Medicom International Conference Series in Cardiology

ACC Scientific Session 2024

American College of Cardiology

06–08 APRIL 2024 • ATLANTA • USA

PEER-REVIEWED CONFERENCE REPORT

ACS: Is ticagrelor monotherapy enough after 1 month of DAPT?

Protection was non-inferior and bleeding events fewer, when switching to ticagrelor alone after 1 month of dual antiplatelet therapy.

read more on PAGE 4

IVUS beats angiography to guide PCI in ACS

Intravascular ultrasound (IVUS)-guided stent implantation resulted in better outcomes compared with angiography guidance in patients with acute coronary syndrome (ACS).

read more on PAGE 11

Vulnerable coronary plaques: a new role for preventive PCI?

A combination of optimal medical treatment and preventive PCI of high-risk plaques resulted in outcome benefits compared with medical treatment alone.

read more on PAGE 14

MEDICOM MEDICAL PUBLISHERS

Editor Prof. Marc Bonaca, University of Colorado, USA

COLOPHON

Editor	Prof. Marc Bonaca University of Colorado, USA
Reviewer	Prof. Moritz Seiffert University Hospital Bergmannsheil Bochum, Germany
Reviewer	Prof. George Bakris University of Chicago Medicine, USA
Publishing Director	Paul Willers
Editorial Operations Manager	Dr Rosalie Molenaar
Medical Science Officer	Dr Rachel Giles
Medical Project Manager	Rune Bruls
Editorial Coordinators	Sanne Lauriks Dr Joery Goossens
Medical Writers	Dr Susanne Kammerer Karin Drooff, MPH
Production Manager	Anouk Neijenhoff
Graphic Design	MOOZ grafisch ontwerp
Graphics	Wim Kempink
Printing	GVO drukkers & vormgevers B.V.
Cover Photo	Shutterstock
ISSN	2468-8762 24:05

MEDICOM
MEDICAL PUBLISHERS

Head Office
Medicom Medische Uitgeverij B.V.
Laarderhoogtweg 25
1101 EB Amsterdam
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

Contents

Letter from the Editor

Dear colleagues,

Thank you for your interest in this edition of Medicom's Conference Report covering the American College of Cardiology (ACC) Scientific Sessions 2024, held in Atlanta, USA. This year's meeting covered a wide array of topics, from cutting-edge treatments for heart failure with preserved ejection fraction to new data on intervention for aortic stenosis.

Late-breaking science challenged current treatment paradigms including the use of beta-blockers in acute myocardial infarction patients with preserved ejection fraction in the era of reperfusion as well as the duration of dual antiplatelet therapy after coronary stenting. Innovative approaches to treatment and prevention including stenting of vulnerable coronary plaques and the role of IVUS in peripheral and coronary revascularization were explored. Finally, new phase 2 results show promise for novel approaches to managing hypertension and lipid disorders, and intriguing subgroup analyses for ApoA1 in patients with acute myocardial infarction raise questions about the role of such therapy in patients with atherosclerosis.

I hope you find the summaries included informative, balanced, and inspiring as we look forward to great promise in scientific innovation that will improve outcomes for patients suffering from cardiovascular and cardiometabolic diseases.

Sincerely,
Prof. 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 Grant support to CPC from Amgen, AstraZeneca, Bayer, Janssen, NovoNordisk, Sanofi
View Dr Bonaca's extended COI statement online: conferences.medicom-publishers.com/specialisation/cardiology/aha-2023.

Heart Failure and Cardiomyopathy

STEP-HFpEF DM: Semaglutide beneficial in patients with HFpEF and diabetes

Patients with type 2 diabetes and heart failure with preserved ejection fraction (HFpEF) had significant improvements for heart failure (HF)-related symptoms, physical limitations, and body weight with semaglutide versus placebo in the phase 3 STEP-HFpEF DM trial.

"We have previously demonstrated in the STEP-HFpEF trial that semaglutide, 2.4 mg once a week, significantly reduced HF symptoms and physical limitations, as well as body weight in patients with obesity-related HFpEF who did not have diabetes," stated Prof. Mikhail Kosiborod (Saint Luke's Mid America Heart Institute, MO, USA) [1]. Prof. Kosiborod and colleagues initiated a special investigation of this cohort after noting a high prevalence of diabetes in HFpEF patients with greater symptom burden and worse functional conditions.

The current phase 3 STEP-HFpEF DM study (NCT04916470) randomised 617 adult patients with HFpEF and type 2 diabetes to receive either weekly semaglutide 2.4 mg after an escalation period of 16 weeks or matching placebo up to week 52. The dual primary endpoints assessed change in body weight and modification in HF-related symptoms measured by KCCQ-CSS. Baseline findings showed a study cohort with 44% women, a median age of 69 years, a BMI of 37 kg/m^2, NT-proBNP of 493 pg/mL, and KCCQ-CSS of 59 points. One-third of the participants were already treated with SGLT2 inhibitors.

At 1 year, participants in the semaglutide group achieved a significantly greater 13.7-point change in KCCQ-CSS compared with 6.4 points in the placebo arm (P<0.001). Weight loss on the study drug at week 52 was determined at -9.8% compared with -3.4% on placebo; this -6.4% difference was also significant (P<0.001). At week 52, change in 6-minute walking distance, C-reactive protein, NT-proBNP, and HF event outcomes also favoured semaglutide compared with placebo.

Serious adverse events were seen in 17.7% of participants on semaglutide and 28.8% of those on placebo (P=0.002), with fewer cardiac disorders in the semaglutide group (6.1% vs 13.1%), and no signs of increased hypoglycaemia or retinal disorders.

"Collectively, the results both from the STEP-HFpEF and STEP-HFpEF DM trials indicate that treatment with semaglutide is a valuable treatment approach in the management of patients with obesity-related HFpEF both with and without type 2 diabetes," Prof. Kosiborod concluded.

1. Kosiborod MN. Once-weekly semaglutide in patients with heart failure with preserved ejection fraction, obesity and type 2 diabetes: main results from the Step-HFpEF DM trial. FCR 1, Session 403, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

IMPROVE-HCM: Promising results for ninerafaxstat in non-obstructive HCM

Ninerafaxstat demonstrated promising safety and trends supporting potential efficacy in patients with symptomatic non-obstructive hypertrophic cardiomyopathy (HCM) in the phase 2 IMPROVE-HCM trial.

Ninerafaxstat is a novel cardiac mitotrope designed to restore myocardial energy homeostasis by shifting cardiac energy metabolism from fatty acid oxidation to glucose oxidation. This innovative approach enhances cardiac efficiency, particularly in conditions of limited oxygen supply, potentially offering a novel therapeutic approach for patients with non-obstructive HCM.

In the phase 2 IMPROVE-HCM trial (NCT04826185), Prof. Martin Maron (Lahey Hospital & Medical Center, MA, USA) and colleagues evaluated the safety and efficacy of ninerafaxstat in patients with symptomatic non-obstructive HCM and objective evidence of exercise limitation [1]. Conducted across 12 academic centres, the trial enrolled 67 adult patients aged 18–80 years with a clinical diagnosis of non-obstructive HCM and exercise limitation, excluding those with specific contraindications. The participants were randomised to receive either ninerafaxstat, 200 mg twice daily, or a placebo and underwent comprehensive assessments before and after the 12-week treatment period.

At 12 weeks, ninerafaxstat demonstrated a safety profile comparable with placebo, with the primary endpoint of treatment-emergent adverse events (TEAEs) occurring in 70.6% of the participants, and serious adverse events (SAEs) in 11.8%. While overall improvement in a standardised heart failure symptom burden (assessed by Kansas City Cardiomyopathy Questionnaire Clinical Summary Score [KCCQ-CSS]) was non-significant, an exploratory subgroup analysis of participants with baseline KCCQ-CSS ≤80 points showed significant improvement with ninerafaxstat (P=0.04). Ninerafaxstat significantly improved functional capacity measured by VE/VCO^2 slope, an important prognostic variable in HCM, compared with placebo (P=0.005), particularly in participants with advanced symptoms (i.e. NYHA class III). Although not significant, NT-proBNP levels showed a trend towards lower levels in patients randomised to ninerafaxstat, suggesting potential cardioprotective effects. Left atrial size also appeared lower ninerafaxstat-treated patients, suggesting improved cardiac function.

These findings support investigation in larger phase 3 trials, underscoring the potential of ninerafaxstat to address the unmet needs of patients with non-obstructive HCM.

1. Maron MS, et al. Efficacy and safety of ninerafaxstat, a novel cardiac mitotrope, in patients with symptomatic nonobstructive hypertrophic cardiomyopathy: Results of IMPROVE-HCM. LB4, Session 411, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

Acute Coronary Syndrome and Acute Myocardial Infarction

ACS: Necessary DAPT after PCI may be shorter than currently advised

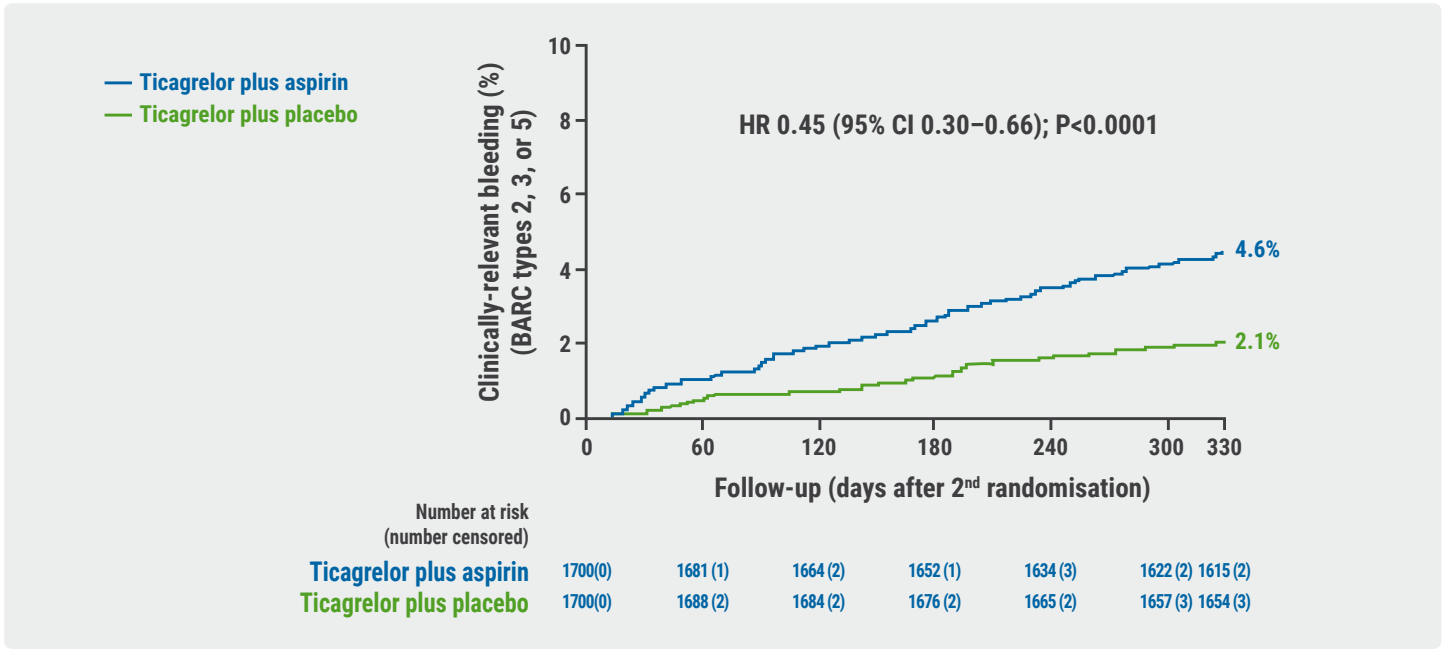
Switching to monotherapy with ticagrelor after 1 month of dual antiplatelet therapy (DAPT) post-percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) appeared non-inferior for major adverse cardiac or cerebrovascular events (MACCE) compared with 12-month DAPT with ticagrelor plus aspirin. Moreover, clinically relevant bleeding events were significantly lower in the ticagrelor monotherapy group.

The current ESC Guidelines recommend DAPT with aspirin plus a potent $P2Y_{12}$ inhibitor over 12 months after ACS and PCI [1]. The current ULTIMATE-DAPT trial (NCT03971500) investigated the consequences of reducing DAPT to ticagrelor monotherapy after 1 event-free month post-PCI on DAPT [2,3]. The 2 primary endpoints, evaluated through 1 year, were non-inferiority in MACCE (i.e. cardiac death, myocardial infarction, ischaemic stroke, definite stent thrombosis, clinically driven target vessel revascularisation) and superiority in bleedings of types 2, 3, or 5 according to the Bleeding Academic Research Consortium (BARC).

The multinational trial randomised 3,400 adults after 30 days with aspirin plus ticagrelor to either continue this regimen or switch to the $P2Y_{12}$ inhibitor plus placebo over 1 year. The trial cohort had a median age of around 63 years and slightly over 25% were women. "70% of the patients had single vessel disease and about 1.3 lesions were treated per patient," added Prof. Gregg Stone (Icahn School of Medicine at Mount Sinai, NY, USA).

The primary endpoint of type 2, 3, or 5 BARC bleedings occurred in 2.1% on ticagrelor only and 4.6% on continued DAPT (HR 0.45; 95% CI 0.30–0.66; P<0.0001; see Figure). The rates of MACCE in both treatment groups were low and were not significantly different: on ticagrelor plus aspirin, 3.7% of the participants experienced a MACCE compared with 3.6% in the ticagrelor plus placebo group (HR 0.98; 95% CI 0.69–1.39; $P_{non\text{-}inferiority}$<0.0001). Of note, the upper confidence interval was 1.39 reflecting a relatively low number of events. The P-value was for non-inferiority with a prespecified margin of 5. Statistical significance was not established for all secondary MACCE endpoints.

Figure: Primary endpoint of BARC types 2, 3, or 5 bleeding in the ULTIMATE-DAPT study [2]



BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio.

"These results, in concert with prior trials, warrant an update to the guidelines and a change in practice to treat most patients with ACS after PCI with 1 month only on DAPT, followed by conversion to single antiplatelet therapy with a potent $P2Y_{12}$ inhibitor, with the strongest evidence to date supporting ticagrelor," Prof. Stone concluded. While de-escalating aspirin has been shown clearly to reduce bleeding, very large trials would be needed to exclude harm in terms of increased ischaemic risk as evidenced by the wide confidence intervals observed in the trial.

1. Byrne RA, et al. Eur Heart J 2023;44(38):3720-3826.
2. Ge Z, et al. Lancet 2024;403(10439):1866–1878.
3. Stone GW, et al. One-month ticagrelor monotherapy after PCI in acute coronary syndromes: principal results from the double-blind, placebo-controlled ULTIMATE-DAPT trial. LB3, Session 406, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

AEGIS-II: ApoA-1 did not reduce MACE in patients with myocardial infarction but may provide benefit in patients with high LDL levels

Infusions with human apolipoprotein A-1 (ApoA-1), a cholesterol efflux enhancer, failed to achieve the primary endpoint of a significant reduction in major adverse cardiovascular events (MACE) in patients with myocardial infarction (MI) and additional risk factors at 90 days. This might not be the end of the HDL hypothesis, as an exploratory analysis suggests a benefit for certain subgroups.

The rationale of the AEGIS-II trial was to optimise the function of HDL in the so-called reverse transport of cholesterol from the periphery of the body to the liver, by increasing HDL-mediated cholesterol efflux capacity. This should be accomplished by infusions with ApoA-1, the main component of HDL cholesterol. In the previous AEGIS-I trial, a single infusion of purified human ApoA-1 (CSL112) indeed increased cholesterol efflux in the setting of MI [1].

The phase 3, international AEGIS-II trial (NCT03473223), presented by Prof. Michael Gibson (Harvard Medical School, MA, USA), enrolled 18,219 participants who had been hospitalised for an MI [2,3]. All participants had multivessel disease and additional cardiovascular risk factors. They were randomly assigned to receive infusions of either CSL112 or a placebo for 4 weeks, with the first infusion given within 5 days of hospitalisation. The study's primary endpoint was the time to the first occurrence of MACE (i.e. MI, stroke, or cardiovascular death) through 90 days.

Participants treated with CSL112 had a 4.8% rate of MACE compared with 5.2% in the placebo group, a difference that was not statistically significant (HR 0.93; 95% CI 0.81–1.05; P=0.24). In an exploratory analysis, the researchers included participants whose LDL cholesterol level was ≥100 mg/dL at baseline despite statin therapy. These participants appeared to have a 30% lower rate of the primary endpoint at 90 days

(HR 0.69; 95% CI 0.53–0.90; P=0.007) while those with LDL cholesterol <100 mg/dL had no apparent benefit. "LDL at baseline modulated the treatment effect; the magnitude of treatment effect increased with the LDL concentrations," Prof. Gibson commented. Overall ApoA-1 appeared to have a reassuring safety profile.

The benefit of ApoA-1 infusions in hyperlipidaemic patients is biologically plausible, but Prof. Gibson emphasised that this observation is hypothesis-generating and requires prospective validation in further studies.

1. Gibson CM, et al. Circulation 2016;134:1918-1930.
2. Gibson CM, et al. N Engl J Med 2024;390:1560–1571.
3. Gibson CM, et al. CSL112 (Apolipoprotein A-I) Infusions And Cardiovascular Outcomes In Patients With Acute Myocardial Infarction (ApoA-I Event Reducing In Ischemic Syndromes II (AEGIS-II) Trial): Primary Trial Results. LB1, Session 402, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

REDUCE-AMI: Re-evaluating the role of routine beta-blockade in patients with acute myocardial infarction

In patients with acute myocardial infarction (MI) and a preserved ejection fraction (EF) of at least 50%, events of death or new MI were not reduced by long-term beta-blocker therapy. Also, there was no evidence of a significant effect of beta-blockers on secondary outcomes or safety endpoints in the REDUCE-AMI trial.

In post-MI patients with reduced EF, beta-blocker treatment has demonstrated a clear mortality reduction, but its benefit for those with a preserved EF who are revascularised is uncertain in the era of reperfusion treatment [1]. To generate more data to clarify this matter, Dr Troels Yndigegn (Lund University, Sweden) and colleagues designed the phase 4 REDUCE-AMI trial (NCT03278509).

This registry-based prospective, randomised, open-label trial included over 5,000 adults who received early coronary angiography and had an EF ≥50% after an MI between 2017 and 2023. The beta-blocker group was treated with either daily 100 mg metoprolol succinate or 5 mg bisoprolol, and participants were encouraged to continue treatment post-discharge. The other study arm received no beta-blockers unless there was an indication beyond secondary prevention. The study cohort had a median age of 65 years and included about 22% women. "There was a high degree of adherence to guideline-directed therapy," Dr Yndigegn noted. Participants were followed over a median of 3.5 years.

The primary composite outcome of all-cause death or new MI showed no significant difference between groups: 199 events were observed for participants on beta-blockers and 208 events for those not on beta-blockers (HR 0.96; 95% CI 0.79–1.16; P=0.64). Also, no reductions were found for any of the secondary outcomes, and the analysis of all prespecified subgroups suggested similar treatment effects regarding the primary outcome.

The safety endpoints showed overall similar risks between the study arms. This included bradycardia, hypotension, asthma, and hospitalisation for stroke.

"All therapies need an expiration date or re-evaluation when there is a change in underlying risk due to advancement in medical therapy; in patients with MI and preserved EF who underwent prompt revascularisation and were on guideline-directed medical therapy, there is no role for beta-blockers to improve clinical outcomes or symptoms," said discussant Prof. Sripal Bangalore (New York University School of Medicine, NY, USA) [2]. He also emphasised that in patients with heart failure with reduced EF, beta-blockers should continue to be the cornerstone of therapy.

1. Yndigegn T. Long-term beta-blocker treatment after acute myocardial infarction and preserved left ventricular ejection fraction - the REDUCE-AMI trial. LB3, Session 406, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.
2. Bangalore S. The REDUCE-AMI trial. Session 414, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

Prof. Javed Butler
MD, MPH, MBA

Meet the Trialist: The EMPACT-MI trial findings

Medicom spoke with Prof. Javed Butler (President of the Baylor Scott and White Research Institute in Dallas, and distinguished Professor of Medicine at the University of Mississippi, USA), about the late-breaking EMPACT-MI trial (NCT04509674) results he presented at the recent ACC 2024 Scientific Session, held in Atlanta, USA [1,2].

The double-blind, placebo-controlled EMPACT-MI trial evaluated patients receiving empagliflozin (n=3,260) or placebo (n=3,262) for cardiovascular (CV) outcomes after acute myocardial infarction (MI). Over 17.9 months, the primary endpoint—hospitalisation for HF (HF) or death from any cause—occurred in 8.2% of the empagliflozin group and 9.1% of the placebo group, showing no significant difference (HR 0.90; 95% CI 0.76–1.06; P=0.21). However, empagliflozin was associated with reduced HF hospitalisations compared with placebo (3.6% vs 4.7%, respectively). Overall mortality rates were similar between the 2 groups. These findings highlight that while empagliflozin may reduce the risk of HF hospitalisation, it does not significantly impact overall survival post-MI, suggesting a targeted but limited role in the management of such patients.

What is your interpretation of these rather surprising results of no impact on overall survival versus a clear impact on HF hospitalisation?

"Some risks were taken in the trial design that didn't necessarily pan out. Let me go into more detail through the machinery of how the trial was designed, which can probably explain things. There is a lot of pressure to decrease the cost and the burden of the trials on the patients and on the sites, prioritising pragmatic clinical trials.

As part of the pragmatic clinical trial, our inclusion-exclusion criteria were very general and everything was remote in follow-up. The correlation among the centres was not very good in 2 places: the cause of death, and outpatient HF. There is much pressure to reduce HF admissions and people are increasingly diagnosing and treating patients in the outpatient HF setting. Because we did not have a central adjudication committee as part of a streamlined trial, we went for all-cause mortality, not CV mortality.

However, that choice comes with a cost; if you have 100 people who die post-MI, you can expect about 75–80 of them will die of CV causes. And of those early post-MI mortalities, a lot of things happen—e.g. ventricular septal ruptures, recurrent MIs, or stent thrombosis—that SGLT2 inhibitors can't do anything about. Then there are the other 20–25% who will not die of CV causes but were counted as events here nevertheless; there's no chance that SGLT2 inhibitors will improve their outcome, right? Another problem was that the follow-up was only 18 months, meaning that actual follow-up after HF development was shy of a year, which would limit mortality events to only early events.

The second component beyond all-cause mortality in the endpoint was hospitalisation due to HF. When we designed the trial, we predicted only 10–15% of the HF burden would be in the outpatient setting, and that it would not greatly influence the outcome. We could not have predicted then that the COVID-19 pandemic would intervene and drive the rates of outpatient care well above our anticipated background, making that

particular endpoint very hard to realise. On top of that, the 2 regions that were very active in the trial, Israel and Ukraine, entered wars.

This has affected the results in 2 ways; firstly, you don't have HF outpatient diagnosis in the endpoint, but it also changes the ratio in the primary endpoint. At the beginning of the trial, we anticipated that if 100 people were to be in your endpoint of the trial, about 40 of those events would be deaths and 60 would be hospitalisations. Here we had the reverse. We had more deaths than HF hospitalisations. We believe that the specific conditions of this trial led to a systematic under-calculation of HF patients.

We live in a P-value-oriented world, and a significant P-value was not reached. However, if we look at the HF results, we see identical results to what we have seen in diabetes, chronic kidney disease, HFrEF, and HFpEF. In short, no effect on mortality but a 23% reduction in HF time to the first event and a 33% reduction in total HF events. Interestingly enough, although not part of the primary endpoint, and only an exploratory analysis, if you do include outpatient HF in the endpoint, even all-cause mortality and HF hospitalisation total are positive. Then, the HF signal is 23% relative risk reduction time to first hospitalisation, 33% total, and 37% for inpatient and outpatient combined."

It sounds like there's a signal, but you can't draw that hard conclusion based on the trial design?

"Absolutely. To give you one more result; we wanted to pressure test this outpatient test. We, therefore, analysed all patients who were not on HF therapy at the time of discharge and then tracked their medicine use post-discharge (ARNI use, any RAS inhibitor use, MRA use, or diuretics) as a surrogate marker for outpatient HF. We identified that post-discharge outpatients HF were much more common in the placebo arm than the treatment arm. So, if you're a strict statistical frequentist, you would say that the trial is negative. However, if you're a Bayesian statistician, you would say that the totality of evidence suggests that you significantly reduce the risk of HF development post-acute myocardial infarction with empagliflozin."

What about discerning between STEMI and non-STEMI? Can we learn anything about who to treat with SGLT2 inhibitors here?

"This is an unbelievably important question. Currently, STEMI patients have excellent prognosis after revascularisation. Looking at real-world data, the non-STEMI to STEMI ratio is 3:1; 75% of the MI are non-STEMI high-risk patients, and one-fourth are STEMI. We see in both PARADISE-MI and EMPACT-MI the exact opposite [3]. Most of the patients are lower-risk STEMI patients with fewer non-STEMI patients.

In EMPACT-MI, the annualised event risk in STEMI patients was about 8%, and 12% in non-STEMI patients. It's the non-STEMI patient who is at a higher risk, yet the benefit of empagliflozin was higher too; the point estimate was 0. 77 in non-STEMI patients. I think that our data demonstrate that the non-STEMI patient can benefit from early use of non-SGLT2 inhibitors."

What's your advice to fellow physicians about how and when to use SGLT2 inhibitors in this setting?

"There was an unbelievably good safety signal in EMPACT-MI. Total AEs, AEs leading to discontinuation, contrast-induced nephropathy: none of them were signals or different between the 2 arms. The way I look at this, if somebody comes in with acute MI and they already have an indication for an SGLT2 inhibitor—if your patient has HF, diabetes, or chronic kidney disease—physicians should feel very comfortable starting it during admission because of the safety profile. Now suppose you have an acute MI patient who has none of the other indications; they don't have HF, they don't have diabetes, they don't have CKD. If that patient has non-STEMI, I would be very much inclined to start with SGLT2 inhibition early. However, if they come in with a STEMI and they get revascularised, then I would watch that patient for a few days. If their LV is still depressed, if they're still congested, then I would start an SGLT2 inhibitor. If their stunned myocardium reverses, and if their EF is totally normalised, and they are feeling great, then maybe it's okay just to watch that patient."

1. Butler J, et al. Empagliflozin After Acute Myocardial Infarction: Results Of The EMPACT-MI Trial. ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.
2. Butler J et al. N Engl J Med 2024;390:1455-1466.
3. Mann DL et al. Am Coll Cardiol 2024;83:904-14.

Interventional Cardiology in 2024

Self-expanding versus balloon-expendable TAVR in patients with small aortic annuli

The SMART study compared the 2 most widely used transcatheter aortic valve replacement (TAVR) devices in patients with severe aortic stenosis and small annuli and found non-inferiority between the supra-annular self-expanding (SEV) and the intra-annular balloon-expandable valve (BEV). However, regarding bioprosthetic valve dysfunction (BVD) in these patients, SEV was superior at 1 year.

Besides influencing long-term results, haemodynamic differences in valve performance can be influential in up to 40% of patients, typically women with small aortic annuli [1,2]. "It's important to study women separately because they present differently and are at greater risk for complications after both surgery and TAVR," Prof. Howard Herrmann (Perelman School of Medicine, PA, USA) further explained [1].

Hence, the SMART trial (NCT04722250), conducted at 83 sites across Europe, North America, and the Middle East, set out to compare the Evolut SEV with the BEV SAPIEN platform for TAVR in this cohort of patients with small aortic annulus. The first co-primary endpoint, a clinical outcome composite of mortality, disabling stroke, and heart failure re-hospitalisation through 12 months, tested for non-inferiority between the devices. The second endpoint assessed BVD for superiority within the implanted population.

As can be expected per design, about 87% of the over 700 included participants were women. The mean baseline age was about 80 years and the mean STS-Predicted Risk of Mortality (PROM) score for operative risk was 3.3% (SEV) and 3.2% (BEV). At 1 year, the clinical outcome endpoint was met with 10.6% in the BEV and 9.4% in the SEV arm ($P_{non\text{-}inferiority}$<0.001. The valve dysfunction endpoint, in contrast, found rates of 41.6% for BEV and 9.4% for SEV through 12 months, demonstrating significant superiority of BEV (P<0.001).

Secondary endpoints included differences in mean gradient, effective orifice area, haemodynamic structural valve dysfunction, BVD in women, and moderate/severe prosthesis patient mismatch. "All five of these secondary endpoints were superior for the SEV at a P-value of less than 0.001," underlined Prof. Herrmann.

Regarding safety outcomes, new pacemaker implants were numerically higher in the SEV group at 1 and 12 months, while prosthetic valve endocarditis after 1 year was higher in the BEV arm. Otherwise, the major safety endpoints were deemed similar between the groups.

"Based on these large differences that we observed in valve performance, we expect that the SEV will demonstrate improved valve durability and outcomes during longer-term follow-up," Prof. Herrmann concluded.

1. Herrmann HC, et al. Self-expanding versus balloon-expandable transcatheter aortic valve replacement in patients with small aortic annuli: primary outcomes from the randomised SMART trial. LB3, Session 406, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.
2. Playford D, et al. J Am Soc Echocardiogr. 2020;33(9):1077-86.

Safety of TAVI non-inferior to SAVR for patients with lower surgical risk

Transcatheter aortic valve implantation (TAVI) in patients with low-to-intermediate surgical risk demonstrated non-inferiority to surgical aortic valve replacement (SAVR) in terms of safety after 1 year, according to the results of the DEDICATE-DZHK6 trial.

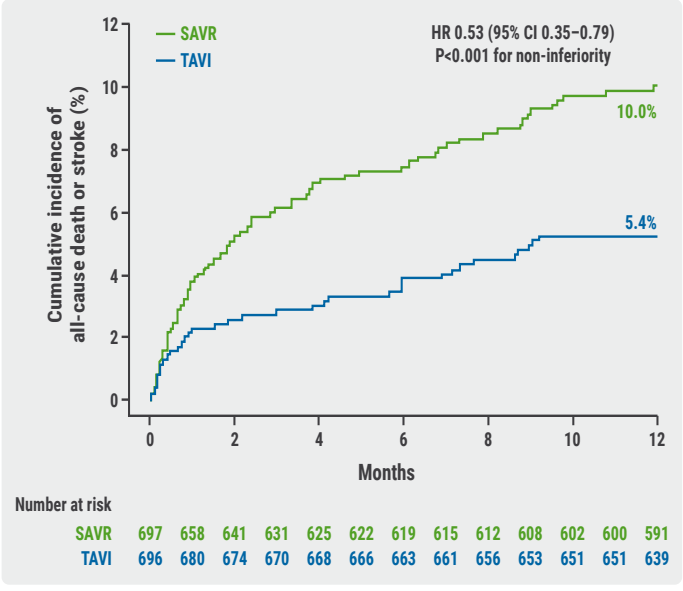
"TAVI has become the preferred treatment option for most patients with symptomatic severe aortic valve stenosis. Current evidence for young, low-risk patients, however, remains restricted to device-specific and industry-sponsored trials and that's potentially limiting the applicability to routine practice," Prof. Moritz Seiffert (BG University Hospital Bergmannsheil, Germany) explained the motivation for the DEDICATE-DZHK6 study (NCT03112980) [1].

This investigator-initiated, multicentre, randomised-controlled trial strove to reflect routine medical care by allowing the use of any kind of contemporary devices per design. It compared TAVI with SAVR in 1,414 participants aged 65–85 years with low-to-intermediate surgical risk. Over 55% of the participants were men and the mean age was about 74 years. The STS-PROM score, a surgical risk calculator, was 1.8% and 1.9% in the 2 study groups, indicating a low-risk cohort.

Prof. Seiffert presented the results of the primary safety endpoint of all-cause death or stroke at 1 year. The primary efficacy endpoint will be evaluated at year 5 of the study. The present analysis tested for non-inferiority of TAVI versus SAVR with a rejectable absolute between-group difference of 1%.

The results of the co-primary endpoint of all-cause death or stroke at 12 months revealed a cumulative incidence rate of 5.4% in the TAVI group compared with 10% in the SAVR group, corresponding to a 47% lower outcome probability (HR 0.53; 95% CI 0.35–0.79) and a P<0.001 for non-inferiority of TAVI (see Figure). Results for TAVI versus SAVR were consistent for the individual components of the primary endpoint including an HR of 0.43 (95% CI 0.24–0.73) for death and HR 0.61 (95% CI 0.35–1.06) for stroke, respectively.

Figure: DEDICATE-DZHK6 primary safety endpoint: all-cause death or stroke a 1 year [1]



CI, confidence interval; HR, hazard ratio; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

"In the DEDICATE trial, an investigator-initiated, independent trial designed to evaluate patients that mirror our daily clinical routine with aortic stenosis at low or intermediate surgical risk, TAVI with a prosthesis selection based on operator-discretion was non-inferior to SAVR with respect to death from any cause or stroke at 1 year," concluded Prof. Seiffert.

1. Seiffert M, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement in patients at low to intermediate risk- one-year outcomes of the randomised DEDICATE-DZHK6 trial. LB5, Session 412, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

Interatrial shunt for HF: neutral primary endpoint but potential benefit in HFrEF

In its composite primary efficacy outcome, the RELIEVE-HF trial did not observe a benefit for an interatrial shunt device in the overall cohort of patients with heart failure (HF). However, further stratified analysis showed a potential benefit in patients with reduced left ventricular ejection fraction (HFrEF) and potential harm for those with preserved EF (HFpEF).

Increased left atrial pressure can be difficult to control with medication [1]. Hence, the rationale for the multicentre, double-blind, sham-controlled RELIEVE-HF trial (NCT03499236) was to explore whether the implantation of an interatrial shunt would be effective for patients with either HFrEF or HFpEF [1]. The 508 participants were randomised to receive a V-Wave® Ventura® shunt or a placebo procedure. To enable differentiation of results according to the type of HF, randomisation was stratified according to reduced EF (≤40%) and preserved EF (>40%).

The effectiveness up to 2 years was assessed by a hierarchical composite of all-cause death, heart transplant or left ventricular assist device (LVAD), recurrent HF hospitalisations, out-patient worsening HF events, and change in Kansas City Cardiomyopathy Questionnaire Overall Summary Scores (KCCQ-OSS). The results on each level were reported in wins and losses for the trial arms.

RELIEVE-HF did not meet this primary efficacy endpoint as no significant difference was found for the win ratio between groups (P=0.20). Similar results were found for the risk of all cardiovascular (CV) events and KCCQ-OSS. "Where the results became particularly informative, is when we looked at the stratified randomisations according to EF," Prof. Gregg Stone (Icahn School of Medicine at Mount Sinai, NY, USA) highlighted.

Participants with HFrEF randomised to the shunt arm had a CV event rate of 49% per year compared with 88.6% in the placebo group (relative rate ratio 0.55; 95% CI 0.42–0.73; P<0.0001). "In patients with HFpEF the exact opposite pattern was seen," revealed Prof. Stone. Their control-arm event rate was 35.9%, while this was 60.2% in the shunt group (relative rate ratio 1.68; 95% CI 1.29–2.19; P=0.0001). The risk of all CV events showed directionally consistent trends for benefit and harm at stratification. Of note, the change in quality-of-life did not differ between the strata, pointing to a relevant placebo effect in KCCQ-OSS outcomes.

Safety in terms of any device-related or procedure-related major adverse cardiac or neurologic events was not observed in any of the 250 participants with a shunt at 30 days and through 2 years.

1. Stone G, et al. A Double-blind, Randomized Placebo Procedure-controlled Trial of an Interatrial Shunt in Patients with HFrEF and HFpEF: Principal Results from the RELIEVE-HF Trial. LB1, Session 402, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

Peripheral artery disease: procedure-guidance by IVUS superior to angiography

Using intravascular ultrasound (IVUS) as guidance for endovascular treatment in patients with femoropopliteal artery disease primary patency outperformed angiography alone in the IVUS-DCB study.

"IVUS provides detailed information on vessel dimensions and plaque characteristics; however, there has been limited clinical data on the benefit of IVUS in the endovascular treatment of femoropopliteal artery disease using drug-coated balloons (DCBs)," Prof. Young-Guk Ko (Severance Cardiovascular Hospital; Yonsei University, South Korea) explained the study background [1].

The investigator-initiated, randomised-controlled IVUS-DCB trial (NCT03517904) compared IVUS-guided with angiography-guided angioplasty with DCB for patients with femoropopliteal artery disease. The main study outcome was defined as primary patency (i.e. absence of clinically driven target lesion revascularisation [CD-TLR] or binary stenosis on imaging) at 12 months. The 237 participants were predominantly men (85%) and had a mean age of around 70 years. The average lesion length was between 204.9 mm and 214.5 mm with about two-third being complex lesions of TransAtlantic Inter-Society Consensus (TASC)2 type C/D.

The immediate procedural outcomes included technical success in 76.5% on IVUS and 61% on angiography (P=0.02) and procedural success in 73.9% compared with 60.2% (P=0.03), respectively. "In the IVUS group, the post-procedural ankle-brachial index was significantly higher, reflecting better haemodynamic results after the treatment," stated Prof. Ko.

In the intention-to-treat analysis at 12 months, the primary outcome results showed superiority for IVUS guidance with patency rates of 83.8% compared with 70.1% in the angiography group (HR 0.46; 95% CI 0.25–0.85; P=0.01). The per-protocol analysis showed similar results. "When we broke down the target lesions according to their complexity into the TASC2 A/B subgroup and the TASC2 C/D subgroup, the clinical benefit in terms of primary patency was evident only in complex lesions," Prof. Ko added.

The percentage of participants free from CD-TLR, a secondary endpoint, was 92.4% compared with 83.0% (HR 0.41; 95% CI 0.19–0.90; P=0.03). Among the significant predictors of re-stenosis identified by a univariate model were lesion length ≥200 mm (P=0.002) and post-procedural minimal lumen diameter (P<0.001).

1. Ko YG. Comparison of Intravascular Ultrasound-guided versus Angiography-guided Angioplasty for the Outcomes of Drug-coated Balloon in the Treatment of Femoropopliteal Artery Disease. LB5, Session 412, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

IVUS-guided PCI beats angiography in patients with acute coronary syndrome

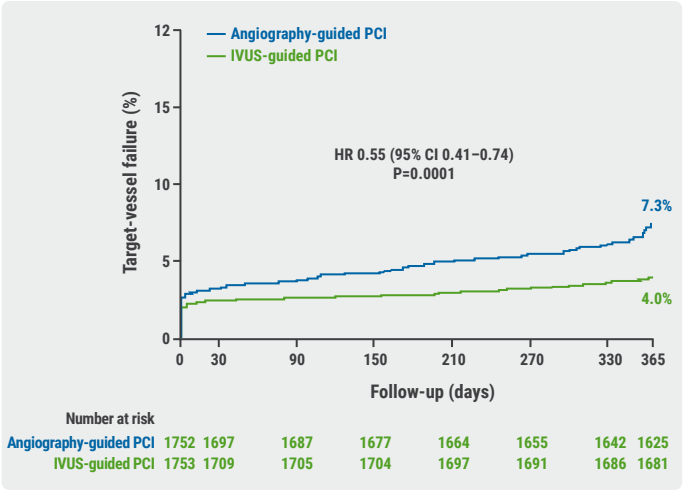
In patients with acute coronary syndrome (ACS), intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) reduced target vessel failure at 1 year compared with angiography-guided PCI in the IVUS-ACS trial. This benefit was driven by reductions in target vessel myocardial infarction (MI) and target vessel revascularisation.

"So far, there were no dedicated randomised-controlled trials of IVUS-guided PCI versus angiography-guided PCI in patients with ACS," Prof. Shao-Liang Chen (Nanjing Medical University, China) explained the rationale for the IVUS-ACS trial (NCT03971500) [1]. Until recently, only 3 small randomised-controlled trials of intravascular imaging-guided versus angiography-guided PCI have been performed in patients with ACS. Therefore, Prof. Chen and his team set up the international, investigator-initiated IVUS-ACS trial to investigate whether IVUS guidance compared with angiography guidance for implantation of second-generation drug-eluting stents improves the outcomes of PCI in these patients [1,2].

All participants presented with ACS within 30 days before randomisation. The analysis included 3,505 participants from 58 centres in China (over 2,000 of the participants), Italy, Pakistan, and the UK, who were randomised to IVUS-guided PCI (n=1,753) or angiography-guided PCI (n=1,752). In the IVUS group, 39.9% had unstable angina, 32.5% had a non-ST elevation myocardial infarction (non-STEMI), and 27.6% had a STEMI. The percentages in the angiography-guided group were similar: 41.4% had unstable angina, 30.7% non-STEMI, and 27.9% STEMI.

The primary study endpoint was target vessel failure, a composite of cardiac death, target vessel MI, or clinically driven target vessel revascularisation 1 year after randomisation. At this time, 4.0% in the IVUS-guided PCI group compared with 7.3% of participants in the angiography-guided PCI group reached this endpoint, a highly significant difference driven by reductions in target vessel MI and target vessel revascularisation (HR 0.55; 95% CI 0.41–0.74; P<0.0001; see Figure). The safety outcomes were similar between the 2 groups.

Figure: Primary endpoint of the IVUS-ACS trial: target vessel failure [1]



CI, confidence interval; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention; TVF, target vessel failure.

Prof. Chen pointed out that all subgroups (including participants with diabetes, multivessel disease, or those receiving antiplatelet therapy) benefitted from the IVUS-guided stent implantation independent of whether they had unstable angina, STEMI, or non-STEMI.

1. Chen SL, et al. Intravascular Ultrasound-guided Versus Angiography-guided Percutaneous Coronary Intervention in Acute Coronary Syndromes: The Multicenter, Randomized, Blinded, IVUS-ACS Trial. Featured Clinical Research 3, Session 413, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.
2. Li X, et al. Lancet 2024;Apr 8. DOI: 10.1016/S0140-6736(24)00282-4.

Addressing frailty in patients undergoing TAVR

A protein supplement together with a home-based exercise intervention improved frailty measures in elderly patients undergoing transcatheter aortic valve replacement (TAVR). This intervention significantly improved strength, mobility, and balance 3 months after the procedure with a comparable effect size to a cardiac rehabilitation programme.

Frailty has been associated with poor outcomes in older adults undergoing TAVR despite high technical success in previous trials [1]. "Therefore, the conceptual framework here is to intervene on the frailty at the same time that we intervene on the heart, to move these frail patients away from poor outcomes and towards favourable outcomes," Dr Jonathan Afilalo (McGill University, Canada) explained the aim of the PERFORM-TAVR trial (NCT03522454), which was conducted at 11 hospitals across Canada [2].

The 180 participants were ≥70 years of age (mean age 83 years) and had objective evidence of physical frailty in standardised scores. The control group received lifestyle education only, while those in the intervention group received lifestyle education in addition to a home-based exercise programme with a supervised component entailing home visits of an hour by a therapist twice a week for 12 weeks after TAVR, complemented with an unsupervised walking programme. In addition, the intervention group received a protein-rich oral nutritional supplement that they consumed twice daily starting 4 weeks before TAVR and continuing for 12 weeks after TAVR.

The primary study endpoint was the short physical performance battery (SPPB) score (range 0–12) at 12 weeks, which consists of a 3-part balance test, a gait speed test, and a chair stand test. "We're really looking at strength, mobility, and balance," Dr Afilalo explained.

The mean SPPB score at baseline was 7.1 for both groups. At 12 weeks, it improved to 8.1 in the intervention group versus 7.1 in the control group, a multivariable-adjusted difference of 0.9 points (95% CI 0.3–1.6; P=0.006). "A 1-point improvement is approximately the same effect size observed with a full-blown cardiac rehabilitation programme. Improving frailty might improve the outcomes of patients undergoing all sorts of interventional procedures," Dr Afilalo concluded.

1. Afilalo J, et al. J Am Coll Cardiol 2017;70:689-700.
2. Afilalo J, et al. Protein and Exercise to Reverse Frailty in Older Men and Women Undergoing Transcatheter Aortic Valve Replacement: The PERFORM-TAVR Trial. Featured Clinical Research 3, Session 413, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

Prof. Gregg Stone
MD, FACC, MSCAI

Meet the Trialist: The "Sweet Spot" from RELIEVE-HF

Medicom spoke with Prof.Gregg Stone (Icahn School of Medicine at Mount Sinai, NY, USA) about the results of the RELIEVE-HF trial (NCT03499236), which he shared during the ACC 2024 Scientific Session, held in Atlanta, USA [1].

The RELIEVE-HF trial evaluated the efficacy of interatrial shunting using the Ventura shunt in heart failure (HF) patients with reduced (HFrEF) and preserved ejection fraction (HFpEF). This global study randomised 508 participants to receive either the shunt or a placebo procedure, alongside optimal medical therapy. The study's primary endpoint—combining mortality, heart transplant or device implantation, HF hospitalisations, outpatient worsening, and quality of life changes—showed no significant difference between the shunt and placebo groups.

Notably, a prespecified subgroup analysis revealed that participants with HFrEF benefitted from the shunt, particularly in reduced HF hospitalisations, whereas HFpEF patients experienced increased death rates and hospitalisations, suggesting the intervention's benefits and risks are contingent on the type of heart failure. These findings highlight the importance of patient selection based on ejection fraction status in clinical decisions regarding interatrial shunting.

RELIEVE-HF highlighted notable differences in outcomes between HFrEF and HFpEF. What does this imply about the underlying pathophysiological distinctions?

"The primary takeaway from RELIEVE-HF is that the Ventura interatrial shunt is very safe for a severely ill HF population, though it didn't demonstrate overall efficacy. However, we observed a significant contrast in treatment effects between patients with reduced and preserved EF. Those with a baseline EF ≤40% saw substantial benefits, including a near 50% reduction in CV events and notably in HF hospitalisations. Conversely, for those with an EF ≥40%, the outcomes were detrimental, showing increased hospitalisations and a tripling in mortality. This suggests a potential role for interatrial shunts in patients with reduced EF, while their use in patients with preserved EF should be extremely cautious, if considered at all.

We have baseline and 1-year transthoracic echocardiographic data. Both HFrEF and HFpEF patients show increased left atrial volume and similar median pressures around 16 mmHg. However, their cardiac structures differ significantly; HFrEF patients have a dilated and weak left ventricle, accommodating the increased flow from the shunt. In HFpEF, the ventricles are normal-sized but stiff, leading to complications when accommodating additional fluid. This results in increased tricuspid regurgitation, pulmonary artery pressure, and potentially detrimental shifts in cardiac output."

Given these findings, would you recommend modifications to selection criteria for future studies or the clinical use of interatrial shunts in HF?

"Considering the baseline event rates in our study, there remains a substantial clinical need in HFrEF patients who had a significantly higher annual event rate compared with HFpEF patients. Future studies like ALLAY-HF (NCT05685303) and RESPONDER-HF (NCT05425459) are targeting a different, lower-risk HFpEF population. From what we've learned, HFrEF patients benefit markedly from shunt interventions, suggesting this group should remain a primary focus in future trials.

In the original REDUCE LAP-HF II trial (NCT03088033), it was surprising to see almost no mortality among the participants, given that they were an HF population [2]. The participants were considered low risk; eligibility required only exercise-induced increased pulmonary capillary wedge pressure. Although the overall results of the trial were negative, there appeared to be a subgroup within this very low-risk cohort that was at an even lower risk, showing lower natriuretic peptide levels and better cardiac function without right heart involvement. I believe there is a sweet spot for a small subset of patients with HFpEF, where shunts may not reduce their already low [...]

Curious?
Continue reading this interview online.

Novel Developments in Risk Factor Management

Preventive PCI of vulnerable intracoronary plaque leads to favourable outcomes

Adding percutaneous coronary intervention (PCI) to optimal medical treatment (OMT) reduced revascularisations for high-risk vulnerable coronary plaques in the PREVENT trial. At 2 years, the cumulative incidence of target vessel failure was 0.4% for those receiving PCI and 3.4% without PCI, showing a statistically significant difference.

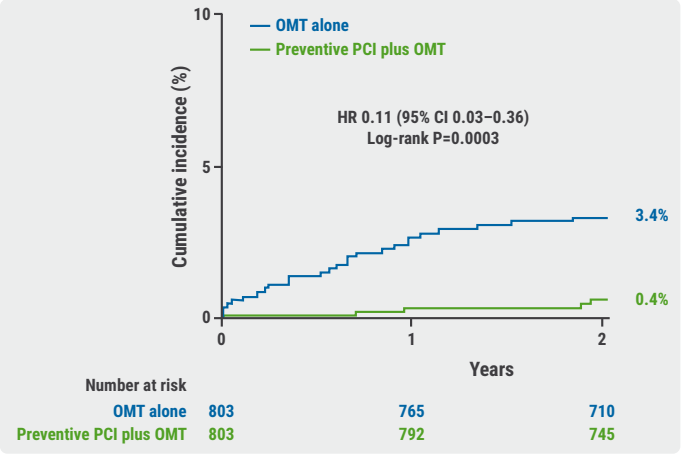
"An intracoronary, imaging-defined vulnerable plaque tends to increase major adverse cardiac events, and OMT is the standard approach to stabilise the vulnerability of the plaque," Prof. Seung-Jung Park (University of Ulsan College of Medicine; Asan Medical Center, South Korea) explained [1]. The multicentre, randomised-controlled PREVENT trial (NCT02316886) compared OMT alone with OMT plus preventive PCI of vulnerable non-flow-limiting coronary plaques [1,2].

The 1,606 participants from research hospitals in South Korea, Japan, Taiwan, and New Zealand were randomised 1:1 to PCI and OMT or OMT alone. Among the inclusion criteria were stenosis >50% and a negative fractional flow reserve (FFR) of ≥0.80. The primary endpoint was a composite of death from cardiac causes, target vessel myocardial infarction (MI), ischaemic-driven target vessel revascularisation, or hospitalisation for unstable/progressive angina, summarised as target vessel failure at 2 years.

The results showed a cumulative incidence of target vessel failure in 0.4% of the OMT plus PCI arm, compared with 3.4% on OMT alone (see Figure). This resulted in a significant HR of 0.11 (95% CI 0.03–0.36; P=0.0003). After a longer follow-up at 7 years, a consistent advantage of preventive PCI was seen with target vessel failure rates of 6.5% versus 9.4%, respectively (HR 0.54; 95% CI 0.33–0.87; P=0.0097).

Furthermore, the composite of any-cause death, any MI, or any repeat revascularisation through 7 years was significantly reduced in the intervention group (HR 0.69; 95% CI 0.50–0.95; P=0.022). Among the individual primary outcome components, only ischaemia-driven revascularisation and hospitalisation for angina were significantly in favour of the PCI group, other components showed no between-group difference. Also, no statistical differences were determined for secondary endpoints like bleeding events and stroke.

Figure: Target vessel failure at 2 years of follow-up in the PREVENT trial [1]



CI, confidence interval; OMT, optimal medical treatment; PCI, percutaneous coronary intervention.

"Our key findings might provide a novel insight into the role of a preventive PCI on non-flow-limiting high-risk vulnerable plaques in the future," concluded Prof. Park. Further information with regard to the definition of optimal medical therapy in this open-label trial may shed further light on the efficacy and safety of this strategy.

1. Park SJ. Preventive PCI or medical therapy alone for atherosclerotic coronary vulnerable plaques. LB5, Session 412, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.
2. Park SJ, et al. Lancet 2024; April 8. DOI: 10.1016/S0140-6736(24)00413-6.

KARDIA-2: Add-on zilebesiran effectively lowers blood pressure

A single subcutaneous dose of zilebesiran in combination with indapamide, amlodipine, or olmesartan demonstrated significant reductions in both ambulatory and office systolic blood pressure (SBP) at month 3. Moreover, the novel blood pressure-lowering drug showed a promising safety profile, suggesting its potential as a novel treatment strategy for hypertension.

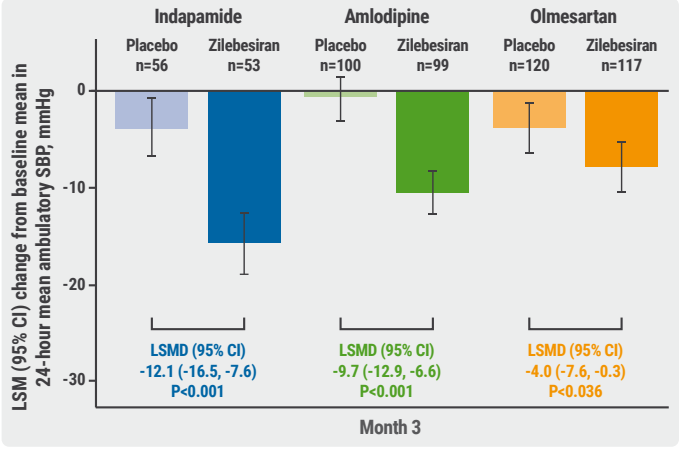
"Despite the availability of effective therapies, many patients with hypertension do not achieve guideline-recommended blood pressure targets, leaving them at an unattended risk for cardiovascular events," said Dr Akshay Desai (Brigham and Women's Hospital, MA, USA) [1]. In part, this may be due to poor adherence to complex multidrug oral treatment regimens.

Zilebesiran, an investigational RNA interference therapeutic, significantly reduced 24-hour mean ambulatory SBP at 3 months with a single subcutaneous injection compared with placebo in the phase 2 KARDIA-1 study [2]. Building on this, the phase 2 KARDIA-2 study (NCT05103332) aimed to assess zilebesiran's efficacy in combination with standard-of-care anti-hypertensive therapy [1].

The study enrolled 1,500 adults with mild-to-moderate hypertension, who were randomised to receive once-daily oral treatment with indapamide, amlodipine, or olmesartan as background therapy. Those with a 24-hour mean SBP of 130–160 mmHg for ≥4 weeks were further randomised to receive zilebesiran 600 mg or placebo as add-on therapy.

At 3 months, participants receiving zilebesiran with either indapamide, amlodipine, or olmesartan demonstrated statistically significant reductions in 24-hour mean ambulatory SBP and office SBP compared with placebo. The LS mean differences were -12.1 mmHg for zilebesiran + indapamide, -9.7 mmHg for zilebesiran + amlodipine, and -4.0 mmHg for zilebesiran + olmesartan (all with P<0.001; see Figure). At 6 months, reductions in office SBP remained significant (P<0.01 for all comparisons) for zilebesiran + indapamide (-13.6 mmHg), zilebesiran + amlodipine (-8.6 mmHg), and zilebesiran + olmesartan (-4.6 mmHg).

Figure: Change from baseline to month 3 in 24-hour mean ambulatory SBP [1]



CI, confidence interval; LSM, least-square mean; LSMD, LSM difference; SBP, systolic blood pressure.

Safety analysis revealed a favourable profile for all combinations, with low incidences of adverse events (AEs) and rare serious AEs. Notably, hypotension/orthostatic hypotension occurred in 7 participants in each combination group but was resolved without intervention. A few participants experienced >30% reduction in eGFR, primarily in the first 3 months, which resolved upon repeat measurement.

"Although our trial was not adequately powered nor of sufficient duration to ensure long-term safety and efficacy, these results do appear to support the potential for combining biannual dosing of zilebesiran with standard-of-care or any hypertensives to achieve additive blood pressure reductions," concluded Dr Desai.

1. Bakris GL, et al. Zilebesiran in Combination with a Standard-of-care Antihypertensive in Patients with Inadequately Controlled Hypertension: Primary Results from the Phase 2 KARDIA-2 Study. LB2, Session 405, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.
2. Bakris GL, et al. JAMA. 2024;331(9):740-749.

BRIDGE-TIMI 73a: Olezarsen halves triglyceride levels

The antisense oligonucleotide olezarsen lowered triglycerides by up to 53% at 6 months compared with placebo in patients with hypertriglyceridaemia and elevated cardiovascular risk in the phase 2b BRIGDE-TIMI 73a trial. Moreover, the agent led to reductions in apolipoprotein B and was generally well tolerated.

"Treatments to reduce high triglycerides are an unmet clinical need," said Dr Brian Bergmark (Brigham and Women's Hospital, MA, USA) [1]. Rare mutations that disrupt apolipoprotein C3 (ApoC3) function are associated with lower levels of plasma triglycerides and ApoC3, and carriers of these mutations were found to have a reduced risk of coronary heart disease [2].

A previous study found that olezarsen, an antisense oligonucleotide that targets ApoC3 mRNA, significantly reduced levels of both triglycerides and ApoC3 in patients with moderate hypertriglyceridaemia. The objective of the BRIDGE-TIMI 73a trial (NCT05355402) was to assess the efficacy and safety of olezarsen in patients with moderate hypertriglyceridaemia (150 to <500 mg/dL) and elevated cardiovascular risk or in patients with severe hypertriglyceridaemia (≥500 mg/dL) [1]. All 154 participants were already receiving standard-of-care anti-lipid medication. They were randomised to receive either 50 mg (n=58) or 80 mg olezarsen (n=57), or a placebo (n=39), subcutaneously every 4 weeks.

At month 6, the primary endpoint of placebo-adjusted change in triglyceride concentrations was -49.3% with 50 mg olezarsen (95% CI -59.0 to -39.5; P<0.001). The corresponding number in the 80 mg group was -49.3% (95% CI -62.7 to 43.3; P<0.001).

The secondary endpoint of ApoC3 protein levels at 12 months dropped by -64.2% in participants in the 50 mg group and by -73.2% in the 80 mg group (P<0.001 for each comparison). Moreover, "if you want to reduce a patient's risk for a heart attack or stroke, you would like to see a reduction in ApoB. And we did see that in this study [by 18% on both doses], which is very encouraging," Dr Bergmark commented.

At 6 months, 85.7% of the participants treated with 50 mg and 93.3% of those treated with 80 mg olezarsen achieved a triglyceride goal of <150 mg/dL, another secondary outcome. This was 11.8% in the placebo group (P<0.001 for both comparisons). As Dr Bergmark pointed out, this triglyceride effect was greater than is possible with currently available treatments.

No major safety concerns emerged during the study and follow-up period. Additional trials of olezarsen including participants with severe hypertriglyceridaemia are ongoing.

1. Bergmark BA, et al. Efficacy and safety of olezarsen in patients with hypertriglyceridemia and high cardiovascular risk: Primary results of the BRIDGE-TIMI 73a trial. LB2, Session 405, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

Plozasiran: A novel approach to severe hypertriglyceridaemia

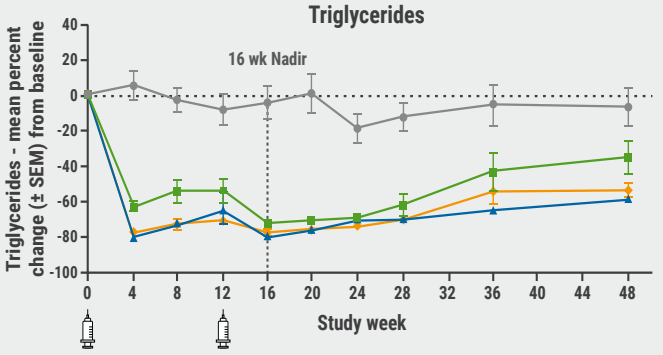
Plozasiran targets apolipoprotein C3 (ApoC3) to tackle severe hypertriglyceridaemia. In the phase 2 SHASTA-2 study, it notably lowered triglyceride levels and ApoC3 concentrations, with over 90% of participants reaching triglyceride levels below the critical acute pancreatitis risk threshold.

Severe hypertriglyceridaemia, a risk factor for acute pancreatitis and cardiovascular disease, is still challenging to treat. Plozasiran selectively targets ApoC3, a regulator of triglyceride metabolism. The phase 2b SHASTA-2 trial (NCT04720534) assessed the safety and efficacy of plozasiran in individuals with severe hypertriglyceridaemia, defined as triglyceride levels >500 mg/dL and fasting triglyceride levels of 500–4,000 mg/dL [1]. Primary endpoints included percentage triglyceride change from baseline and over time, with evaluation at week 24 and week 48. Additionally, ApoC3, apoB, LDL-cholesterol, non-HDL-cholesterol, HDL-cholesterol, and remnant cholesterol were assessed. Safety was also a key consideration.

Over 48 weeks, participants receiving 50 mg of plozasiran exhibited remarkable reductions in both triglyceride levels and ApoC3 concentrations:

- ApoC3 levels decreased by 78% at week 24, persisting at a reduction of 48% by week 48 (P<0.0001);
- triglyceride levels showed a significant reduction of 74% at week 24, with a sustained reduction of up to 58% by week 48 (P<0.0001; see Figure).

Figure: Plozasiran significantly decreased triglycerides in patients with severe hypertriglyceridemia [1]



LS Mean % Change frome baseline at weeks 24 & 48

	Placebo	Plozasiran 10 mg	Plozasiran 25 mg	Plozasiran 50 mg
Week 24	-17%	-66% (P<0.0001)	-70% (P<0.0001)	74% (P<0.0001)
Week 48	-7%	-31% (P<0.05)	-58% (P<0.0001)	53% (P<0.0001)

Placebo — Plozasiran 10 mg — Plozasiran 25 mg — Plozasiran 50 mg

LS, least square; SEM, standard error of the mean.

Moreover, a vast majority of participants (over 90%) achieved triglyceride levels below 500 mg/dL, a critical threshold associated with elevated acute pancreatitis risk, by week 24. These reductions were accompanied by improvements in other atherogenic lipid parameters, including remnant cholesterol and non-HDL-cholesterol.

These promising results from the SHASTA-2 study underscore plozasiran's potential in severe hypertriglyceridaemia management. Thus, a phase 3 study in a broader patient population is underway.

1. Gaudet D, et al. Plozasiran (ARO-APOC3), an investigational RNAi therapeutic, demonstrates profound and durable reductions in APOC-3 and Triglycerides (TG) in patients with severe hypertriglyceridemia (SHTG), SHASTA-2 final results. LB4, Session 4115, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

High-risk and very high-risk patients meet LDL-cholesterol targets with lerodalcibep

The results of the LIBerate-HR study showed LDL-cholesterol reductions of 50–60% after 1 year of treatment with lerodalcibep. The dual treatment target of ≥50% decrease in LDL-cholesterol and reaching the adequate LDL-cholesterol goal was attained by 90% of participants on the novel PCSK9 inhibitor.

After encouraging phase 2 results, the third-generation PCSK9 inhibitor lerodalcibep advanced to phase 3 testing for long-term efficacy and safety [1]. The LIBerate-HR trial (NCT04806893) enrolled 922 adults with high to very high cardiovascular disease risk who were not reaching their LDL-cholesterol targets on oral lipid-lowering medication. The participants were randomised to lerodalcibep, 300 mg every 4 weeks (n=615), or a placebo (n=307). Efficacy endpoints were analysed in 3 population sets: per protocol (PP), modified intention-to-treat (mITT), and ITT with multiple imputation washouts, adjudicating discontinuing participants to an outcome similar to placebo.

On average, the participants were 65 years old and about 46% were women. "The entry level of LDL-cholesterol despite being on a maximum dose of statin and other oral lipid-lowering agents, was 116 mg/dL," underlined Prof. Eric Klug (University of the Witwatersrand, South Africa).

The co-primary endpoints of percentage change at week 52 and mean of weeks 50 and 52 significantly favoured the study drug in all groups. Placebo-adjusted reduction rates at week 52 were -60.27% (PP), -56.19% (mITT), and -49.67% (ITT). The means of weeks 50/52 were -65.85%, -62.69%, and -55.33%, respectively. Furthermore, 90% of the active treatment cohort achieved their LDL-cholesterol goal together with a ≥50% decrease in LDL-cholesterol compared with 16% on placebo. Significant reductions were also determined for other lipids like non-HDL-cholesterol and apolipoprotein B. "Adverse events and key safety laboratory findings were similar in both arms," noted Prof. Klug. An exception were injection site reactions with 6.9% (lerodalcibep) versus 0.3% (placebo).

"Lerodalcibep offers a novel, effective alternative to existing PCSK9 inhibitors," Prof. Klug commented. He also pointed out that its long ambient stability allowed for patients' home use.

1. Klug E. Randomised, double-blind, placebo-controlled, phase 3, study to evaluate lerodalcibep long-term efficacy and safety in patients with, or at very-high or high risk, for cardiovascular disease on stable lipid-lowering therapy. LB2, Session 405, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

No cardioprotective effect of ACE inhibitors in patients with cancer

In the phase 3 PROACT trial, the ACE inhibitor enalapril did not show benefit in patients with cancer against anthracycline-related cardiotoxicity. The participants in this trial were undergoing high-dose anthracycline chemotherapy for breast cancer or lymphoma.

The multicentre, open-label, phase 3 PROACT trial (NCT03265574) enrolled 111 participants undergoing treatment for breast cancer (62%) or non-Hodgkin lymphoma (38%) who were randomised to enalapril or placebo [1]. All participants had negative troponin levels at baseline and then received 6 cycles of anthracycline chemotherapy at a mean dose of 328 mg/m^2 doxorubicin equivalent. Dr David Austin (South Tees Hospitals, UK) and colleagues assessed participants' troponin levels during their chemotherapy treatment and at 1 month following their last anthracycline dose.

At the end of the study period, no significant between-group difference was found in the proportion of participants who had experienced a troponin T release (the primary study endpoint): this occurred in 77.8% of the enalapril group and 83.3% of the standard-of-care group (adjusted odds ratio 0.65; P=0.405).

"We did not see evidence that we could reduce this biomarker of cardiotoxicity during chemotherapy," said Dr Austin. "The conclusion from PROACT is that we would not support putting enalapril into a standard care preventative pathway in these patients."

1. Austin D, et al. PROACT: Can we prevent chemotherapy-related heart damage in patients with breast cancer and lymphoma? LB4, Session 411, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.

Best of the Posters

SGLT2 inhibition in heart failure more advantageous for women than men

A meta-analysis compared the benefit of heart failure therapy with SGLT2 inhibitors versus placebo in women and men showing a risk reduction for women.

Currently, SGLT2 inhibitors form part of the guideline-recommended standard-of-care in the treatment of heart failure with various ejection fractions, as they have demonstrated benefits in cardiac and renal protection, independent of HbA1c, blood pressure, weight, and kidney function [1,2]. In heart failure trials, women are mostly underrepresented leading to a lack of sex-specific cardiovascular (CV) outcome data [1,3]. To gain further insight into this matter, Dr Mounica Vorla (University of Louisville School of Medicine, KY, USA) and colleagues performed a meta-analysis of randomised, placebo-controlled trials that provided results stratified by sex [1]. Pooled risk ratios (RR) for the primary composite outcomes were determined using a random effects model that included data from 11 studies.

For women, this comparison of SGLT inhibition with placebo led to a pooled RR of 0.76 (95% CI 0.69–0.82; P<0.00001). For men, the pooled RR was 0.80 (95% CI 0.73–0.87; P<0.00001). Furthermore, the results of the meta-analysis observed reductions in all-cause and CV death, along with hospitalisation for heart failure. Of note, the study authors conceded some limitations to their analysis, including the lack of patient-level data and heterogeneity between the included trials.

1. Vorla M, et al. SGLT2 inhibitors in women and cardiovascular outcomes - meta-analysis of sex differences in eleven randomised controlled clinical trials. Session 1039-11, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.
2. Rosano G, et al. Card Fail Rev. 2020:6:e31.
3. Bozkurt B, Khalaf S. Methodist Debakey Cardiovasc J. 2017;13(4):216-223.

Anxiety and depression: Lifestyle influential in MACE prevention

Pursuing a favourable lifestyle may have a greater impact on the risk of major adverse cardiovascular events (MACE) in people with anxiety and/or depression than in those without. A healthy lifestyle was also associated with neuro-inflammatory changes.

The presented retrospective cohort study included 37,383 individuals from the Mass General Brigham Biobank from 2010–2020 [1]. In this cohort, Dr Shady Abohashem (Massachusetts General Hospital-Harvard Medical School, MA, USA) and colleagues assessed the efficacy of lifestyle factors, measured by a lifestyle score, on the risk of cardiovascular disease (CVD) in people with and without anxiety and/or depression. The study also evaluated neuro-inflammatory markers like stress-related neural activity. The primary endpoint was a lifestyle score named LS (A) that was calculated as a composite of favourable lifestyle behaviours: exercise at ≥500 metabolic equivalents of task (METs)/week, average sleep of 7–9 hours daily, and alcohol of 1–14 units/week.

In a Cox model that adjusted for CVD risk factors, an overall lower chance of MACE (i.e. myocardial infarction, unstable angina, or stroke) was associated with the highest score category of lifestyle over 10 years (HR 0.53; 95% CI 0.48–0.59). Also, each change of lifestyle category was linked to a reduced risk of MACE (HR 0.82; 95% CI 0.79–0.84). Assessing people without versus people with anxiety and/or depression showed a greater decrease in risk for people with anxiety and/or depression, translating into an additional relative risk reduction of 64% with a P<0.001 for effect modification.

In a subset of individuals with data on neuro-immune measures, LS (A) was linked to a graded reduction in stress-related neural activity on FDG PET/CT imaging. For heart rate variability and C-reactive protein, significant associations to LS (A) were also observed. A mediation analysis further suggested that the neuro-inflammatory pathways may be partially involved in the benefit of a favourable lifestyle. Future research investigating measures of lifestyle modification could be specifically beneficial to individuals with anxiety and/or depression by providing preventive recommendations for this population.

1. Abohashem S, et al. Lifestyle behaviours associate with greater reduction in cardiovascular disease risk among people with anxiety and/or depression: mediated by a reduction in stress related brain activity. Session 910-05, ACC 2024 Scientific Session, 6–8 April, Atlanta, USA.