intervention arm while 2,972 were in the usual care arm.

The intervention consisted of 2 components: audit and feedback to hospitals with pre-existing quality improvement teams directed towards care pathways and outcomes, and education and mentorship to hospitals by the CONNECT-HF Academy, a team of experts on quality improvement and HF. The primary outcome measure was time to first HF rehospitalisation or death during the 12-month follow-up, and the co-primary endpoints were a composite of HF rehospitalisation or death and a change in an opportunity-based composite score for quality of HF care.

At the 12-month follow-up, there was no statistically significant difference in the primary outcome between the 2 groups (adjusted HR 0.92; 95% CI 0.81–1.05; P=0.21) (see Figure).

Figure: CONNECT-HF results for the primary outcome of heart failure rehospitalisation or death [1]



Similarly, no statistically significant difference was observed in the composite score for quality of HF care between the groups. Prof. DeVore highlighted some of the individual quality measures of this composite score, noting that the use of medical therapy did not improve beyond baseline measures following 12 months of intervention. Specifically, the use of ACE inhibitors, ARBs, ARNIs, β-blockers, and MRAs lagged well below target doses.

The researchers concluded that the quality improvement intervention of the CONNECT-HF based on clinician education, audit, and feedback failed to improve outcomes in patients with HFrEF above current quality improvement processes. Major gaps in GDMT remain, and new approaches are required to improve care.

1. DeVore A. Care optimization through patient and hospital engagement clinical trial for heart failure: primary results of the CONNECT-HF randomised clinical trial. ACC 2021 Scientific Session, 15–17 May.

Sacubitril/valsartan does not reduce NT-proBNP versus valsartan alone in HFrEF

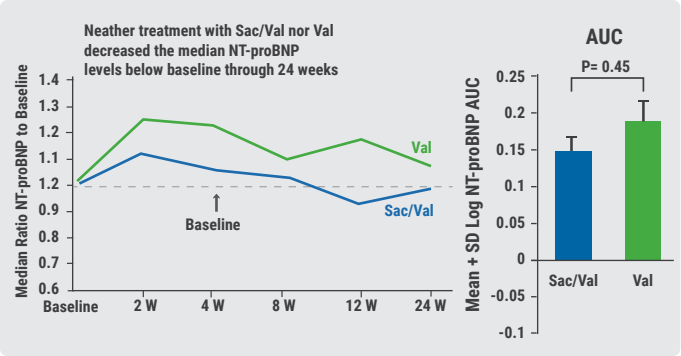
Sacubitril/valsartan was not superior to valsartan at lowering N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients with heart failure and reduced ejection fractions (HFrEF) in the phase 4 LIFE trial [1]. It also did not improve clinical outcomes or reduce the risk of death in these patients when compared with valsartan alone. There was a statistically significant higher risk of hyperkalaemia associated with sacubitril/valsartan.

Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor that demonstrated superior morbidity and mortality outcomes in patients with chronic HFrEF when compared with enalapril in the PARADIGM-HF trial [2]. However, very few (<1%) of the patients included in the PARADIGM-HF trial had advanced heart failure (defined as New York Heart Association [NYHA] class 4), and so evidence was lacking on the safety and efficacy of sacubitril/valsartan in this group of patients.

The LIFE trial (NCT02816736) was a phase 4, prospective, multicentre, double-blinded, double-dummy, active comparator trial that evaluated the efficacy of sacubitril/valsartan compared with valsartan alone at lowering NT-proBNP levels in patients with advanced HFrEF (NYHA class 4), following a 24-week intervention period. The researchers chose NT-proBNP level as the main outcome measure because it reflects haemodynamic and clinical status.

Prof. Douglas Mann (Washington School of Medicine, MO, USA) noted that the LIFE trial was impacted by the COVID-19 pandemic. They had originally planned to recruit 400 patients but were forced to suspend enrolment on 23 March 2020 due to the pandemic. As a result, their analysis was limited to 335 participants, 167 of whom were randomised to the sacubitril/valsartan arm, and the remaining 168 to the valsartan alone arm. The primary endpoint was the area under the curve (AUC) for the proportional change in NT-proBNP levels from baseline through 24 weeks. Neither of the groups decreased their median NT-proBNP levels to below baseline levels during the treatment period (see Figure).

Figure: Primary endpoint for the LIFE trial, AUC for the proportional change in the ratio of NT-proBNP levels to baseline [1]



AUC, area under the curve; NT-proBNP, pro-B-type natriuretic peptide.

Secondary endpoints included tolerability and an efficacy composite of the number of days that participants were:

- alive and not in hospital;
- neither listed for nor undergoing transplant;
- not implanted with a left ventricular device;
- not on inotropic therapy for ≥7 days; and
- not hospitalised twice for HF.

No differences in secondary endpoints between the groups were seen, except for a small but statistically significant increase in non-life-threatening hyperkalaemia in the sacubitril/valsartan arm (17% vs 9%; P=0.035).

The results do not demonstrate the superiority of sacubitril/valsartan over valsartan alone in lowering NT-proBNP levels in patients with advanced HFrEF.

1. Mann DL. Sacubitril/valsartan in patients with advanced heart failure with reduced ejection fraction (LIFE trial). ACC 2021 Scientific Session, 15–17 May.
2. McMurray JJV, et al. New Eng. J. Med 2014;371:993–1004.

Novel use of ivabradine in reversible cardiomyopathy

Ivabradine may reduce the risk of tachycardia-induced cardiomyopathy when used in refractory cases of tachycardia, as was suggested by findings from a case report [1].

Paragangliomas are rare tumours that result in persistent tachycardia and hypertension. Dr Eric Torkildsen (Lehigh Valley Health Network, PA, USA) shared a case report of a 62-year-old man with a history of metastatic hereditary

paraganglioma, non-ischaemic cardiomyopathy with recovered ejection fraction, and recent pericardial effusion, who presented with worsening dyspnoea and sinus tachycardia.

Echocardiographic findings included global hypokinesis, no evidence of re-accumulation of pericardial fluid, and a reduced ejection fraction of 20–25%. Angiographic findings demonstrated non-obstructive disease. Based on these findings, the patient was diagnosed with a hyperadrenergic state secondary to the hereditary paraganglioma.

Management with metoprolol succinate, phenoxybenzamine, and metyrosine failed to achieve rate control. Dr Torkildsen's team decided to try ivabradine, a hyperpolarisation-activated, cyclic, nucleotide-gated channel blocker, which lowers heart rate [2]. Ivabradine was titrated to a dose of 7.5 mg twice daily for 6 weeks; thereafter, echocardiographic findings showed a return to normal systolic function.

In conclusion, Dr Torkildsen stressed that early recognition and management of reversible cardiomyopathy is imperative to prevent cardiac remodelling and maximise chances of a favourable recovery. Management with ivabradine led to favourable outcomes in this presented case of a 62-year old gentleman with a hereditary paraganglioma and tachycardia-induced cardiomyopathy.

1. Torkildsen E. Novel use of ivabradine in the management of a catecholamine-induced cardiomyopathy secondary to a metastatic hereditary paraganglioma. ACC 2021 Scientific Session, 15–17 May.
2. Tse S, Mazzola N. Pharmacy & Therapeutics 2015;40(12):810–814.

Interventional and Structural Cardiology

Men and women benefit equally from early aspirin withdrawal following PCI

A recent subgroup analysis of the TWILIGHT trial showed that while post-percutaneous coronary intervention (PCI) bleeding occurs more frequently in women; this is mostly attributable to baseline differences. Recurrent ischaemic events were similar between the sexes [1,2].

The TWILIGHT study (NCT02270242) was a double-blind, placebo-controlled study comparing the use of ticagrelor plus aspirin with the use of ticagrelor plus placebo (ticagrelor monotherapy) for 1 year in high-risk patients who had undergone PCI and had already completed 3 months of dual antiplatelet therapy. TWILIGHT demonstrated that ticagrelor monotherapy reduced the risk of bleeding compared with dual antiplatelet therapy.

Dr Birgit Vogel (Icahn School of Medicine, NY, USA) presented a pre-specified analysis that explored heterogeneity of outcomes between the sexes (23.9% women). The investigators stratified ischaemic and bleeding outcomes by sex among the 7,119 randomised participants. The 2 endpoints of this analysis were a primary bleeding event (defined as Bleeding Academic Research Consortium type 2, 3, or 5), and a primary ischaemic event (defined as a composite of death, myocardial infarction, or stroke) at 1 year after randomisation.

Women more frequently experienced the primary bleeding endpoint than men (6.8% vs 5.2%; HR 1.32; 95% CI 1.06–1.64; P=0.01). However, after multivariable adjustment, this increased risk was no longer significant (adjusted HR 1.20; 95% CI 0.95–1.52; P=0.12). The rate of ischaemic endpoints was similar between the sexes.

The clinical benefits of aspirin withdrawal following 3 months of dual antiplatelet therapy with ticagrelor were comparable between men and women. However, there was a hypothesis-generating trend for lower mortality with ticagrelor monotherapy in women, but not in men.

1. Vogel B. Sex-Specific Outcomes in High-Risk Patients Receiving Ticagrelor with or without Aspirin After Percutaneous Coronary Intervention: Results from the TWILIGHT Study. ACC 2021 Scientific Session, 15–17 May.
2. Vogel B, et al. JAMA Cardiol. 2021;May 15. DOI: 10.1001/jamacardio.2021.1720.

Similar outcomes with fractional flow reserve and angiography-guided revascularisation

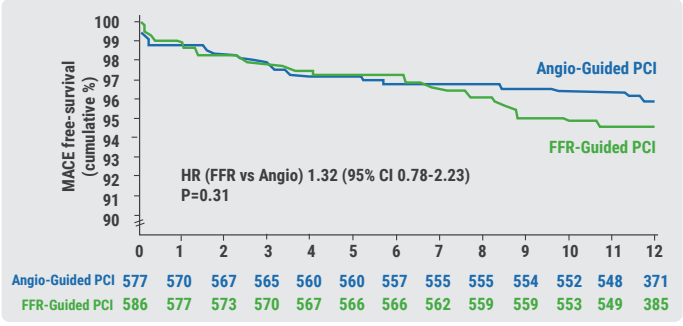
Fractional flow reserve (FFR)-guided revascularisation did not demonstrate benefit over angiography-guided revascularisation in the FLOWER-MI trial [1,2]. In patients with ST-elevated myocardial infarction (STEMI) and

multivessel disease (MVD), complete revascularisation is associated with better clinical outcomes than culprit lesion only revascularisation. However, it remained unclear whether FFR could be useful in guiding revascularisation of non-culprit lesions in STEMI patients with MVD.

Angiography-based visual assessment of the degree of coronary artery stenosis is not a reliable indicator of haemodynamically significant obstruction; therefore, FFR can help guide appropriate decisions regarding percutaneous coronary intervention (PCI) of those vessels with significant lesions. However, trials investigating the use of FFR-guided revascularisation in patients with STEMI and MVD were lacking. To this end, the FLOWER-MI study (NCT02943954) randomised 1,163 patients to either angiography-guided PCI (n=577) or FFR-guided PCI (n=586). The study enrolled participants with STEMI who had undergone successful PCI and were judged to have at least 1 additional non-culprit lesion for which revascularisation could be recommended.

The primary outcome was the rate of major adverse cardiovascular events (i.e. composite of all-cause mortality, non-fatal myocardial infarction, and unplanned hospitalisation resulting in urgent revascularisation) at 1 year. This outcome occurred in 32 (5.5%) participants in the FFR arm and 24 (4.2%) participants in the angiography arm, yielding a hazard ratio of 1.32 (95% CI 0.78–2.23; P=0.31) (see Figure).

Figure: Primary outcome (MACE at 1 year) in the FLOWER-MI trial. Adapted from [2]



Angio, angiography; CI, confidence interval; HR, hazard ratio; FFR, fractional flow reserve; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention.

These results failed to demonstrate a benefit of FFR-guided revascularisation over angiography-guided revascularisation in patients with STEMI and MVD in reducing major adverse cardiovascular events. However, the researchers caution that the wide confidence interval precludes any definitive conclusions.

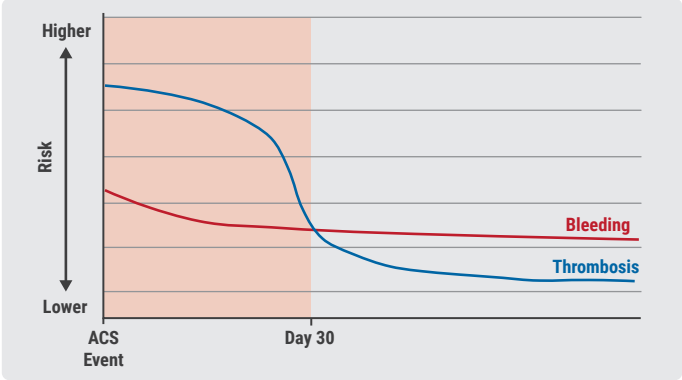
1. Puymirat E. Fractional Flow Reserve-guided Versus Angio-guided Multivessel Revascularization In ST-Elevation Myocardial Infarction Patients. The FLOWER-MI Randomised Trial. Abstract 407-08, ACC 2021 Scientific Session, 15–17 May.
2. Puymirat E. N Engl J Med 2021;May 16. DOI:10.1056/NEJMoa2104650.

TALOS-AMI: Exploring outcomes after switching to clopidogrel versus ticagrelor at 1 month from MI

The open-label, non-placebo controlled TALOS-AMI study raises the hypothesis that net outcomes (i.e. bleeding and ischaemic) may be similar in selected patients by switching at 1 month from myocardial infarction (MI) [1].

The risk of thrombosis is highest in the first 30 days following acute MI. Bleeding is also higher; however, the curve may be less steep depending on patient bleeding risk and experience with prior antithrombotics, (see Figure) [2]. Currently, patients who have experienced acute MI followed by PCI receive DAPT with aspirin and a $P2Y_{12}$ inhibitor. It was unknown whether de-escalation to a less potent, more variable $P2Y_{12}$ inhibitor following the 30-day post-PCI would be associated with less bleeding.

Figure: The risk of thrombosis versus bleeding following acute myocardial infarction [2]



The TALOS-AMI trial (NCT02018055) aimed to address this question. The open-label study, presented by Prof. Kiyuk Chang (Seoul St. Mary's Hospital, South Korea), compared outcomes of 2,679participants who, after 1 month of taking aspirin plus ticagrelor following acute MI and PCI, were randomised to clopidogrel (n=1,349) versus ticagrelor (n=1,348). Participants were monitored for 11 months (i.e. 1 year following MI and PCI).

The primary outcome was a composite of cardiovascular death, MI, stroke, or bleeding academic research consortium (BARC) bleeding type 2, 3, or 5 between 1 month and 12 months post PCI. At 1 year, 59 (4.6%) primary outcome events had occurred in the clopidogrel group compared with 104 (8.2%) events in the ticagrelor group, yielding a hazard ratio of 0.55 (95% CI 0.40–0.76; P<0.001 for both non-inferiority and superiority).

Prof. Chang and colleagues concluded that in patients who had experienced AMI and had no adverse events in the first month following PCI, a de-escalation DAPT strategy in selected patients switching from ticagrelor to clopidogrel was associated with lower net outcomes versus continued DAPT using ticagrelor. This observation was driven mostly by non-severe bleeding events, and power to distinguish a cost in terms of ischaemic outcome was limited.

The researchers acknowledged that this trial had significant limitations; it was open-label and not placebo-controlled. In addition, it was underpowered to detect a difference in ischaemic risk, especially in contrast to the PLATO trial, which randomised more than 18,000 patients and demonstrated superiority of ticagrelor versus clopidogrel in ACS [3]. Additionally, the study was conducted entirely in South Korea, and there is a high prevalence of *CYP2C19* loss-of-function alleles in Koreans; for this reason, this de-escalation strategy should also be evaluated in a more heterogeneous population.

1. Chang K. A Prospective, Multi-centre, Randomised, Open-label Trial to Compare Efficacy and Safety of Clopidogrel Versus Ticagrelor in Stabilized Patients with Acute Myocardial Infarction After Percutaneous Coronary Intervention. Abstract 407-10, ACC 2021 Scientific Session, 15–17 May.
2. Rodriguez F, Harrington RA. N Engl J Med 2021 Feb 4;384(5):452–460.
3. Wallentin L, et al.N Engl J Med 2009;361:1045-1057.

Clopidogrel monotherapy associated with better net outcomes relative to aspirin monotherapy 6-18 months after PCI

The open-label HOST-EXAM study showed that clopidogrel monotherapy was associated with better net outcomes relative to aspirin in patients who were event-free for 6–18 months following percutaneous coronary intervention (PCI) with a drug-eluting stent (DES) over a 2-year follow-up period [1,2].

In patients who have undergone PCI, guidelines suggest 6–12 months of dual antiplatelet therapy (DAPT), typically with aspirin plus a $P2Y_{12}$ inhibitor such as clopidogrel. After the initial 6–12 month period, lifetime aspirin monotherapy is recommended. Prof. Hyo-Soo Kim (Seoul National University Hospital, South Korea) and colleagues aimed to explore whether an alternative monotherapy could achieve superior clinical outcomes compared with aspirin.

To address this question, the multicentre, open-label HOST-EXAM study (NCT02044250) randomised 5,438 patients who had completed 6–12 months of event-free DAPT following PCI; 2,710 (49.8%) participants were enrolled in the clopidogrel only group, and 2,728 (50.2%) were enrolled in the aspiring only group. Of the 2,710 participants in the clopidogrel only group, 62 were excluded from the per protocol analysis (8 withdrew consent, 41 were lost to follow-up, and 13 did not receive the allocated agent). Of the 2,728 participants in the aspirin only group, 73 were excluded from the per protocol analysis (1 withdrew consent, 50 were lost to follow-up, and 22 did not receive the allocated agent.) The remaining 5,338 participants were followed for 24 months.

The primary endpoint was a composite of all-cause death, acute coronary syndrome including non-fatal MI, stroke, the need for revascularisation while under antiplatelet therapy, or Bleeding Academic Research Consortium (BARC) type ≥3 bleeds. At 2 years, 152 (5.7%) primary endpoint events had occurred in the clopidogrel group compared with 207 (7.7%) in the aspirin group (HR 0.73; 95% CI 0.59–0.70; P=0.0035).

These results demonstrated that clopidogrel monotherapy was associated with better net outcomes, driven by bleeding, to aspirin monotherapy following an event-free 6–18 months period of DAPT after PCI with DES.

The researchers acknowledged several limitations of this trial. It was open-label and conducted only in South Korea. East Asians tend to have a higher prevalence of loss-of-function mutations of the CYP2C19 gene, yet they tend to have lower rates of thrombosis and higher rates of bleeding events following PCI (the "East Asian paradox") [1,3]. Furthermore, most of the enrolled patients had followed a DAPT regimen for about 1 year; thus, results may not be generalisable to those who have been on DAPT for a shorter period. The investigators have launched the HOST-EXAM extended study, which will continue to follow these participants for a median of 10 years [1].

1. Kim HS. Aspirin Vs. Clopidogrel During Chronic Maintenance Monotherapy After Percutaneous Coronary Intervention: The Host Exam Randomised Controlled Trial. Abstract 407-12, ACC 2021 Scientific Session, 15–17 May.
2. Koo BK, et al. Lancet. 2021;May 16. DOI: 1016/S0140-6736(21)01063-1.
3. Jeong YH. Curr Cardiol Rep. 2014;16(5):485.

Ischaemic Heart Disease

No difference in ischaemic risk or bleeding with low vs high-dose aspirin for secondary prevention: Lessons and questions from the ADAPTABLE trial

Low-dose aspirin (81 mg daily) was associated with similar rates of ischaemic events and bleeding events as high-dose aspirin (325 mg daily) in preventing stroke, myocardial infarction (MI), or death in patients with known atherosclerotic cardiovascular disease (ASCVD) according to the findings of the ADAPTABLE trial, but a high degree of cross over adds complexity to the results [1,2].

Prof. William Schuyler Jones (Duke Clinical Research Institute, NC, USA) presented the ADAPTABLE study (NCT02697916), which aimed to compare the effectiveness of 2 doses of aspirin at preventing major adverse cardiac events (MACE) in patients with ASCVD (defined as a history of prior MI, prior coronary angiography showing ≥75% stenosis of at least 1 epicardial coronary vessel or prior coronary revascularisation procedures, or history of chronic heart disease).

The ADAPTABLE trial was a pragmatic, open-label, patient-centred, randomised clinical trial conducted in 15,076 patients with ASCVD within the National Patient-Centered Clinical Research Network (PCORnet). Participants (n=15,067) were assigned to take either 325 mg of aspirin daily (n=7,536) or 81 mg of aspirin daily (n=7,540). The primary outcome was a composite of death from any cause, hospitalisation for MI, or hospitalisation for stroke.

After a median follow-up of 26.2 months, 590 (7.28%) participants in the 81 mg dosage arm and 569 (7.51%) participants in the 325 mg dosage arm had reached the primary endpoint (HR 1.02; 95% CI 0.91–1.14). The primary safety endpoint was hospitalisation for major bleeding. Less than 1% of the participants in either group experienced a significant bleed (53 or 0.63% in the 81 mg daily dose group and 44 or 0.60% in the 325 mg daily dose group). Participants could switch their dose of aspirin during the study if they chose to do so. Among the lower dose group, 7.1% of patients chose to switch to the higher dosage, while among the higher dose group, 41.6% chose to switch to the lower dose.

The researchers concluded that there were no observed differences in cardiovascular events or major bleeding between higher and lower dose of aspirin in patients with ASCVD. These findings stand in contrast to prior randomised trials in ACS (e.g. OASIS-7), which observed higher bleeding rates with high versus low dose aspirin. In this context, the high rate of cross over, particularly from higher to lower dose treatment, is an important limitation of the study.

1. Jones WS. Aspirin Dosing: A Patient-centric Trial Assessing Benefits And Long-term Effectiveness Trial (ADAPTABLE). ACC 2021 Scientific Session, 15–17 May.
2. Jones WS, et al. N Engl J Med 2021;384:1981-1990.

Rivaroxaban reduces total ischaemic events after peripheral artery revascularisation

An analysis of the VOYAGER PAD trial showed that rivaroxaban (2.5 mg twice daily) reduced both first and subsequent adverse limb and cardiovascular events in patients with peripheral artery disease (PAD) and should therefore be considered as adjunctive therapy following lower extremity revascularisation (LER) [1,2].

Patients with PAD are known to have an elevated risk (1 in 5) of major adverse limb events (MALE) (i.e. acute limb ischaemia or major limb amputation due to a vascular cause) and major adverse cardiovascular events (MACE) following LER despite antiplatelet therapy. The previously published VOYAGER PAD (NCT02504216) results demonstrated that the direct oral anticoagulant rivaroxaban combined with usual care lowered the risk of first events [3].

VOYAGER PAD randomised 6,564 participants with PAD who had recently undergone LER to receive either 2.5 mg rivaroxaban twice daily (n=3,286) or a matching placebo (n=3,278) in addition to usual care. The primary outcome measure of the main study was time to first MALE or MACE. Rivaroxaban reduced the incidence of first events by 15%. A pre-specified analysis aimed to investigate the number of both first and total MALE and MACE in patients with PAD who had undergone LER [1].

Dr Rupert Bauersachs (Klinikum Darmstadt, Germany) presented the results of this pre-specified analysis. The primary endpoint included MALE and MACE as well as additional vascular events (including venous thromboembolism and

peripheral revascularisations). A total of 4,714 first and subsequent events occurred among the entire study population in VOYAGER PAD. Of the 1,614 first events, 745 occurred in the rivaroxaban group and 869 in the placebo group. Of the 3,100 remaining subsequent events, 1,659 occurred in the placebo group compared with 1,441 in the rivaroxaban group. Rivaroxaban reduced both total primary endpoint events (HR 0.86; 95% CI 0.75–0.98; P=0.02) and total vascular events (HR 0.86; 95% CI 0.79–0.95; P=0.003), equating to an estimated avoidance of 4.4 primary and 12.5 vascular events per 100 participants over 3 years (see Figure).

Figure: Accrual of total primary and total vascular events per 100 patients [1]

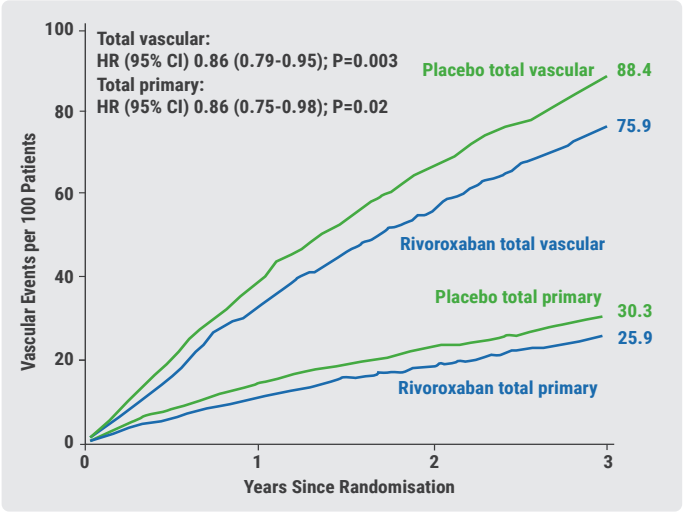


Figure kindly provided by Prof. Bonaca.

Dr Bauersachs concluded that aspirin plus 2.5 mg rivaroxaban given twice daily versus aspirin alone to patients with PAD who have undergone LER reduced both first and subsequent MALE and MACE; this benefit is even greater when considered in the context of recurrent events. In light of these favourable data, the researchers recommended that rivaroxaban given with aspirin should be considered adjunctive therapy in this patient population to prevent first and subsequent MALE and MACE.

1. Bauersachs RM. Reductions in Total Ischaemic Events with Rivaroxaban in Patients with Symptomatic Pad after Revascularization: The VOYAGER PAD Trial. Abstract 406-13, ACC 2021 Scientific Session, 15–17 May.
2. Bauersachs RM, et al. J. Am. Coll. Cardiol. 2021;May 16.
3. Bonaca MP, et al. N Engl J Med 2020;382:1994–2004.

Better outcomes with invasive strategy if anatomic complete revascularisation is possible

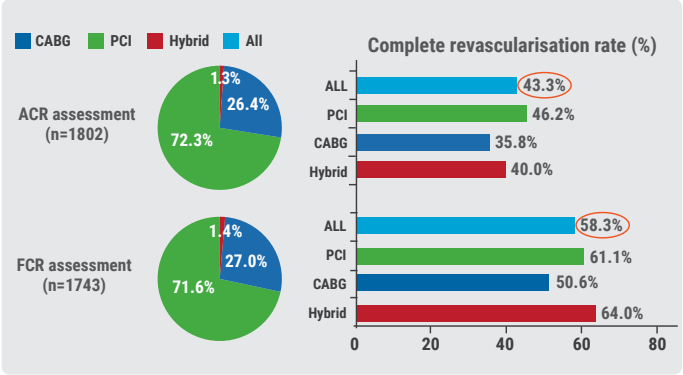
In patients with chronic coronary disease, better long-term outcomes may be achieved using an invasive approach over a conservative approach when anatomic complete revascularisation (ACR) is achievable [1]. These were the findings of a sub-analysis of the ISCHEMIA trial.

Many observational studies have shown that complete revascularisation (CR; encompassing both ACR and ischaemic, or functional complete revascularisation [FCR]) following percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) procedures is associated with fewer subsequent major adverse cardiac events (MACE) than incomplete revascularisation (IR) [1,2]. However, this association is not always found, and few studies have adjusted for differences in baseline clinical and anatomic covariates [1,2]. Evidence was also lacking on the impact of CR on patients receiving an invasive versus a conservative management strategy. This was the motivation for a pre-planned sub-analysis of the ISCHEMIA trial (NCT01471522), which was presented by Dr Gregg Stone (Mount Sinai Medical Centre, NY, USA).

Previously published results from the ISCHEMIA trial (n=5,179) found no evidence that the use of an initially invasive strategy reduced the risk of ischaemic cardiovascular events or death from any cause when compared with an initially conservative strategy (optimal medical therapy alone) [3]. The current ISCHEMIA sub-study had 2 objectives: (1) to compare the outcomes of ACR and FCR with IR in patients who underwent an initially invasive strategy, and (2) to examine the impact that CR may have had in those patients who underwent an initially invasive strategy compared with an initially conservative strategy.

To satisfy the first objective, angiographic core laboratory assessments were conducted on 2,296 patients to determine the degree of completeness of revascularisation following PCI and CABG. Among patients in the invasive strategy arm, 1,802 had achieved ACR versus anatomic IR (a CR rate of 43.3%), and 1,743 had achieved FCR versus functional IR (a CR rate of 58.3%). In the ACR group, revascularisation had been achieved by PCI in 72.3%, CABG in 26.4%, and a hybrid approach in 1.3% of cases (see Figure 1 on the next page). In the FCR group, revascularisation was achieved by PCI in 71.6%, CABG in 27.0%, and a hybrid approach in 1.4% of cases. Clinical predictors of completeness of revascularisation were anatomic, including the number of chronic total occlusions, the number of diseased vessels and lesions, and SYNTAX score. Multivariable analysis showed that CABG was associated with a higher rate of CR than PCI.

Figure 1: Completeness of revascularisation in patients using an invasive strategy [1]

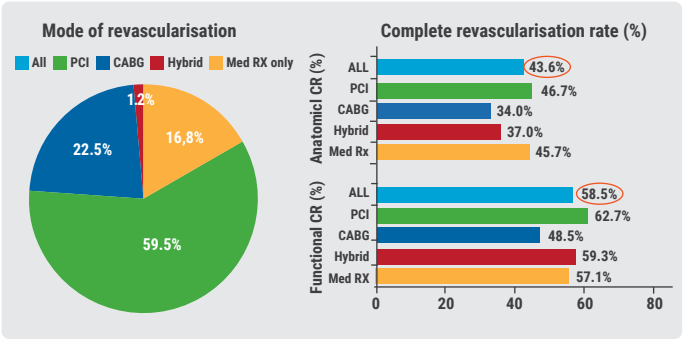


ACR, anatomic complete revascularisation; CABG, coronary artery bypass graft; FCR, functional complete revascularisation; PCI, percutaneous coronary intervention.

Comparing the impact of complete versus incomplete revascularisation on the primary endpoint of cardiovascular death, myocardial infarction, hospitalisation for cardiac arrest, heart failure, or unstable angina, the adjusted hazard ratio in the ACR group was 0.79 (95% CI 0.55–1.15; P=0.22), while in the FCR group it was 0.96 (95% CI 0.68–1.34; P=0.80).

To fulfil the secondary objective, all 2,296 patients who had undergone an initially invasive strategy were compared with the 2,498 patients who had been treated conservatively, using an inverse probability weighted analysis. Overall rates of revascularisation were similar to those observed in the first group; 43.6% had achieved ACR, and 58.5% had achieved FCR (see Figure 2). Comparing primary outcomes in the ACR showed an overall 3.5% difference, favouring the invasively managed group over the conservatively managed group; this effect was somewhat smaller in the FCR group, showing an overall 2.3% difference, also favouring the invasively managed group. The overall results from the ISCHEMIA trial show a 2.5% difference, favouring the invasively managed group over the conservatively managed group.

Figure 2: Completeness of revascularisation in patients treated using an invasive strategy versus a conservative strategy [1]



ACR, anatomic complete revascularisation; CABG, coronary artery bypass graft; FCR, functional complete revascularisation; PCI, percutaneous coronary intervention.

The researchers cautioned that these results represent associations and not necessarily causality; however, they also concluded that these results suggest that in patients with chronic coronary syndrome, better outcomes may be achieved with an invasive approach over a conservative approach if ACR can be achieved. For this reason, the likelihood of safely achieving ACR should be considered when choosing the treatment strategy for patients in this population.

1. Stone GW. Impact of completeness of revascularization on clinical outcomes in patients with stable ischaemic heart disease treated with an invasive versus conservative strategy: the ISCHAEMIA trial. ACC 2021 Scientific Session, 15–17 May 2021.
2. Gaba P, et al. Nat Rev Cardiol. 2021;18:155–168.
3. Maron DJ, et al. N Engl J Med 2020;382:1395–1407.

Moderate hypothermia not superior to mild hypothermia following out-of-hospital heart attack

Among patients who had experienced an out-of-hospital cardiac arrest (OHCA), inducing moderate therapeutic hypothermia (cooling to 31°C) did not result in better neurological or mortality outcomes than inducing mild hypothermia (cooling to 34°C) in the CAPITAL CHILL trial [1].

While current guidelines for the management of patients who have experienced OHCA recommend targeted temperature management, it remains unclear what the optimal target temperature should be to achieve the most favourable outcomes. A pilot study of 36 patients suggested that better outcomes may be achieved by inducing hypothermia below the guideline-prescribed range of 32–34°C [2]. The CAPITAL-CHILL trial (NCT02011568), presented by Dr Michel Le May (University of Ottawa, ON, Canada), was the first randomised controlled trial to explore outcomes achieved by cooling OHCA patients to 31°C.

CAPITAL-CHILL was a prospective, single-centre, randomised, double-blinded clinical trial that randomised 367 comatose survivors of OHCA to be cooled using an endovascular cooling device to a temperature of either 34° (n=183) or 31° (n=184) for a 24-hour period following OHCA. The primary outcome measure was the number of patients who experienced either a poor neurological outcome (as judged by a rehabilitation medicine specialist) or death at 6 months. The Disability Rating Scale (DRS) was used to rate the neurological outcome.

At 6 months, the primary outcome was met by 48.4% of the participants in the moderate hypothermic group and 45.4% of the participants in the mild hypothermic group (relative risk [RR] 1.07; 95% CI 0.86–1.33; P=0.56). In the mild hypothermic group, 41.0% of the patients died compared with 43.5% of the patients in the moderate hypothermic group (RR 1.06; 95% CI 0.83–1.35; P=0.63).

The researchers concluded that their findings do not support changing current guidelines regarding post-OHCA therapeutic hypothermia.

1. Le May M. Therapeutic Hypothermia Following Out-Of-Hospital Cardiac Arrest: A Randomised Trial Comparing Mild and Moderate Therapeutic Hypothermia (CAPITAL-CHILL Trial). Abstract 411-08, ACC 2021 Scientific Session, 15–17 May.
2. Lopes-de-Sa E, et al. Circulation 2012;126(24):2826–2833.

Prevention and Health Promotion

STRENGTH trial fails to demonstrate cardioprotective effect of omega-3 fatty acids

Elevated levels of eicosapentaenoic acid (EPA) were not associated with a reduced risk of major adverse cardiac events (MACE) in a post-hoc analysis of the STRENGTH trial data [1]. Additionally, elevated levels of docosahexaenoic acid (DHA) were not associated with any harm.

Controversy has surrounded the putative ability of omega-3 fatty acids EPA and DHA to protect against MACE. The REDUCE-IT trial (NCT01492361) reported that participants (n=8,179) who took 2 g of icosapent ethyl twice daily had a lower risk of ischaemic events than those who took a placebo (HR 0.75; 95% CI 0.68–0.83; P<0.001) [2]. In contrast, the STRENGTH trial (NCT02104817) (n=13,078) reported that 4 g a day of omega-3 carboxylic acid (CA) did not reduce ischaemic events compared with a corn oil comparator (HR 0.99; 95% CI 0.90–1.09; P=0.84) [3].

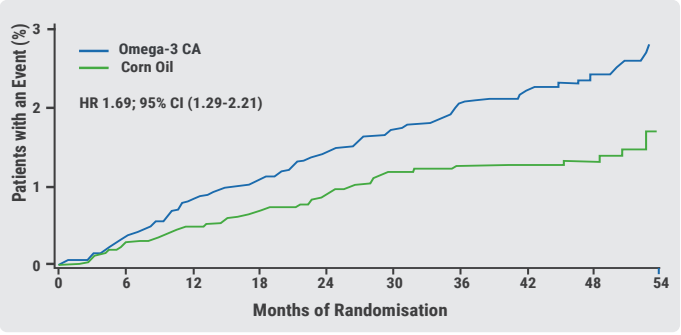
Dr Steven Nissen (Cleveland Clinic, OH, USA) presented the results of a secondary analysis of 10,382 participants in the STRENGTH trial fro whom EPA and DHA levels were available for 12 months following randomisation [1,4]. EPA levels were divided into tertiles. The primary endpoint was a 4-item MACE composite (i.e. cardiovascular death, non-fatal myocardial infarction or stroke, need for coronary revascularisation, or unstable angina requiring hospitalisation). The outcome measure was the HR for the top tertile of achieved EPA and DHA levels in the omega-3 CA group compared with the corn oil group.

At 12 months, median plasma EPA level in the corn oil group was 19 µg/mL. In the top tertile of the omega-3 CA group, EPA level was 151 µg/mL; a 443% increase. Comparing MACE in the top tertile of the EPA levels in the omega-3 CA group to the corn oil group yielded an HR of 1.03 (95% CI 0.88–1.21; P=0.69). Adjustment for baseline fatty acid levels, region, cardiovascular disease, age, sex, diabetes, creatinine, non-high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, antiplatelet agents, β-blockers, and renin-angiotensin inhibitors yielded a HR of 0.98 (95% CI 0.83–1.16; P=0.81).

At 12 months, median plasma DHA level in the corn oil group was 58 µg/mL. In the top tertile of the omega-3 CA group, the DHA level was 118 µg/mL; a 68% increase. Comparing MACE in the top tertile of DHA levels in the omega-3 CA group with placebo yielded an HR of 1.12 (95% CI 0.96–1.31; P=0.16). The adjusted HR was 1.02 (95% CI 0.86–1.20; P=0.85).

Dr Nissen noted that all the recent trials that administered high doses of omega-3 CA showed an increase in atrial fibrillation (AF); the STRENGTH trial showed a 69% increase in AF. The associated HR was 1.69 (95% CI 1.29–2.21) (see Figure). Thus, harms can be associated with high doses of omega-3 CA.

Figure: Time to onset of atrial fibrillation in the STRENGTH trial [1]



CA, carboxylic acid; CI, confidence interval; HR, hazard ratio.

Dr Nissen noted that analysis by tertiles reduces the statistical power but he also remarked that the 95% CIs were quite narrow.

Findings of this secondary analysis of the STRENGTH trial suggest that despite an increase in plasma levels of EPA and DHA, there was no apparent cardiovascular benefit. Furthermore, there is potential harm (AF) that can result from the use of high doses of omega-3 CA.

1. Nissen S. Relationship Between Omega-3 Fatty Acid Levels and Major Adverse Cardiovascular Outcomes in Patients with High Cardiovascular Risk (STRENGTH). ACC 2021 Scientific Session, 15–17 May.
2. Bhatt DL, et al. N Engl J Med 2019;380:11–22.
3. Nicholls SJ, et al. JAMA 2020;324(22):2268–2280.
4. Nissen SE, et al. JAMA Cardiol. 21 May 16;e211157.

Evinacumab lowers triglyceride levels in severe hypertriglyceridaemia

Evinacumab resulted in a dramatic reduction in fasting triglyceride levels compared with placebo in a small phase 2 study, but treatment response varied by genotype [1]. Severe hypertriglyceridaemia (sHTG), defined as a fasting triglyceride level of ≥500 mg/dL, is a known risk factor for acute pancreatitis.

Angiopoietin-like protein 3 (ANGPTL3) helps to regulate plasma lipid levels via the inhibition of lipoprotein lipase (LPL) and endothelial lipase-mediated hydrolysis of triglycerides and phospholipids [2]. A loss-of-function (LOF) variant of the *ANGPTL3* gene results in lower levels of blood triglycerides. Evinacumab is a fully human monoclonal antibody inhibitor of ANGPTL3.

A phase 2, randomised, placebo-controlled trial (NCT03452228) explored the feasibility of evinacumab as a therapeutic option for sHTG. The trial assigned 51 patients to 1 of 3 different cohorts; cohort 1 (n=17) comprised patients with familial chylomicronaemia syndrome (FCS) and LOF mutations of the LPL pathways; cohort 2 (n=15) contained patients with multifactorial chylomicronaemia syndrome (MCS) in addition to LPL pathway LOF mutations; and cohort 3 (n=19) consisted of patients with MCS but no known LPL pathway mutations. Baseline characteristics were well-balanced between the cohorts.

The treatment protocol consisted of a 12-week double-blind treatment period followed by a 12-week single-blind treatment period. Participants were randomised at a 2:1 ratio in each cohort and received either intravenous (IV) placebo every 4 weeks or IV 15 mg/kg evinacumab every 4 weeks. Prof. Robert Rosenson (Icahn School of Medicine, NY, USA) presented the primary endpoint results from the double-blind treatment period in cohort 3.

The primary endpoint was change in serum triglyceride levels at week 12 among participants in cohort 3. At week 12, the least squares mean reduction in triglyceride was -27.1% (95% CI -71.2 to 84.6), and the corresponding median reduction in triglyceride was -68.8% (95% CI -84.1 to -38.8); an absolute median triglyceride reduction of 905 mg/dL.

Thus, in patients with sHTG due to MCS but with no known LOF mutations in LPL pathways, evinacumab significantly decreased the levels of fasting triglyceride. However, the response was variable across genotypes. Further investigation is warranted to better understand these differences. The investigators also called for further investigation into the effects of evinacumab in people with sHTG, in particular those who experienced acute pancreatitis. A phase 2b trial is already planned (NCT04863014) to assess evinacumab's ability to prevent acute pancreatitis.

1. Rosenson RS. A Phase 2 Trial of the Efficacy and Safety of Evinacumab in Patients with Severe Hypertriglyceridemia. Abstract 406-19, ACC 2021 Scientific Session, 15–17 May.
2. Tikka A, Jauhiainen M. Endocrine 2016;52(2):187–193.

Health equity and the role of the cardiologist: 7 priorities to consider

Residents of rural areas, people in need of chronic care, people with a disability, racial minorities, low-income groups, women, and lesbian, gay, bisexual, and transgender persons are some of the many groups who experience health disparities. In the 52nd annual Louis F. Bishop keynote lecture, Prof. Michelle Albert (University of California, CA, USA) talked about potential solutions to address health disparities in cardiovascular care [1].

In her keynote lecture entitled "Bringing health equity to the frontlines of cardiovascular healthcare," Prof. Albert made a clear distinction between 'equity' and 'equality.' Whereas equality distributes resources equally to everyone, equity allocates resources based on need. Prof. Albert identified 7 top priorities that need to be considered in an attempt to address systemic health inequities:

1. Understanding the determinants of health inequities
2. Access to quality cardiovascular healthcare
3. Reforming cardiovascular care teams
4. Enfolding social determinants into cardiovascular care
5. Cardiovascular professional societies as core influencers
6. Healthcare workforce diversification
7. Dismantling structural racism

Prof. Albert proposed solutions for each of these priorities.

Understanding the determinants of health inequities

The life expectancy of Black and Native Americans lags behind that of Asian Americans and white Americans by a decade, a difference that is driven mostly by cardiovascular mortality. Women have 3 to 4 times increased mortality compared with men; this difference is again driven mostly by cardiovascular mortality and, most recently, by the COVID-19 pandemic. The COVID-19 pandemic has amplified health inequities that are driven by economics, segregation, housing discrimination, unequal access to healthcare, and institutional neglect of weakened communities. Some of the solutions proposed to resolve these disparities include expansion of access to healthcare, improving internet access, providing safe transportation, and implementing policy initiatives designed to address health disparities.

Prof. Albert referred to a frequently cited study that examined attitudes about race held by medical doctors using the Race Attitude Implicit Association Test (IAT) [2]. The authors recommended steps to reduce implicit bias included raising awareness of inequalities and one's own biases, along with increasing empathy and motivation to prevent prejudice. Health training institutions are advised to adopt the Society of General Internal Medicine Health Disparities curriculum.

Reforming cardiovascular care teams

Prof. Albert argued that the current system in the US is more disease- and illness-based than prevention-focused. In cardiovascular healthcare, this translates to focusing on procedures such as ablation and use of devices as opposed to primary prevention measures such as controlling blood pressure and cholesterol levels, promoting a healthy lifestyle, and helping patients adhere to their treatment regimen. To assist with more prevention-based healthcare, Prof. Albert suggested more active screening, and the inclusion of, for example, primary physicians, pharmacists, and dieticians in cardiovascular care teams.

Enfolding social determinants into cardiovascular care

Prof. Albert stated that the day-to-day activities of cardiologists (i.e. clinical interventions, counselling, and education) have less of an impact on health than socioeconomic factors and societal context. Five key social determinants of health are economic stability, education, social and community context, health care, and neighbourhood and built environment (i.e. housing). Re-envisioning the cardiovascular team requires a more holistic approach, which incorporates patient advisors, community health workers, and social workers into the team. Efforts of the team need to be directed towards both the individual and the community level.

Cardiovascular societies as core influencers

Prof. Albert outlined several steps that cardiovascular societies can take to address health inequities:

1. Move from "late-breaking clinical trials" and high-profile publications to "late-breaking studies" that are inclusive and reflect health equity.
2. Foster diversity within the ranks.
3. Promote measurement and accountability within the workforce.
4. Ensure that guidelines address health equity and social determinants of health.
5. Science panels and clinical study teams, including principal investigators, must reflect diversity.
6. Societies must promote and support community-based implementation of science guidelines (Prof. Albert noted that the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease was the first guideline to incorporate social factors into its recommendations [3]).
7. Professional organisations need to fund science and research that focuses on equity.

Healthcare workforce diversification

"Medicine is not a diverse profession […], we need a workforce that addresses the unmet needs of our society," stated Prof. Albert. Only 4% of physicians are Black and 6% are Hispanic. More members from minority groups should be recruited and accepted into medical school. Also, more funding support must be provided to members of these groups. Research has shown that physician-patient racial concordance improved outcomes. Prof. Albert shared an excellent infographic to summarise factors involved workforce diversification (see Figure on the next page).

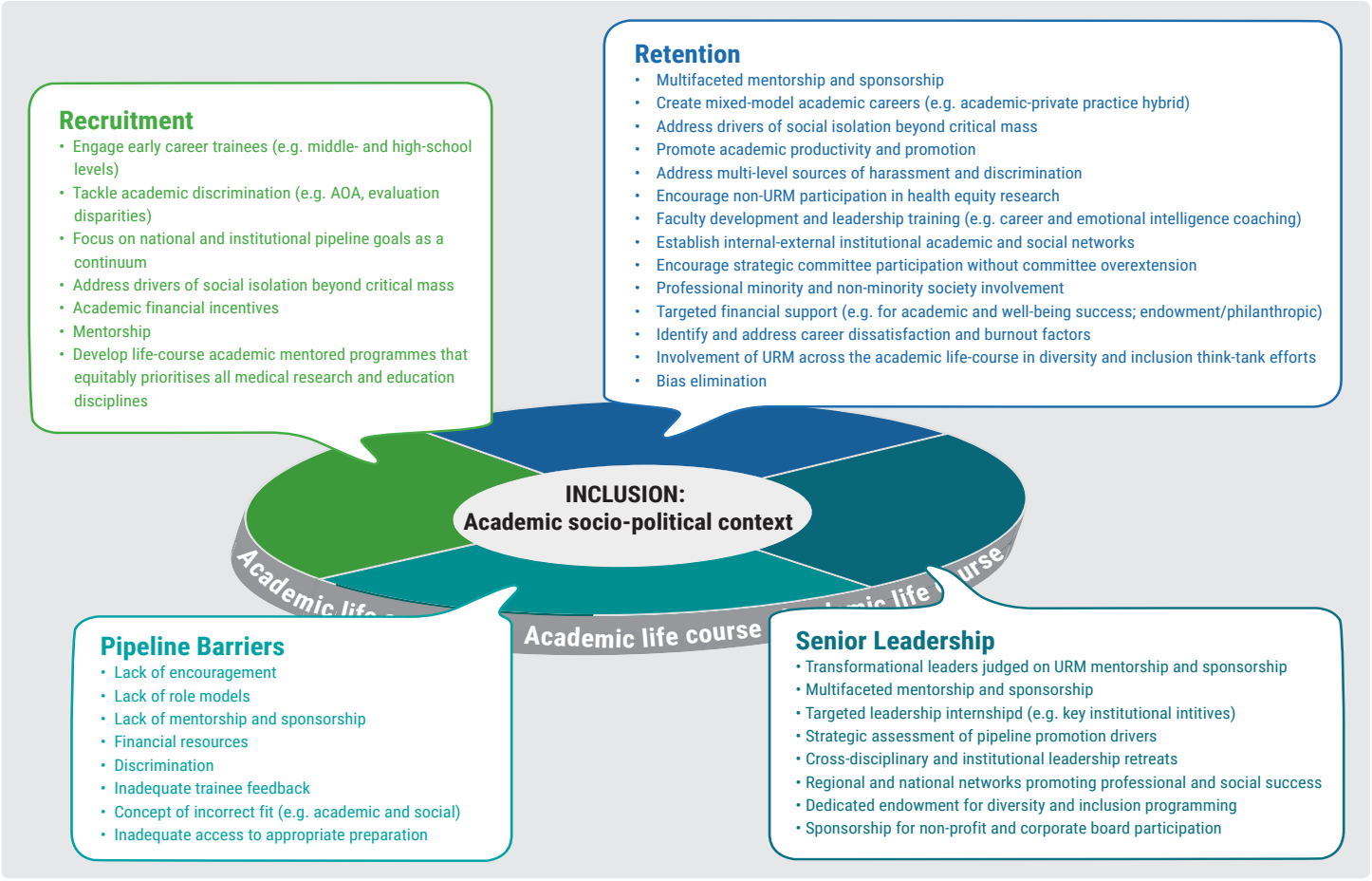
Dismantling structural racism

Prof. Albert reviewed how structural racism is a fundamental driver of health disparities; dating back to slavery, racism has resulted in poor access to healthcare, poorly funded schools, poor housing, and poor access to capital. All of these factors combine to increase toxic stress levels, which in turn increase the risk of stroke, cardiovascular death, and vulnerability to COVID-19 infection.

This excellent keynote lecture served as an inspiration and a call to action for steps that can be immediately implemented to address health disparities in our society.

1. Albert MA. "Bringing health equity to the frontlines of cardiovascular healthcare." 52nd annual Louis F. Bishop keynote lecture, 2021 ACC Scientific Session, 15–17 May.
2. Sabin JA, et al. J Health Care Poor Underserved 2009;20(3):896-913.
3. Arnett DK, et al. Circulation 2019;140(11):e596-e646.
4. Albert MA. Circulation 2018;138:451–454.

Figure: Approaches to diversification of the healthcare workforce [4]



From Albert MA. #Me_Who Anatomy of Scholastic, Leadership, and Social Isolation of Underrepresented Minority Women in Academic Medicine. Circulation 2018;138:451–454. Copyright © 2018, Wolters Kluwer Health

COVID-19

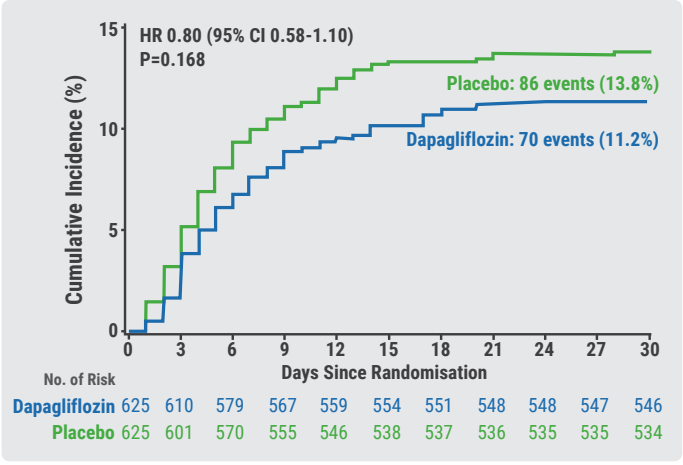
Dapagliflozin fails to show a significant protective effect in COVID-19 patients

Dapagliflozin did not achieve statistical significance for the primary endpoints of prevention of organ dysfunction or recovery when administered to patients with COVID-19 in the DARE-19 trial. However, there were numerically fewer occurrences of organ failure and death with dapagliflozin compared with placebo and numerically fewer adverse events than with the placebo.

Prof. Mikhail Kosiborod (Saint Luke's Mid America Heart Institute, MO, USA) presented the results of the DARE-19 (NCT04350593) trial [1]. DARE-19 was an international, multicentre, randomised, double-blind, placebo-controlled study of 1,250 patients who were hospitalised with COVID-19. These patients were at high risk for multiple organ failure and death. Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, is known to have a protective effect in conditions such as type 2 diabetes, heart failure, and chronic kidney disease. Investigators hypothesised that this protective effect could also extend to patients with COVID-19. Patients were randomised to receive either 10 mg of dapagliflozin per day (n=625) or a placebo (n=625) for 30 days. Dual primary endpoints were prevention of organ failure –cardiac, respiratory, or kidney decompensation– or death from any cause, and recovery.

At 30 days, 86 events of organ failure or death had occurred in the placebo group (13.8%) and 70 events in the dapagliflozin group (11.2%) (HR 0.80; 95% CI 0.58–1.10; P=0.168) (see Figure). In terms of recovery, 57% of the patients in the dapagliflozin group and 57.3% of the patients in the placebo group were discharged by day 6. There were fewer adverse events in the dapagliflozin group than in the placebo group.

Figure: Primary endpoint (i.e. organ failure or death at 30 days) in the DARE-19 trial [1]



Prof. Kosiborod concluded that this evidence does not support the discontinuation of SGLT2 inhibitors in patients with COVID-19.

1. Kosiborod MN. Effects of Dapagliflozin On Prevention of Major Clinical Events and Recovery in Patients with Respiratory Failure Due To COVID-19 – Main Results from the DARE-19 Randomised Trial. Abstract 406-11, ACC 2021 Scientific Session, 15–17 May.

Therapeutic anticoagulation not superior to prophylactic anticoagulation in COVID-19

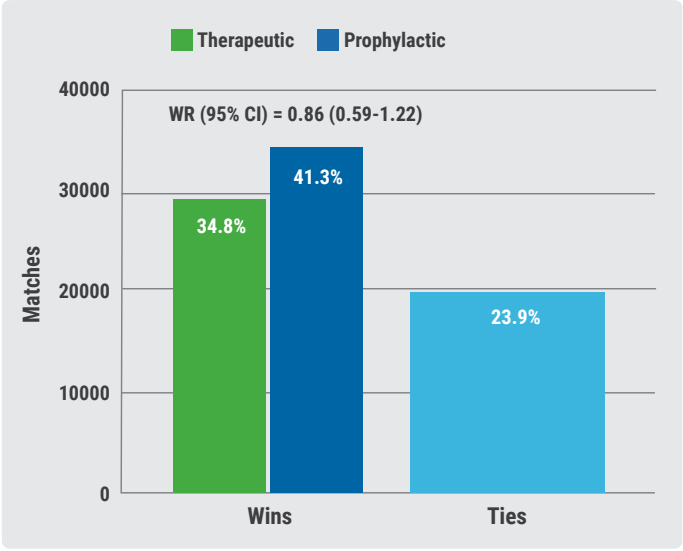
Rivaroxaban did not demonstrate improved clinical outcomes when compared with in-hospital prophylactic anticoagulation in patients who were hospitalised for COVID-19 and had elevated D-dimer levels. Furthermore, those treated with rivaroxaban showed increased rates of bleeding compared with those receiving prophylactic anticoagulation in the Coalition ACTION trial [1,2].

Patients with COVID-19 frequently experience venous and arterial thromboembolism. Elevated levels of D-dimer, a thrombotic biomarker, are harbingers of poorer clinical outcomes (i.e. disease progression and mortality). Data is needed regarding the type, dosage, and duration of an anticoagulation strategy.

Prof. Renato Lopes (Duke University Medical Center, NC, USA) presented the results of the Coalition ACTION trial (NCT04394377), which was designed to investigate the effectiveness of a full anticoagulation strategy compared with a prophylactic anticoagulation strategy in patients who had been hospitalised for COVID-19 and had elevated D-dimer levels. One group (n=311) received a 30-day course of rivaroxaban (20 mg once daily); the comparison group (n=304) received the standard in-hospital prophylactic venous thromboembolism protocol. The primary outcome was a hierarchical analysis of mortality, length of hospital stay, and duration of oxygen therapy over the 30-day intervention period. Results were analysed using an unmatched win ratio method, stratified by clinical severity.

At 30 days, analysis of primary outcome data demonstrated that 41.3% of participants in the prophylactic group had won compared with only 34.8% of participants in the rivaroxaban group. The remaining 23.9% were tied (see Figure).

Figure: Primary outcome results at 30 days in the COALITION ACTION trial [1]



The primary safety outcome of the study was a major or clinically relevant non-major bleed, as designated by the International Society on Thrombosis and Haemostasis criteria. In the rivaroxaban group, 26 bleeds occurred (8.4%) versus 7 bleeds in the prophylactic group (2.3%), yielding a relative risk ratio of 3.64% (95% CI 1.61–8.27). In terms of all-cause mortality, 35/310 patients (11.3%) in the rivaroxaban group died compared with 23/304 patients in the prophylactic anticoagulation group (7.6%), yielding a relative risk ratio of 1.49 (95% CI 0.90–2.46).

The investigators concluded that therapeutic anticoagulation with rivaroxaban in patients hospitalised for COVID-19 did not improve clinical outcomes and increased bleeding when compared with in-hospital prophylactic anticoagulation.

1. Lopes RD. Randomised Clinical Trial to Evaluate A Routine Full Anticoagulation Strategy in Patients with Coronavirus Infection (SARS-CoV-2) Admitted to Hospital: The Coalition ACTION Trial. Abstract 409-14, ACC 2021 Scientific Session, 15–17 May.
2. Lopes RD, et al. Lancet 2021;397(10291):2253-63.

Atorvastatin does not reduce mortality in COVID-19

Patients who were hospitalised with COVID-19 and given atorvastatin fared no better than patients who were given a placebo, with respect to reducing venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or all-cause mortality [1]. Results of the INSPIRATION trial also found no difference between the groups in terms of the main safety outcomes of clinically diagnosed myopathy or elevated liver enzymes.

Some patients with COVID-19 exhibit a dramatic immune response, resulting in increased thrombotic events and a hyperinflammatory state. The intensity of the immune response can lead to the development of acute respiratory distress syndrome (ARDS) and ultimately death. Statins are known to have pleiotropic effects that include both anti-inflammatory and anti-thrombotic effects. Previous studies have shown a beneficial effect of statins on hyper-inflammatory phenotypes of ARDS (but not hypo-inflammatory phenotypes) [2,3]. Furthermore, antecedent statin use has been associated with decreased mortality in COVID-19 hospitalised patients. Dr Behnood Bikdeli (Brigham and Women's Hospital, MA, USA) and colleagues aimed to investigate whether statins could benefit patients who were severely affected with COVID-19.

The INSPIRATION trial (NCT04486508) randomised 605 patients who were critically ill with COVID-19 to receive either 20 mg of atorvastatin daily (n=303) or a placebo (n=302) over a 30-day period. Of the original 303 patients in the atorvastatin arm, 290 were included in the prespecified primary analysis; of the original 302 patients in the placebo arm, 297 were included in the prespecified primary analysis. The primary endpoint was a composite of 30-day venous or arterial thrombosis, treatment with ECMO, or all-cause mortality. In the atorvastatin arm, 95/290 (32.7%) reached the primary endpoint compared with 108/297 (36.3%) in the placebo arm (HR 0.84; 95% CI 0.63–1.11; P=0.22).

The main safety outcomes were a rise in liver enzymes of >3 times normal and clinically diagnosed myopathy. In the atorvastatin group, only 5 (1.7%) patients experienced a rise in liver enzymes compared with 6 (2.0%) in the placebo group. No patients were diagnosed with myopathy.

The investigators concluded that the administration of 20 mg atorvastatin daily to ICU-admitted patients with COVID-19 was no more beneficial than a placebo. However, they suggested that a smaller treatment effect could not be excluded. They identified the need for further research that explores the potential role of statins if administered sooner; that is, before the hyperinflammatory pathway is activated.

1. Bikdeli B. Atorvastatin vs Placebo in Critically-ill Patients with Covid-19: The Inspiration-S Double Blind Randomised Controlled Trial. Abstract 409-16, ACC 2021 Scientific Session, 15–17 May.
2. Heijnen NFL, et al. J Thorac Dis 2019;11(Suppl 3):S296-S299.
3. Calfee CS, et al. Lancet Respir Med 2018;6(9):691-698.

Valvular Heart Disease

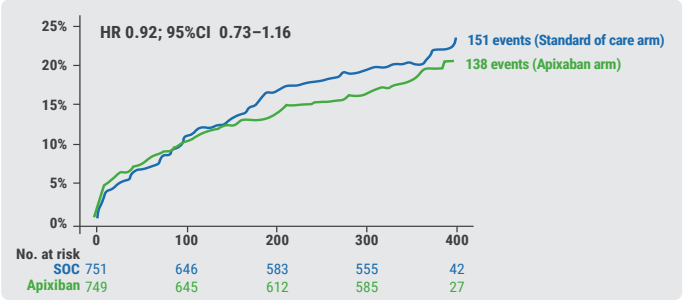
Apixaban outcomes similar to current standard of care following TAVR

The bleeding safety profile of apixaban was similar to that of the current standard of care, and the net clinical benefit of administering apixaban following transcatheter aortic valve replacement (TAVR) was not superior to current standard-of-care antithrombotic approaches in the ATLANTIS trial [1].

Prof. Jean-Philippe Collet (Sorbonne Université, France) presented results of the multicentre, phase 3, prospective, open-label, randomised ATLANTIS (NCT02664649) trial. ATLANTIS sought to compare the efficacy of apixaban, an anti-Xa, direct oral anticoagulant, with the current standard of care in patients who had undergone TAVR. The investigators randomised 1,510 participants to receive either apixaban (n=749) twice daily or usual care (n=751) for 1 year following TAVR. Randomisation was stratified according to the presence of an indication for anticoagulation other than the TAVI procedure (e.g. atrial fibrillation). The primary outcome was a composite of death, myocardial infarction, stroke, systemic or pulmonary embolism, cardiac, bioprosthetic, or deep-vein thrombosis, or major bleeding at 1-year follow-up.

After 1 year, 138 (18.4%) events had occurred in the apixaban arm and 151 (20.1%) in the standard-of-care arm (HR 0.92; 95% CI 0.73–1.16; see Figure).

Figure: Primary endpoint in intention-to-treat groups (standard of care vs apixaban) [1]



	Apaxiban (n=749)	Standard of care (n=751)	P-value for interaction	Hazard Ratio (95% CI)
Primary outcome*	138 (18.4%)	151 (20.1%)		0.92 (0.73-1.16)
No indication for OAC (n=1049)	89 (16.9%)	191 (19.3%)	0.57	0.88 (0.66-1.17)
Indication for OAC (n=451)	49 (21.9%)	50 (21.9%)		1.02 (0.68-1.51)

*Per-protocol analyses (n=1299) were consistent with ITT analyses for the primary endpoint (HR 0.89; 95% CI 0.71-1.13)

Analysis of the subgroup of participants who required anticoagulation (n=451) showed 49 (21.9%) events in the apixaban group and 50 (21.9%) in the standard-of-care group (HR 1.02; 95% CI 0.68–1.51). In the subgroup of participants with no indication for anticoagulation (n=1,049), 89 (16.9%) events had occurred in the apixaban group and 101 (19.3%) in the standard-of-care group (HR 0.88; 95% CI 0.66–1.17).

A slightly higher number of non-cardiovascular deaths occurred in the cohort of patients taking apixaban with no need for anticoagulation. This difference was not statistically significant.

Results of the ATLANTIS trial suggest that apixaban following TAVR is not superior to current standard-of-care antithrombotic management in terms of net clinical benefit.

1. Collet JP. Oral Anti-Xa Anticoagulation After Trans-aortic Valve Implantation for Aortic Stenosis: The Randomized ATLANTIS Trial. ACC Scientific Session, 15–17 May 2021.

Preliminary results encouraging for EVOQUE tricuspid valve replacement

In patients with significant tricuspid regurgitation (TR) who received a new tricuspid valve replacement system, results at 30 days showed a reduction of TR and improvement of symptoms in the TRISCEND study. At 30 days, most patients (77.4%) had experienced no major adverse events. The device was deemed technically feasible, with an acceptable safety profile [1].

The TRISCEND study (NCT04221490) was an early feasibility study to assess the performance and safety of the Edwards' EVOQUE tricuspid valve replacement system. This prospective, single-arm, multicentre study enrolled 56 patients with symptomatic moderate or greater TR to receive the EVOQUE valve replacement. At 30 days, 47 participants were available for follow-up.

The participants were quite elderly (mean age 79 years) and had severe TR symptomatic (92% graded as severe or greater). Aetiology of TR was deemed functional in 68% of participants, degenerative in 11%, and mixed/other in the

remaining 21%. All devices were implanted via right femoral vein access. The primary outcome measure was freedom from device- or procedure-related adverse events within a 30-day time frame. Endpoints were device and procedural success, a reduction in TR, and a composite of major adverse events. Follow-up was planned at 30 days, 6 months, 1 year, and annually for up to 5 years post-procedure.

Dr Susheel Kodali (Columbia University Medical Center, NY, USA) reported the 30-day results from the TRISCEND trial. Of the 47 patients who were followed up, 46 (98%) experienced a reduction in severity of TR to none or trace; 100% achieved a ≥1-grade reduction; and 95% a ≥2-grade reduction in TR severity. Approximately 10% of patients achieved a ≥5-grade reduction in TR at 30 days.

No major adverse events was observed in 77.4% of the participants at 30 days. The most common adverse event was severe bleeding, experienced by 12 (22.6%) of the participants. None of the bleeding events were life-threatening or fatal.

Dr Kodali also noted that echocardiography performed at discharge showed worsening right ventricular function in about 25.5% of patients. At 30 days, this parameter had improved, with right ventricular dysfunction evident in only 4.5% of the participants. This parameter will continue to be monitored at the next scheduled follow-up at 6 months.

Key secondary outcomes included changes from baseline to 30 days in the New York Heart Association (NYHA) class, 6-minute walk test, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. At 30 days, there was a dramatic improvement in NYHA class, and both the 6-minute walk test and KCCQ scores showed significant improvement.

Encouraged by these preliminary results, researchers have now initiated TRISCEND 2 (NCT04482062), a prospective, multicentre, randomised, controlled, pivotal clinical trial that will evaluate the safety and effectiveness of the EVOQUE system with optimal medical therapy compared with optimal medical therapy alone in the treatment of patients with at least severe tricuspid regurgitation.

1. Kodali S. Transfemoral Tricuspid Valve Replacement in Patients with Tricuspid Regurgitation: 30-day Results of the TRISCEND Study. ACC 2021 Scientific Session, 15–17 May.