Medicom International Conference Series in Cardiology

AHA Scientific Sessions 2022

American Heart Association

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PEER-REVIEWED CONFERENCE REPORT

Results from the BEST-CLI trial

In patients with chronic limb-threatening ischaemia, bypass surgery was associated with a reduction in the composite of major adverse limb events, all-cause mortality, major interventions, and above-ankle amputation compared with endovascular treatment.

read more on PAGE 9

Empagliflozin reduces kidney disease progression and CV events

Empagliflozin significantly reduced the risk of progression of kidney disease or death from cardiovascular causes by 28% in the phase 3 EMPA-KIDNEY trial, with a 14% decrease in hospitalisation.

read more on PAGE 13

Olpasiran: dramatic reductions in Lp(a)

Olpasiran, a small interfering RNA, successfully reduced lipoprotein(a) (Lp[a]) levels by >90% in patients with atherosclerotic cardiovascular disease in the phase 2 OCEAN(a)-DOSE trial.

read more on PAGE 15

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Cover photo	Heather Bozman, Pexels
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MEDICOM
MEDICAL PUBLISHERS

Head Office
Medicom Medical Publishers
Ruijterlaan 1-A
3742 AE Baarn
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

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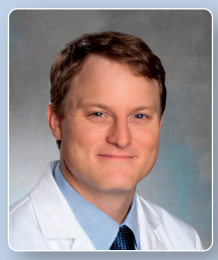
Letter from the Editor



Dear colleagues,

Thank you for your interest in this edition of Medicom's Conference Report covering the American Heart Association's 2022 Scientific Sessions in Chicago, USA. This year's meeting was filled with late breaking clinical trials, innovative science, and therapeutic device applications for heart failure patients.

This year's AHA meeting covered a breadth of topics. In the following pages you will read about new data for patients with heart failure including diuretic choice, iron repletion, and benefits of intensive titration of proven therapies; novel approaches to hypertension including endothelin antagonism, renal denervation, and mindfulness; results from the long-awaited BEST-CLI trial asking what the best first approach is to revascularization in patients with critical limb threatening ischemia; and novel approaches to patients with arrythmia. Late-breaking data were presented on the use of SGLT2 inhibitors in patients with chronic kidney disease; evaluating novel and existing lipid modifying therapies, testing novel digital therapeutics for diabetes, and therapies to reduce risk in outpatients with COVID-19.

The summaries provided are intended to give an overview of the science with references to facilitate further learnings. All are written independently and are peer-reviewed for balance. We hope you find this edition informative, engaging, and balanced and thank you again for your readership.

Sincerely,
Marc P. 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, USA. He is the Director of Vascular Research and an Associate Professor of Medicine at the University of Colorado School of Medicine, USA, and the inaugural holder of the William R. Hiatt Endowed Chair in Cardiovascular Research. Prof. Bonaca earned his medical degree from the University of Connecticut School of Medicine, USA and his Master Degree in Public Health at Harvard University, USA. He served as a Medical House Officer at Brigham and Women's Hospital and Harvard Medical School, USA. 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, USA, and became an Investigator at the TIMI Study Group. Prof. Bonaca's research focus is on ischemic risk in patients with atherosclerotic vascular disease, risk prediction, and risk modification using 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.

What Is New in Heart Failure

Torsemide not superior to furosemide after hospitalisation for heart failure

Treatment with loop diuretic torsemide did not show a survival benefit for patients with heart failure (HF) post-discharge compared with furosemide in the phase 3 TRANSFORM-HF trial. The results also showed no difference in total hospitalisations at 12 months.

The, randomised, phase 3 TRANSFORM-HF trial (NCT03296813) compared long-term clinical outcomes of treatment with furosemide versus torsemide after hospitalisation in patients with HF [1]. "We focused on the recruitment of hospitalised patients with HF, wielding eligibility criteria that included patients regardless of ejection fraction, as long as there was a long-term plan for a loop diuretic," Prof. Robert Mentz (Duke University Hospital, NC, USA) explained. The open-label dosing regimens were left at the discretion of the treating clinician. Follow-up was performed without in-person study visits after 30 days, 6 months, and 12 months. The primary endpoint was all-cause mortality.

TRANSFORM-HF randomised 2,859 patients (out of a planned 6,000) between 2019 and 2022 in a 1:1 fashion. Baseline characteristics showed well-balanced groups with a mean age of 65 years, 37% women, and 34% self-identified as Black. Around 64% had a reduced ejection fraction of ≤40% and, among those, more than 80% received treatment with β-blockers and more than two-thirds received medications affecting the renin-angiotensin-system. Upon trial entry, 67% of the participants were already treated with a loop diuretic, primarily furosemide. At baseline, the total daily dose was equivalent to 66 mg of furosemide in both groups. After discharge, the furosemide equivalent dose in both arms was about 80 mg.

All-cause mortality over 12 months was high in both treatment arms with 374 (26.2%) deaths on furosemide and 373 (26.1%) on torsemide. This translated into 17.0 events/100 patient-years (PY) in both arms and a corresponding hazard ratio of 1.02 (95% CI 0.89–1.18; P=0.77). In terms of the composite secondary endpoint of all-cause mortality or hospitalisation over 12 months, the findings were very similar: 704 events (49.3%) in the furosemide group versus 677 events (47.3%) in the torsemide arm (107.6 events/100 PY vs 99.2 events/100 PY, respectively), leading to a hazard ratio of 0.92 (95% CI 0.83–1.02; P=0.11).

At 12 months, the total hospitalisation rate also did not significantly differ between the study groups. At discharge after the index event, 5.4% of participants had crossed over from furosemide to torsemide or vice versa, while 2.8% of participants did not receive a loop diuretic at all. After 30 days of follow-up, these percentages rose to 6.7% of participants crossing over and 7.0% of participants not receiving a loop diuretic.

The trial overall did not show superiority of torsemide. Prof. Mentz stressed that insights from the pragmatic trial design and execution could inform future studies aiming to assess real-world effectiveness in diverse populations.

1. Mentz RJ. Comparative effectiveness of torsemide versus furosemide in heart failure: Primary results of the TRANSFORM-HF trial. LBS.01, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

IRONMAN failed primary endpoint but shows potential long-term benefits of iron repletion in HF patients

The IRONMAN trial narrowly missed its primary endpoint but did appear to suggest long-term benefits of intravenous (IV) iron supplementation for heart failure (HF) patients with an iron deficiency.

Iron deficiency is common in patients with HF and is associated with more severe symptoms and an adverse prognosis. Prof. Paul Kalra (Portsmouth Hospitals University NHS Trust; University of Glasgow, UK) and his team designed the randomised, multicentre, phase 4 IRONMAN trial (NCT02642562) to investigate whether long-term administration of IV iron improves outcomes among adults with HF and iron deficiency compared with the current guideline-recommended care [1,2]. Although the 2021 ESC Guideline recommends IV iron supplementation with ferric carboxymaltose for patients with iron deficiency recently hospitalised for symptomatic HF and with LVEF ≤50% and

iron deficiency, the evidence level is IIa and it is not routinely incorporated into patient care [3]. The investigators here wanted to explore the clinical efficacy of IV iron administration when HF patients were in hospital.

The study included 1,137 hospitalised adults with HF and iron deficiency in the UK. The average age of the participants was 73 years and 26% were women. The participants were randomised 1:1 to receive IV iron plus standard care or standard care alone. The intervention group received additional doses at the 1-month review and every 2 months if iron deficiency returned. The participants were followed up for a median duration of ~2.5 years, with follow-up clinic visits every 4 months. The primary endpoint was the composite of hospitalisation for worsening HF or cardiovascular (CV) death.

During the COVID-19 pandemic in 2020 and 2021, recruitment slowed or ceased at many sites. To account for these difficulties and in line with regulatory (FDA, EMA) guidance, a prespecified COVID-19 sensitivity analysis was performed on the data from the 1,063 participants who had joined the trial before 31 March 2020 and whose treatment was not affected by the pandemic.

Without consideration of the impact of COVID-19, participants in the 2 arms showed no significant difference for the primary endpoint of recurrent HF hospitalisation or CV death (HR 0.82; 95% CI 0.66–1.02; P=0.07). In a secondary analysis participants in the intervention group appeared to have a better quality of life after 4 months, and long-term IV iron use was also associated with lower rates of serious adverse cardiac events compared with standard care. The risk of infection did not increase in the IV iron-receiving participants compared with standard care.

The prespecified COVID-19 sensitivity analysis observed a potential benefit of IV iron on the main study outcome, reducing the risk of heart failure hospitalisation and cardiovascular death (RR 0.76; 95% CI 0.58-1.00; P=0.047).

Although the trial was neutral overall, in the context of other data supporting iron, they may be viewed as supportive of iron repletion. "I think, the IRONMAN trial gives us reassurance that correction of iron deficiency by administering high-dose IV iron improves the well-being and prognosis for a broad range of patients with HF," Prof. Kalra concluded.

1. Kalra PR. IRONMAN: a randomized trial of intravenous ferric derisomaltose in heart failure with reduced ejection fraction. LBS.02, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.
2. Kalra PR, et al. Lancet. 2022;Nov 5. DOI: 10.1016/S0140-6736(22)02083-9.
3. McDonagh TA, Eur J Heart Fail. 2022;24(1):4–131.

Up-titration of HF therapies following HF discharge saves lives

The STRONG-HF trial demonstrated that rapid up-titration of heart failure (HF) therapies under close follow-up is safe, decreases mortality and HF readmissions, and improves the quality of life (QoL) of patients with HF. According to the authors, the next step is to educate physicians to implement the procedure of STRONG-HF in daily clinical practice.

"Very few patients with acute HF are closely monitored or treated with the full doses of HF therapies," claimed Prof. Alexandre Mebazaa (Université Paris Cité, France) [1]. The multicentre, randomised STRONG-HF trial (NCT03412201) investigated the safety and efficacy of rapid up-titration of HF therapies and close follow-up of patients with an episode of acute HF once discharged from the hospital.

The trial randomised 1,800 participants with acute HF and ready to be discharged from hospital to standard care or up-titration HF therapies. In the up-titration arm, participants received half of the optimal doses of HF therapies before discharge and up-titration to full optimal doses of HF therapies at week 2. They underwent safety checks at weeks 1, 3, and 6 post-discharge. Full optimal doses or half-to-full optimal doses of HF therapies were less frequently prescribed in the standard-care arm (assessed at 90 days and 180 days post-discharge). The primary endpoint was a composite of HF readmission and all-cause mortality on day 180. Notably, it was recommended by the Data and Safety Monitoring Board to terminate the study prematurely because the difference between the 2 experimental arms on the primary endpoint was larger than expected and it was deemed unethical to retain participants at standard care. The authors acted on this recommendation and terminated the study with 1,069 included patients.

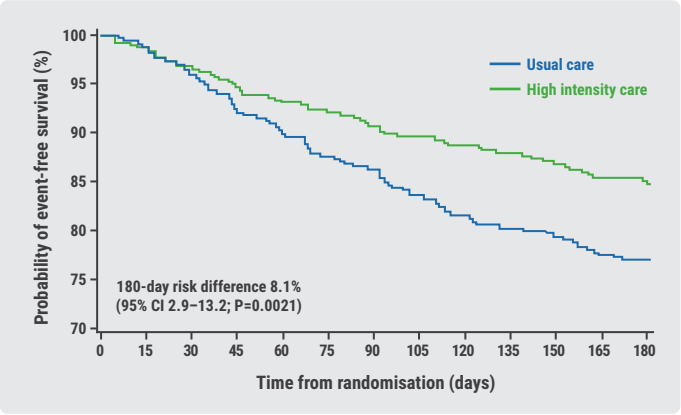
The participants in the up-titration arm showed a decreased risk of HF readmission or all-cause mortality on day 180 compared with the standard-care arm (absolute risk difference 8.1%; 95% CI 2.9–13.2; P=0.0021; see Figure). The 90-day EQ-5D VAS scores reflected greater improvements in

QoL in the up-titration than in the standard-care arm (change from baseline 10.7 vs 7.2; P<0.0001). Haemodynamic and congestion parameters were also significantly improved in the up-titration compared with the standard-care arm. Although the adverse event (AE) rate was numerically higher in the up-titration arm (41.1% vs 29.5%), there was no difference in the rate of serious AEs (16.2% vs 17.2%) or fatal AEs (4.6% vs 6.0%) between the 2 study groups.

"Post-discharge rapid up-titration of HF therapies under close monitoring is safe and effective in patients with acute HF," concluded Prof. Mebazaa.

1. Mebazaa A, et al. Successful post-discharge management of heart failure. Emerging Heart Failure Science, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Figure: Probability of event-free survival over time upon up-titration versus standard care [1]



Hypertension: Novel Developments

The endothelin system: a new target for resistant high blood pressure

Two different doses of the dual endothelin receptor antagonist aprocitentan were superior to placebo in lowering the systolic blood pressure (SBP) in patients with resistant hypertension, results from the PRECISION trial show.

The phase 3 PRECISION trial (NCT03541174) investigated the endothelin receptor antagonist aprocitentan as a treatment option for patients with resistant hypertension [1].

The study consisted of 3 parts and included 730 participants: a 4-week double-blind part with randomisation to either placebo or aprocitentan (12.5 mg or 25 mg), a consecutive single-blinded part of 32 weeks of 25 mg aprocitentan for all participants, and a withdrawal part with re-randomisation to either placebo or 25 mg of aprocitentan for 12 weeks. The study population had a mean age of 62 years, 60% men, over 60% of participants were treated with ≥4 baseline anti-hypertensives, about 20% of participants had heart failure and more than half had diabetes.

The primary endpoint was mean office SBP after 4 weeks of treatment (part 1) and the secondary endpoint was blood pressure (BP) change after the first 4 weeks of the withdrawal phase (part 3, week 40).

"With both doses of aprocitentan there was a clinically meaningful and significant BP reduction of around 15.3 mmHg, and this is significantly more pronounced than the effect with placebo [11.5 mmHg], thereby meeting the primary endpoint," Prof. Markus P Schlaich (University of Western Australia, Perth) revealed, referring to a P-value of 0.0042 for 12.5 mg and a P-value of 0.0046 for 25 mg aprocitentan versus placebo [2]. Over part 2 of the trial (continuous aprocitentan for all participants), the lowered BP results were maintained at both doses. At week 4 of withdrawal (part 3), office SBP was again significantly reduced (delta 5.8 mmHg; P<0.0001) in the aprocitentan compared with the placebo arm. Hence, the key secondary endpoint was met. "Importantly, very similar results were seen for diastolic BP," Prof Schlaich added. The ambulatory BP results were also significantly in favour of both aprocitentan doses.

"As expected, oedema or fluid retention was the most common adverse event, usually occurring in the first 4 weeks, and easily clinically managed with additional diuretic therapy," Prof. Schlaich stated. This side effect led to treatment discontinuation in 7 participants. "Dual

endothelin antagonism with aprocitentan may represent a new alternative pharmacological approach to treat resistant hypertension," Prof Schlaich concluded.

1. Schlaich MP. Sustained blood pressure lowering effect with the dual endothelin receptor antagonist aprocitentan in resistant hypertension: results from a randomized, controlled study including a withdrawal phase. LBS.09, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.
2. Schlaich MP, et al. Lancet. 2022;400(10367):1927-1937.

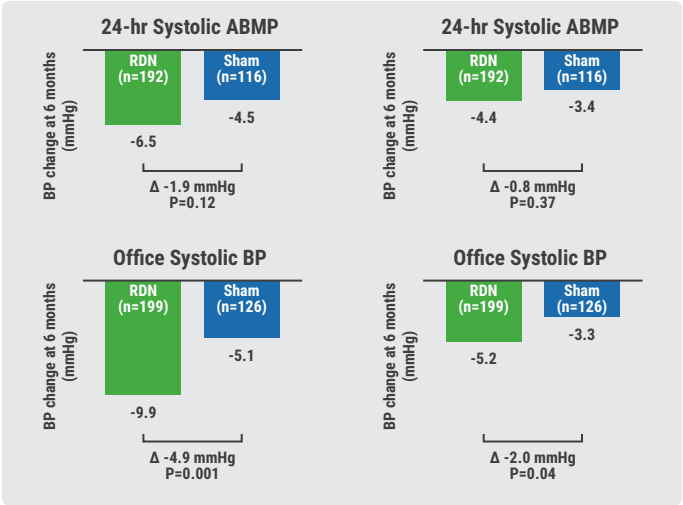
Can renal denervation lower BP on top of antihypertensive drugs?

The SPYRAL HTN-ON MED trial did not meet its primary endpoint of reducing 24-hour ambulatory systolic blood pressure (SBP) by radiofrequency renal denervation (RF-RDN) in hypertensive patients on antihypertensive medications.

Dr David Kandzari (Piedmont Heart Institute, GA, USA) and co-investigators conducted the international sham-controlled SPYRAL HTN-ON MED trial (NCT02439775) to investigate the efficacy and safety of RF-RDN in patients with uncontrolled hypertension on antihypertensive medications [1]. 337 participants with an SBP between 150 and 180 mmHg were randomised 2:1 to RF-RDN plus antihypertensive medication or a sham procedure plus antihypertensive medication. The primary efficacy outcome was the change in 24-hour ambulatory SBP at 6 months and the primary safety endpoint was the major adverse event (MAE) rate at 1 month.

Only 1 MAE (0.4%) was reported after 1 month in the RF-RDN arm, meeting the performance goal of 7.1% (P<0.001). With a reduction of 6.5 mmHg in 24-hour SBP in the intervention arm and a reduction of 4.5 mmHg in the control arm, the anticipated difference in the primary efficacy endpoint was not met (P=0.12). In contrast, the reduction of office SBP (-9.9 vs -5.1; P=0.001) and office diastolic BP (-5.2 vs -3.3; P=0.04) at 6 months was more pronounced in the RF-RDN compared with the control arm (see Figure). A win ratio analysis of 24-hour SBP and medication burden reduction demonstrated a benefit of the RF-RDN arm over the control arm, with a win ratio of 1.50 (P=0.005).

Figure: Blood pressure changes at 6 months of RF-RDN treatment in the presence of antihypertensive drugs [1]



ABPM, ambulatory blood pressure monitoring. RDN, renal denervation. BP, blood pressure. Δ, difference.

Dr Ajay Kirtane (Columbia University Irving Medical Center, NY, USA) presented the results of the trial. "We know that medications to lower blood pressure work. Any trial attempting to isolate the effect of RF-RDN versus sham should therefore aim to keep the administration of antihypertensive medication at the same level in both treatment arms," he argued. Data from the SPYRAL HTN-ON MED trial showed that the amount of medication given and medication burden was significantly increased in the control arm compared with the intervention arm at 6 months. "Despite missing its primary endpoint, I think that the SPYRAL HTN ON-MED trial confirmed that RF-RDN lowers BP. It is just difficult to isolate the effect of RF-RDN in on-medication trials," Dr Kirtane closed.

1. Kandzari DE, et al. Effect of radiofrequency renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month primary results from the SPYRAL HTN-ON med expansion randomized trial. LBS.09, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Quadruple, ultra-low-dose treatment did not meet primary endpoint in hypertension

The QUARTET USA trial did not meet its primary endpoint of reducing automated systolic blood pressure (BP) after 12 weeks. Nonetheless, the quadruple (4-drug), ultra-low-dose combination therapy numerically reduced blood pressure (BP) more than candesartan monotherapy did in a predominantly Black and Hispanic study population with mild-to-moderate hypertension.

"Low hypertension control rates reflect the need for new approaches to control this condition," argued Dr Mark Huffman (Washington University School of Medicine, USA). Previously, the Australian QUARTET study (ACTRN12616001144404) had demonstrated that a quadruple drug combination of antihypertensive medication at ultra-low doses was more efficacious than irbesartan standard-dose monotherapy in reducing the systolic BP and diastolic BP of mostly White and Asian participants in Australia [1]. Here, Dr Huffman and colleagues assessed the efficacy of quadruple, ultra-low-

dose treatment for hypertension in an American population of patients with mild-to-moderate hypertension in the QUARTET USA (NCT03640312) [2]. The study randomised 62 participants (Black n=11; Hispanic n=45) 1:1 to the intervention arm (candesartan 2 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg, daily) or the control arm (candesartan 8 mg, daily). An add-on of amlodipine 5 mg daily was allowed if BP reached >130/80 mmHg at week 6. The primary outcome was the mean change in automated systolic BP after 12 weeks.

The adjusted mean change in systolic BP at week 12 was lower (Δ -4.8 mmHg; 95% CI -10.7–1.2) and the adjusted mean change in diastolic BP was also lower in the quadruple therapy compared with the control arm (Δ -4.9; 95% CI -8.6–-1.1). The safety results showed a higher rate of adverse events (AEs) in the quadruple therapy arm than in the control arm (62.5% vs 46.7%). Likewise, serious AEs were more frequently reported in the quadruple therapy arm (6.3% vs 0%), but according to the authors, these events were not related to the study drugs. In contrast to these findings, the rate of AEs leading to treatment discontinuation was higher in the control arm than in the quadruple arm (26.7% vs 6.3%).

Dr Huffman commented that the limited sample size of the study may be responsible for the fact that the observed differences in systolic BP between the 2 study groups were not statistically significant. "The QUARTET USA study confirms the BP lowering effect of a quadruple ultra-low-dose treatment previously reported for the Australian population in a different study population, with lower baseline BP. This strengthens the case for this novel approach," concluded Dr Huffman.

1. Chow CK, et al. Lancet. 2021;398(10305):1043–1052.
2. Huffman M, et al. Efficacy and safety of a quadruple ultra-low-dose treatment for hypertension (QUARTET USA): A randomized controlled trial. LBS.04, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Mindfulness programme contributes to office blood pressure lowering

A customised mindfulness programme may be a valuable supplemental non-pharmaceutical way to achieve blood pressure (BP) control in hypertensive patients. After 6 months, participants in the mindfulness programme displayed significantly lower systolic BP compared with controls.

According to Prof. Eric Loucks (Brown University, RI, USA), mindfulness may support patients to adhere to lifestyle measures that achieve BP control such as physical activity, dietary changes, reduced alcohol consumption, medication adherence and weight loss.

The parallel-group, phase 2, randomised clinical trial MB-BP (NCT03256890) trained participants in skills such as attention control, self-awareness and emotion regulation, and then applied that training to health behaviour changes suitable to improve BP control [1]. The researchers compared enhanced standard care (e.g. a home blood pressure monitor, BP education material, facilitated access to a physician if needed) with the participation in an 8-week mindfulness-based programme, customised for people with elevated BP.

All 200 adult participants were recruited from the Providence, Rhode Island area and had elevated/high BP (>120 mmHg systolic or >80 mmHg diastolic BP). In total, 81% of the participants were White adults and 73% had a college education. Participants were randomised 1:1 to the mindfulness programme or the enhanced standard care group. Participants in the MB-BP group went to a group orientation session, eight 2.5-hour weekly group sessions and one 7.5-hour, one-day group retreat. Recommended home mindfulness practice was at least 45 minutes a day, six days a week.

At 6 months, participants in the mindfulness group displayed a reduction in mean systolic BP of 5.9 mmHg (95% CI -9.1– -2.8; P<0.001), compared with a 1.4 mmHg reduction in systolic BP in the enhanced usual care group in pre-specified unadjusted analyses. In a posthoc analysis that adjusted for the BP and sex strata that participants were randomised within, there was a between-group difference of 4.3 mmHg (95% CI -8.7–0.1) at 6 months follow-up. There were no notable changes in diastolic BP for either group. Participants in the mindfulness group also reduced their sedentary sitting behaviour by an average of 351 minutes each week, were more likely to eat heart-healthy food and reported improved perceived stress and mindfulness levels compared with the participants in the enhanced standard care group, possibly contributing to the BP lowering effect of mindfulness.

Importantly, most participants were college-educated White adults, which limits its generalisability to people from diverse racial and ethnic groups or to those who have other education levels. "I would like to see a replication of this work by external groups with longer follow up, and more generalised participants," Prof. Loucks concluded.

1. Loucks EB, et al. The effect of adapted mindfulness training in participants with elevated office blood pressure: the mindfulness-based blood pressure reduction (MB-BP) randomized clinical trial. LBS.04, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Interventional Cardiology in 2022

Grafting with the radial vein: an underrated option in CABG surgery?

Coronary artery bypass graft (CABG) procedures using the radial artery as a conduit were superior to a free right internal thoracic artery (RITA) and a saphenous vein graft (SVG), the RAPCO trial shows.

Considering bypass grafting to the left anterior descending artery, the use of the internal thoracic artery is the long-accepted primary choice. "But controversy exists on the choice for the second conduit," Prof. David Hare (Austin Health, Australia) stated [1]. The RAPCO trial (NCT00475488) consisted of 2 separate integrated trials that compared the use of the radial artery versus the free right internal thoracic artery (RAPCO-RITA) and, separately, the radial artery versus a saphenous vein graft (RAPCO-SVG). Prof. Hare presented the 15-year clinical outcomes.

RAPCO-RITA randomised 394 participants, under 70 years of age (under 60 years of age for those with diabetes) 1:1 to radial artery or free RITA grafting. The baseline data showed a mean age of participants of 59 years, around 10% were women, and 11% of participants had diabetes. The composite clinical outcome of major adverse cardiac events (MACE) consisted of all-cause mortality, acute myocardial infarction, and/or repeat coronary revascularisation.

The rate of MACE was significantly reduced by the use of radial artery versus RITA with a hazard ratio of 0.74 (95% CI 0.55-0.97; P=0.04). "Looking at the composition of the MACE, all-cause mortality, which had an absolute reduction of 8% after 15 years and a relative risk reduction of 31%, probably predominates in the MACE calculation," Prof. Hare elaborated.

In RAPCO-SVG, 225 participants were included, and, in line with the somewhat different inclusion criteria, the mean age was around 73 years, 19% were women, and 45% of participants had diabetes. After allocation to grafting with either a radial artery or SV, the rate of MACE was again significantly lower with radial artery grafting versus SVG: HR 0.71 (95% CI 0.52-0.98; P=0.04) at 15 years.

Prof. Hare mentioned that, currently, less than 10% of the 200,000 annual coronary artery bypass surgeries performed in the US involve radial artery grafts. From the RAPCO trial results, he suggested that all isolated CAGB operations should consider using a radial graft and assess if it is suitable and can be used without contraindications. "Whether radial grafts also perform better than current methods in instrumented procedures, however, needs to be further researched," closed Prof. Hare.

1. Hare DL, et al. Radial artery patency and clinical outcomes (RAPCO) randomised trials - The 15-year clinical outcomes comparing radial artery with right internal thoracic artery or with saphenous vein grafting. LBS.03, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Methylprednisolone does not reduce risk of adverse outcomes in infants undergoing heart surgery

Administration of perioperative methylprednisolone did not reduce the risk of adverse clinical outcomes in infants undergoing heart surgery with cardiopulmonary bypass (CPB), according to the STRESS trial. However, secondary and subgroup analyses suggested that some patients receiving corticosteroids may benefit from this therapy, especially non-premature infants undergoing lower complexity operations or those with a longer cardiopulmonary bypass (CPB) time.

"Perioperative corticosteroids have been used for decades to treat the inflammatory response in patients undergoing heart surgery with cardiopulmonary bypass," started Dr Kevin Hill (Duke Children's Hospital & Health Center, NC, USA). "This inflammatory response is most severe in infants and neonates undergoing heart surgery as the total blood volume in these patients is relatively small compared with the bypass circuit." However, the safety and efficacy of the use of perioperative corticosteroids have not been established in children undergoing heart surgery with CPB.

The pragmatic STRESS trial (NCT03229538), designed within a registry using the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD), randomised 1,200 infants (<1 year) undergoing heart surgery with CPB 1:1 to methylprednisolone (30mg/kg) or placebo [1]. The primary outcome was a ranked composite of adverse clinical outcomes, ranging from operative mortality to post-operative length of stay.

No significant difference observed was observed with methylprednisolone versus placebo for the primary composite outcome (adjusted OR 0.86; 95% CI 0.71–1.05; P=0.14). The risk factor-unadjusted analysis of the primary outcome, which was a secondary outcome of the study, revealed a clinical benefit of the methylprednisolone arm over the placebo arm (OR 0.82; P=0.047). Also, fewer participants in the intervention arm experienced bleeding requiring operation (OR 0.34; P=0.016). The safety analysis revealed that participants in the methylprednisolone group were more likely to receive post-operative insulin than participants in the placebo group (P<0.001). On the other hand, participants in the methylprednisolone group were less likely to receive post-operative hydrocortisone (P=0.004), which is most commonly administered to patients with low cardiac output syndrome.

Overall, the trial did not demonstrate the superiority of methylprednisone and the observation of more insulin use suggests further studies are needed to evaluate the optimal approach. Dr Stephanie Fuller, a discussant of the trial, congratulated Dr Hill on the successful design of a 'trial within a registry', significantly reducing the time, effort, and cost that is usually associated with randomised controlled trials. "This is truly the future of paediatric randomised trials," Dr Fuller concluded.

1. Hill KD, et al. Steroids to reduce systemic inflammation after infant surgery: The STRESS trial. LBS.03, AHA Scientific Sessions 2022, 05–07 November Chicago, USA.

Extracorporeal membrane oxygenation not superior to conservative therapy in cardiogenic shock

In patients with rapidly deteriorating or severe cardiogenic shock, the immediate implementation of extracorporeal membrane oxygenation (ECMO) did not outperform an early conservative strategy, consisting of inotropes and vasopressors, and secondary ECMO in case of haemodynamic worsening.

"According to the 2021 guidelines of the European Society of Cardiology (ESC) for the management of heart failure, patients with cardiogenic shock should receive oxygen for early haemodynamic stabilisation (class I recommendation)," explained Prof. Petr Ostadal (Charles University, Czech Republic) [1]. "Furthermore, inotropes/vasopressors (class 2b) may be considered and ventilatory support (class 2a) and short-term mechanical circulatory support (MCS) should be considered (class 2a) in this population."

The multicentre, randomised, investigator-initiated, academic ECMO-CS trial (NCT02301819) compared an early conservative therapy with inotropes and vasopressors (n=59) to immediate ECMO implementation (n=58) in participants with severe or rapidly deteriorating cardiogenic shock [2]. Importantly, secondary ECMO was allowed in case of haemodynamic worsening in the conservative arm, defined as a rise of lactate by 3 mmol/L. The primary endpoint was a composite of all-cause mortality, resuscitated circulatory arrest, and implementation of another mechanical circulatory support device at 30 days.

ECMO did not significantly alter the rate of the primary outcome compared with the conservative therapy in the study population (HR 0.72; 95% CI 0.46–1.12; P=0.21). The use of another mechanical circulatory support was more frequently observed in the conservative arm than in the ECMO arm (42.4% vs 17.2%; HR 0.38; 95% CI 0.18–0.79) and 23 participants in the conservative arm required secondary ECMO support (39.0%). The safety analysis did not reveal differences in the incidence of serious adverse events such as bleeding, leg ischaemia, stroke, pneumonia, or sepsis, between the 2 study arms. Furthermore, the type of shock, rapidly deteriorating or severe, did not appear to have a distinctive influence on the primary outcome.

Overall, the trial did not demonstrate the superiority of ECMO within the sample size studied. Prof. Ostadal concluded that the early haemodynamic stabilisation using inotropes and vasopressors, with secondary use of ECMO in case of haemodynamic worsening, is comparable to the immediate implementation of ECMO in participants with acute cardiogenic shock.

1. McDonagh TA, et al. Eur Heart J. 2021;42(36):3599–3726.
2. Ostadal P, et al. Extracorporeal membrane oxygenation in the therapy of cardiogenic shock: primary results from the multicenter, randomized ECMO-CS Trial. LBS.03, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Surgery with adequate saphenous vein partly better than endovascular treatment in CLTI

According to the BEST-CLI trial, in patients with chronic limb-threatening ischaemia (CLTI), bypass surgery was associated with a reduction in the composite of major adverse limb events (MALE), all-cause mortality, major interventions, and above-ankle amputation compared with endovascular treatment. The benefit was driven by repeat procedures and was present only in patients with a single-segment great saphenous vein and not for those in need of other conduits.

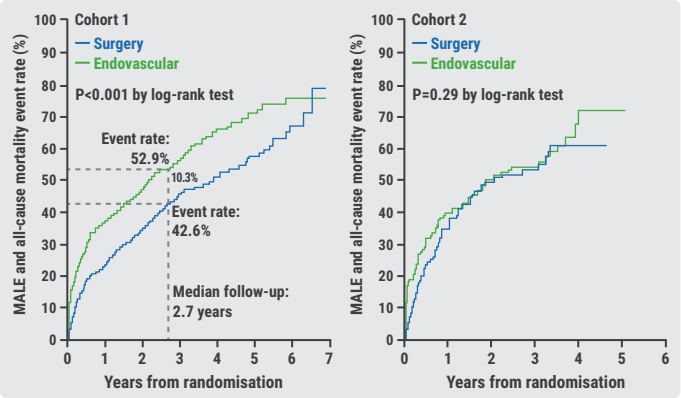
In a separate analysis of the same trial, treatment strategies were associated with improvements in health-related quality of life (HR-QoL). This effect was seen early after the intervention and was maintained during follow-up. Endovascular therapy outperformed bypass surgery significantly on some QoL measures in patients with available single-segment great saphenous veins; the magnitude of these differences was of uncertain clinical significance.

Revascularisation is indicated to prevent limb amputation through the improvement of perfusion. The optimal revascularisation approach remains unclear. "We aimed to compare the 2 principal revascularisation strategies for CLTI" explained Prof. Alik Farber (Boston Medical Center, MA, USA), describing the motivation for the presented BEST-CLI study (NCT02060630) [1]. Prof. Farber presented the effectiveness results, while Dr Matthew Menard (Brigham and Women's Hospital, MA, USA) provided the results of the QoL measures [2].

The investigation consisted of 2 parallel trials with no pooling of data. Overall enrollment was lower than planned. Cohort 1 (C1) included 1,434 participants with a single-segment great saphenous vein (SSGSV), currently thought to benefit most from bypass conduit. Cohort 2(C2) included 396 participants who lacked SSGSV and were in need of alternative conduits. Per cohort, participants were randomised to either endovascular or open-surgical therapy. The composite primary endpoint consisted of major adverse limb events (MALE) or all-cause mortality. MALE represented above ankle amputation or first major reintervention.

Baseline characteristics comprised a mean age of 67, nearly 29% women and over 70% with diabetes in cohort 1, with similar characteristics in cohort 2. In cohort 1, 698 bypass and 1,250 endovascular procedures were executed. MALE or all-cause mortality occurred at a rate of 52.9% in the endovascular and 42.6% in the surgical group, translating to a hazard ratio of 0.68 (95%CI 0.59–0.79; P<0.001; see Figure). "This finding was driven by significantly more repeat interventions in the endovascular arm," Prof. Farber explained, adding that above-ankle amputations were lower in the surgical group compared with the endovascular arm (P=0.04). The benefit of surgical treatment was consistent in most prespecified subgroups. No significant difference was found for all-cause death over up to 7 years of follow-up, or major adverse cardiovascular events at 30 days.

Figure: MALE and all-cause mortality event rate per treatment arm in cohorts 1 and 2 [1]



In cohort 2, the rate of MALE and all-cause mortality and secondary endpoints was similar between treatment strategies (42.8% vs 47.7% HR 0.79; 95% CI 0.58-1.06; P=0.12), surgical vs endovascular therapy group, Figure). There were however more re-interventions observed in the endovascular arm compared with the surgical arm (P=0.002).

Regarding the QoL measures, in cohort 1, both the endovascular group (change from baseline +2.0) and the surgery group (+2.1) showed clinically meaningful improvements in the VascuQoL score. The small, significant between-group difference observed was in favour of the endovascular group (0.14; P=0.02) but did not reach a trial defined threshold for a clinically meaningful difference (0.36). Similarly, endovascular therapy and bypass surgery resulted in clinically meaningful improvements in the EQ-5D (+0.2 for both arms), with no difference between the 2 study groups. The remaining QoL measures in cohort 1, SF-12 and PNRS, displayed comparable results, with meaningful improvements for both interventions, and selected benefits for the endovascular therapy arm. In cohort 2, the various QoL measures showed improvements for both treatments, but no differences between therapies.

"Bypass with adequate saphenous vein should be offered as a first-line treatment option for suitable candidates with CLTI, as part of fully informed, shared decision-making," Prof. Farber concluded.

1. Farber A. Best endovascular versus best surgical therapy for patients with chronic limb threatening ischemia (BEST-CLI) trial: clinical results. LBS.07, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.
2. Menard MT, et al. Best endovascular versus best surgical therapy for patients with chronic limb threatening ischemia (BEST-CLI) trial: Quality of life analyses. LBS.07, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Arrhythmia – State of the Art

First-line ablation limits progression to persistent AF

Fewer patients with atrial fibrillation (AF) progressed to persistent AF when receiving first-line ablation compared with first-line antiarrhythmic drug therapy, data from the PROGRESSIVE-AF trial showed. Secondary outcomes confirmed the superiority of first-line ablation in the young, relatively healthy study population.

"AF is a chronic and progressive condition and persistent AF is linked to adverse clinical events, such as stroke, heart failure, and death," explained Dr Jason Andrade (University of Montreal, Canada) [1]. "Since catheter ablation modifies the pathogenic mechanism of AF, early initiation of this procedure may lead to improved clinical outcomes."

The PROGRESSIVE-AF trial (NCT05514860) randomised 303 patients with AF (mean age 58 years) 1:1 to first-line catheter ablation or first-line antiarrhythmic drugs. The primary endpoint was the time-to-first occurrence of an episode of persistent atrial tachyarrhythmia.

At 3 years, the incidence of persistent AF was reduced by 75% in the ablation compared with the antiarrhythmic drug group (HR 0.25, 95% CI 0.09–0.70). The observed effect was consistent across subcomponents of the primary outcome, namely atrial tachyarrhythmias lasting more than 7 days (HR 0.30; 95% CI 0.10–0.93) and cardioversion for atrial tachyarrhythmia lasting between 2 and 7 days (HR 0.14; 95% CI 0.02–0.85). Furthermore, 42.7% of the patients in the ablation arm were free of any recurrence of atrial tachyarrhythmia after 3 years compared with 9.3% in the antiarrhythmic drug arm (HR 0.49; 95% CI 0.37–0.65). Quality of life after 3 years of follow-up was also significantly better in patients randomised to the ablation arm. The Atrial Fibrillation Effect on Quality-of-Life (AFEQT) revealed mean differences from baseline of 28.1 versus 24.8 respectively, while the mean difference from baseline of EQ-5D-assessed quality of life was 0.06 versus 0.01 and the relative risk for symptoms of AF was 4.8% versus 17.1% respectively (all comparisons ablation vs antiarrhythmic drug). At 3 years, fewer adverse events were reported in the ablation group (11.0%) than in the antiarrhythmic drug group (23.5%; RR 0.47; 95% CI 0.28–0.79). Also, serious AEs were numerically less frequently observed in the ablation arm (4.5% vs 10.1%; RR 0.45; 95% CI 0.19–1.05).

Dr Andrade concluded that first-line treatment with ablation led to a lower risk of progression to persistent AF than first-line treatment with antiarrhythmic drug therapy. Dr Carina Blomström Lundqvist agreed that first-line ablation reduces AF progression compared with initial antiarrhythmic drug therapy, but that the optimal patient and timing remain unclear: "The CLOSE-to-CURE study (NCT02925624)[2] demonstrated that patients respond very well to ablation, even if they are in a progressed stage of the condition and have a high AF burden."

1. Andrade JG, et al. The impact of "first-line" rhythm therapy on atrial fibrillation progression: the PROGRESSIVE-AF trial. LBS.08, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.
2. Strisciuglio T, et al. EP Europace. 2020;22(8):1189–1196.

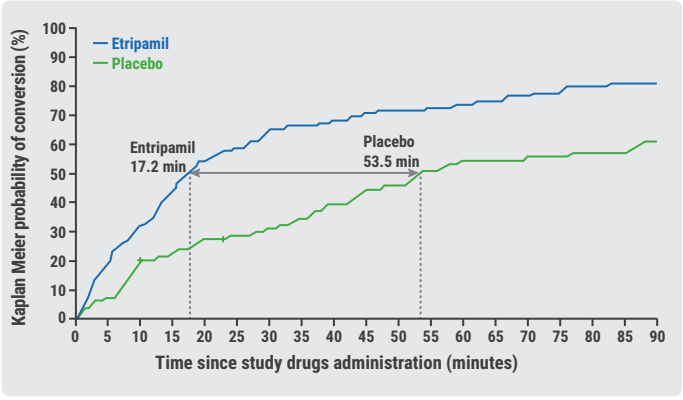
Doubling the dose of self-administered etripamil terminates PSVT

Self-administered etripamil was safe and terminated paroxysmal supraventricular tachycardia (PSVT) more frequently than placebo, the primary analysis of the phase 3 RAPID Study (NODE-301 part 2) demonstrated.

The novel investigational L-type calcium channel blocker etripamil, formulated for intranasal spray, delivered a rapid conversion of PSVT to normal sinus rhythm in the phase 2 NODE-1 trial (NCT02296190) [1]. The current phase 3 RAPID study (NODE-301 - Part 2, NCT03464019) randomised 692 participants with an ECG-documented diagnosis of PSVT 1:1 to etripamil or placebo in an at-home treatment setting [2]. After participants recognised symptoms they applied cardiac monitoring, attempted a vagal manoeuvre, and administered the study drug (etripamil 70 mg) or placebo. If symptoms persisted for 10 minutes, a second, equal drug dose was self-administered. The primary endpoint was PSVT conversion to sinus rhythm over 30 minutes. At the current data cut point of the RAPID study, 255 patients had been treated for PSVT, making up the safety population, and 184 patients had verified PSVT and had been treated for it, comprising the efficacy population. Dr James Ip (Weill Cornell Medicine, NY, USA) presented the primary results of the study.

At 30 minutes, 64.3% of the patients in the etripamil arm had converted from PSVT to a normal sinus rhythm compared with 31.2% of the patients in the placebo arm (HR 2.62; 95% CI 1.66–4.15; P<0.001). The observed difference in conversion rates between the 2 arms remained significant at 300 minutes (82.7% vs 72.0%; HR 1.70; P<0.001, etripamil vs placebo). The median time to conversion from PSVT to a normal sinus rhythm was 17.2 minutes in the etripamil and 53.5 minutes in the placebo arm (see Figure). These results were consistent across subgroups.

Figure: Median time to conversion from PSVT to normal sinus rhythm per treatment group [1]



This being the first study in which a second dose of etripamil was tested, no new safety issues were reported, according to Dr Ip. "Importantly, no cases of second-degree or third-degree atrioventricular block were reported." The rate of treatment-related adverse events (AEs) was higher in the etripamil (50.4%) than in the placebo arm (16.7%), but no serious AEs were observed. The most commonly observed AEs in the etripamil arm were nasal discomfort (23.0%), nasal congestion (12.6%), and rhinorrhoea (8.9%).

Dr Julia Indik (University of Arizona, AZ, USA) congratulated Dr Ip on the results of the RAPID Study but mentioned that the cost-effectiveness of this approach needs to be determined. "What is the number-needed-to-treat to avoid an emergency room visit, and will this balance out the cost of self-administered therapy? Also, we need to investigate patient satisfaction concerning the nasal adverse symptoms that are associated with etripamil."

1. Stambler BS, et al. JACC. 2018;72(5):489–497
2. Stambler BS, et al. Self-administered etripamil for termination of spontaneous paroxysmal supraventricular tachycardia: Primary analysis from The RAPID study. LBS.08, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Novel Developments in Primary and Secondary Prevention

Digitally delivered cognitive behavioural therapy successful in type 2 diabetes

The BT-001 pivotal trial demonstrated that nutritional cognitive behavioural therapy (nCBT) delivered through a digital app persistently reduced haemoglobin (Hb)A1c levels in patients with type 2 diabetes. Furthermore, nCBT was safe and associated with reduced blood pressure, weight, and need for medication intensification, as well as improved patient-reported outcomes.

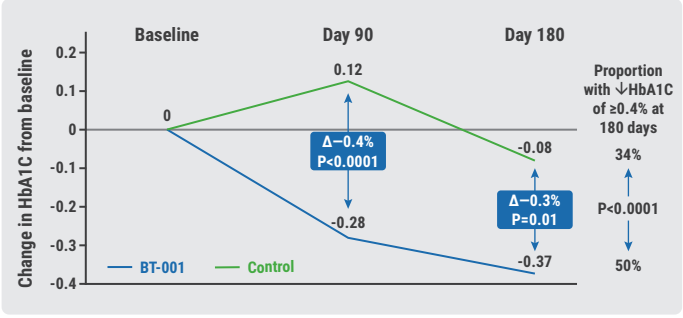
Prof. Marc Bonaca (University of Colorado, CO, USA) explained that core thoughts and beliefs in patients with type 2 diabetes lead to unhelpful behaviours, such as sedentary behaviour and unhealthy food choices, ultimately resulting in an aggravation of their condition [1]. CBT can help patients exit this vicious circle. "However, the problem with CBT, and nCBT in particular, is a lack of access," said Prof. Bonaca. "It is expensive for patients to follow CBT and it is often hard to find an available therapist."

To address this issue, Prof. Bonaca and his co-investigators assessed a digital app that delivers nCBT digitally through lessons and skill development. The BT-001 trial (NCT04886388) randomised 669 participants with type 2 diabetes to either the BT-001 app or a control app to assess the efficacy and safety of this novel tool. The primary efficacy endpoint was the mean change in HbA1c level from baseline after 90 days [2]. The principal safety outcome was adverse

events (AEs). Prof. Bonaca presented the results after 180 days of follow-up [1].

At 90 days, the mean HbA1c level of patients in the BT-001 arm had been significantly reduced compared with that of patients in the control arm (-0.28% vs +0.11%; Δ 0.39; P<0.0001) [2]. After 180 days, the mean HbA1c level of participants in the BT-001 arm was even further reduced, with a sustained significant difference between the BT-001 and the control arm (-0.37% vs -0.08%; Δ0.29; P=0.01; see Figure). Notably, the mean HbA1C levels of participants in the control arm decreased as well, which could be explained by the significantly larger proportion of participants that needed pharmacological treatment intensification in the control group than in the BT-001 group (21% vs 14%; P=0.002). The number of lessons that participants followed in the BT-001 app was associated with the reduction in HbA1c level; the more lessons, the larger the reduction (P=0.017). The mean change in body weight (-5.5 vs -1.9 pounds; P=0.005) and mean change in systolic blood pressure (-4.7 mmHg vs -1.8 mmHg; P=0.042) favoured the BT-001 arm over the control arm. Moreover, the SF-12 physical component score and the PHQ9 depression score displayed better results for participants using the BT-001 app compared with controls (Δ_{SF-12} 1.8; P=0.009 and ΔPHQ9 -0.83; P=0.009). Finally, after 180 days of follow-up, fewer treatment-emergent AEs (55% vs 42%; P<0.001) and serious treatment-emergent AEs (7% vs 3%; P=0.01) were observed in the BT-001 compared with the control arm.

Figure: Difference in HbA1c from baseline in BT-001 and control group until day 180 [2]



HbA1C, Haemoglobin A1C.

"nCBT delivered via a digital therapeutic app significantly and persistently reduced HbA1c, potentially providing a scalable treatment option for patients with type 2 diabetes," concluded Prof. Bonaca.

1. Bonaca MP, et al. Randomized, controlled trial of digital nutritional cognitive behavioral therapy in patients with type 2 diabetes mellitus: Primary outcomes of the BT-001 pivotal trial at 180 days. FS.08, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.
2. Hsia J, et al. Diabetes Care. 2022; Oct 1. DOI: 10.2337/dc22-1099.

Empagliflozin reduces risk of kidney disease progression and CV events in patients with CKD

Empagliflozin significantly reduced the risk of the composite outcome of progression of kidney disease or death from cardiovascular (CV) causes by 28% in the phase 3 EMPA-KIDNEY trial. The results also showed a 14% decrease in hospitalisation due to any cause.

Associate Prof. David Preiss (University of Oxford, UK) presented data from the EMPA-KIDNEY trial (NCT03594110), and a meta-analysis on the effect of sodium-glucose cotransporter-2 (SGLT2) inhibition [1]. The EMPA-KIDNEY trial randomised 6,609 patients with chronic kidney disease at risk of progression to either 10 mg of empagliflozin once daily or placebo [1,2]. The trial included patients with an estimated glomerular filtration rate (eGFR) ≥20 and <45 mL/minute/1.73 m^2 of body-surface area. The primary composite outcome was CV death or kidney disease progression. The median follow-up was 2 years. At baseline, the mean age was 64 years, ~33% were women, and the mean eGFR was 37 mL/min/1.73m^2. "We aimed to recruit many patients without diabetes," Dr Preiss elaborated, resulting in more than half of randomised participants not having diabetes.

A primary outcome event happened significantly less often in participants treated with empagliflozin compared with placebo: 13.1% versus 16.9% (P<0.001). This corresponded to a hazard ratio reduction of 0.72 (95% CI 0.64–0.82). Similar differences were found when stratifying according to prior vascular disease. Dr Preiss emphasised that the effect was mainly driven by the renal component of the primary outcome. "The number of cardiovascular deaths (128 of 990 events) was smaller than expected," he detailed. All-cause hospitalisation was significantly reduced by 14% (95% CI 0.78–0.95) by treatment with empagliflozin, an effect that was consistent across subgroups including diabetes status and eGFR. Analyses of recurrent CV events, such as HF hospitalisation, and major adverse CV events, all showed clear but non-significant trends for a reduction with empagliflozin. According to Dr Preiss, the lack of significance was likely due to underpowering of the study regarding CV outcomes.

To shed further light on the cardiovascular efficacy of SGLT2 inhibitors, Dr Preiss also revealed results from a collaborative meta-analysis of 13 large SGLT2 inhibitor trials [1,3]. "Over 90,000 participants were available for these analyses, 80% had diabetes," Dr Preiss stated, underlining that this still meant over 19,000 patients did not have diabetes. CV outcome analysis demonstrated an overall significant reduction of CV death or HF hospitalisation with SGLT2 inhibition by 23% (95% CI 0.74–0.81). Stratification into patients with and without diabetes led to consistent results in both subgroups. "For this analysis, we had rather limited information on the patient group with chronic kidney disease but without diabetes," he added. As for CV death alone, the SGLT2 inhibitors resulted in a decrease of 14% overall, with relative risks of 0.86 (95% CI 0.80–0.92) for diabetic and 0.88 (95% CI 0.78–1.01) for non-diabetic patients.

"Our results suggest that SGLT2 inhibitors such as empagliflozin should be offered to all adults with chronic kidney disease at risk of kidney disease progression and CV complications, regardless of whether they have type 2 diabetes," Dr Preiss expressed.

Prof. Naveed Sattar (University of Glasgow, UK), a discussant of the trial, added that these excellent results should encourage us to investigate SGLT2 inhibitors in patients with other conditions, including pre-diabetic patients, kidney transplant recipients, patients with non-alcoholic fatty liver disease (NAFLD), and patients with a recent myocardial infarction (post-MI).

1. Preiss D. Empagliflozin and cardiovascular outcomes in patients with chronic kidney disease: the EMPA-KIDNEY trial. LBS.05, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.
2. Herrington WG, et al. N Engl J Med, Nov 4, 2022. DOI: 10.1056/nejmoa2204233.
3. The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Lancet. 2022;400(10365):1788–1801.

RESPECT-EPA misses primary endpoint but hints towards improvements in CV outcomes by EPA

The RESPECT-EPA trial did not demonstrate a statistically significant effect of highly purified eicosapentaenoic acid (EPA) on top of statins for the reduction of adverse cardiovascular (CV) events compared with statins alone in patients with chronic coronary artery disease (CAD) and low EPA/arachidonic acid (AA) ratio.

The Japanese JELIS trial (NCT00231738) displayed clinical benefits of highly purified EPA in individuals with and without CAD [1]. "However, other, more recent, trials have delivered conflicting results concerning the clinical benefits of EPA on top of optimal medical therapy in patients with CAD," said Dr Hiroyuki Daida (Juntendo University, Japan). The current open-label RESPECT-EPA trial (UMIN000012069) assessed the safety and efficacy of EPA on top of statins in patients with chronic CAD and an EPA/AA ratio <0.4 [2]. The included participants (n=2,506) were randomised 1:1 to statin therapy plus 1,800 mg highly purified EPA per day or standard statin therapy. The primary endpoint was the occurrence of any of the following CV events: CV death, nonfatal myocardial infarction, nonfatal cerebral infarction, unstable angina pectoris requiring emergency hospitalisation plus a coronary revascularisation procedure, and revascularisation procedure based on clinical findings.

After 6 years of follow-up, participants in the EPA group had a numerically lower risk of CV events than participants in the control group, but the difference was not statistically significant (10.9% vs 14.9%; HR 0.79; 95% CI 0.62-1.00; P=0.055. Notably, the cumulative event curve was the same across the EPA and control groups at 2 years follow-up (both arms at 4.7%), with data slightly in favour of EPA at 4 years (8.6% vs 8.8%), but the curves diverged by 6 years (10.9% vs 14.9%), suggestive of long-term effects. Similar results occurred with the secondary composite endpoint of sudden cardiac death, myocardial infarction, unstable angina, and coronary revascularisation endpoint, with a significant difference occurring at 6 years (8.0% in the EPA group vs 11.3% with the control group; HR 0.73; P=0.031). There was no significant difference in all-cause mortality between the 2 groups at any time point. Dr Daida added that a posthoc analysis, excluding participants in the control group who displayed an EPA increase from baseline of > 30 µg/mL (n=182), did show a significant effect of additional EPA on the primary endpoint (HR 0.73; P=0.020). Finally, the safety analysis showed a higher rate of gastrointestinal disorders (3.4% vs 1.2%; P<0.001) and atrial fibrillation (3.1% vs 1.6%; P=0.017) in the EPA compared with the control group. Other safety outcomes, such as bleeding risk, were comparable between the 2 study groups.

Prof. Pam Taub (University of San Diego, CA, USA) commented on the results of the RESPECT-EPA trial in the context of other EPA trials. "There appears to be a benefit with EPA in terms of risk reduction for adverse CV events, but the magnitude of this benefit is unclear," she said. "The largest effect of EPA was reported in the REDUCE-IT trial (NCT01492361) in which

participants had the lowest baseline EPA levels and displayed the largest increase in EPA after therapy [3]. Next to that, the baseline high-sensitive (hs) CRP was higher in the study population of the REDUCE-IT trial, with larger reductions after EPA therapy, compared with the study population of the RESPECT EPA and JELIS trials." Therefore, lower baseline EPA levels and higher baseline hsCRP levels may be indicative of a good response to EPA therapy. "However, more clinical and mechanistic data is needed to resolve this issue," Prof. Taub concluded.

1. Yokoyama M, et al. Lancet. 2007;369(9567):1090–1098.
2. Daida H, et al. Randomized trial for evaluating secondary prevention efficacy of combination therapy - statin and eicosapentaenoic acid (RESPECT-EPA). LBS.05, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.
3. Bhatt DL, et al. N Engl J Med 2019;380:11–22.

Pemafibrate fails to reduce cardiovascular events in diabetes but may benefit the liver

Pemafibrate did not reduce the risk for cardiovascular events in patients with type 2 diabetes and dyslipidaemia, despite lowering the levels of triglycerides, very-low-density lipoprotein-cholesterol (VLDL-C), remnant cholesterol, and apolipoprotein (apo)-CIII. Nevertheless, an exploratory analysis showed that pemafibrate may decrease the risk of hepatic adverse events and non-alcoholic fatty liver disease.

Post-hoc analyses of fibrate trials indicated that patients with type 2 diabetes, hypertriglyceridaemia, and low high-density lipoprotein-cholesterol (HDL-C) may benefit from fibrate therapy in terms of a reduced risk for cardiovascular events [1]. The multinational, randomised, double-blind, placebo-controlled PROMINENT trial (NCT03071692) examined this issue by randomising participants with type 2 diabetes and mild-to-moderate hypertriglyceridaemia (TG >200 to 499 mg/dL) and HDL-C <40 mg/dL who were treated with guideline-directed LDL-C lowering therapies (n=10,497) 1:1 to pemafibrate 0.2 mg twice daily or placebo. The primary efficacy outcome was a composite of myocardial infarction, ischaemic stroke, coronary revascularisation, or cardiovascular death. Dr Aruna Pradhan (Brigham and Women's Hospital, MA, USA), the first author of the study, noted that 96% of the participants were treated with statins at baseline [2].

Pemafibrate lowered triglycerides, VLDL-C, remnant cholesterol, and apo-CIII significantly more than the placebo did, with reductions of 26.2%, 25.8%, 25.6%, and 27.6%, respectively. Interestingly, levels of apolipoprotein B and LDL-C increased on pemafibrate relative to placebo. After a median follow-up of 3.4 years, there was no difference between the 2 study groups regarding the primary endpoint (HR 1.03; 95% CI 0.91–1.15; P=0.67). Additionally, secondary endpoints and subgroup analyses revealed no potential benefits of pemafibrate over placebo concerning cardiovascular outcomes.

Dr Pradhan highlighted that the rate of serious adverse events was similar for the 2 arms of the study (HR 1.04; 95% CI 0.98–1.11) but that renal adverse events (HR 1.12; 95% CI 1.04–1.20) and venous thromboembolism (HR 2.05; 95% CI 1.35–3.17) were more common in the intervention arm. Notably, the risk for liver disease (HR 0.83; 95% CI 0.69–0.99) and non-alcoholic fatty liver disease in particular (HR 0.78; 95% CI 0.63–0.96) was lower in the pemafibrate arm compared with the placebo arm.

Prof. Karol Watson (University of California, Los Angeles, CA, USA) commented that fibrates have indeed not been demonstrated to reduce the risk for cardiovascular events in clinical trials since the introduction of statins. "On the bright side, there will be studies evaluating the effects of fibrates in liver conditions, given the encouraging data from the PROMINENT trial".

1. Saely CH, et al. N Engl J Med 2010;363(7):692–695.
2. Pradhan AD, et al. PROMINENT: pemafibrate to reduce cardiovascular outcomes by reducing triglycerides in patients with diabetes. LBS.01, American Heart Association Meeting 2022, 05–07 November, Chicago, USA.

Olpasiran leads to dramatic reductions in Lp(a) concentrations

Olpasiran, a small interfering RNA, successfully reduced lipoprotein(a) (Lp[a]) levels by >90% in patients with atherosclerotic cardiovascular disease (ASCVD) in the phase 2 OCEAN(a)-DOSE trial. The agent was well tolerated with only modest increases in mild injection site reactions.

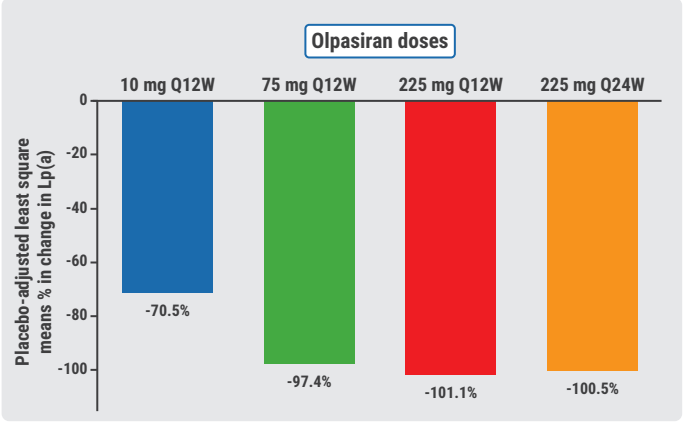
According to a previously published register study in a predominantly European population, concentrations of Lp(a) are associated with ASCVD [1]. About 20% of patients with pre-existing ASCVD had a high Lp(a) concentration (≥150 nmol/L) and this was an independent risk factor for cardiovascular events.

Olpasiran is a small interfering RNA designed to lower the body's production of apolipoprotein(a), a key component of

Lp(a). Associate Prof. Michelle O´Donoghue (Brigham and Women's Hospital, MA, USA) presented the results of the double-blind, placebo-controlled treatment period of the phase 2 OCEAN(a)-DOSE trial (NCT04270760), evaluating olpasiran in 281 adult participants with Lp(a) levels >150 nmol/L and evidence of ASCVD [2]. Participants were randomly allocated to olpasiran in one of the 4 different doses for 12 or 24 weeks (10 mg q12 weeks, 75 mg q12 weeks, 225 mg q12 weeks or 225 mg q24 weeks). The primary endpoint was the percentage change in Lp(a) from baseline to week 36 compared with placebo. The study included 34 sites in 7 countries all over the world.

The median baseline Lp(a) concentration of participants was approximately 260 nmol/L. At week 36, olpasiran treatment led to impressive reductions in Lp(a) levels. This reduction was >95% in the highest 2 dose groups. The primary endpoint was met, with a -70.5% change in the 10 mg dose group, and >90% in all other dose groups (see Figure). Moreover, almost all participants achieved an Lp(a) value below the established risk threshold of 125 nmol/l on doses >75 mg (66.7% at 10 mg dose and >98% at higher doses). The treatment effect was independent of age, sex, race, region, baseline Lp(a), baseline low-density lipoprotein-cholesterol (LDL-C), and given high-potency lipid-lowering therapy. "You can appreciate there was no evidence of effect modification across any of these prespecified subgroups," Dr O´Donoghue said. Therapy with olpasiran also lowered LDL-C. Overall, the agent was well tolerated with an increased occurrence of injection site reactions and related hypersensitivity reactions. However, these were described as mild in severity and resolved without treatment.

Figure: Percentage change in Lp(a) concentrations adjusted for placebo at 36 weeks of treatment with increasing doses of olpasiran [2]



Prof. Stephen Nicholls (Victorian Heart Hospital at Monash University Clayton, Australia), the discussant of this trial, emphasised the existence of "known unknowns" of Lp(a), such as whether lowering Lp(a) will reduce cardiovascular risk and how much Lp(a) lowering will be required to achieve this.

1. Patel AP, et al. Arterioscler Thromb Vasc Biol. 2021;41(1):465–74
2. O´Donoghue ML. Reduction of lipoprotein(a) with small interfering RNA: The results of the Ocean(a)-DOSE trial. LBS.05, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Dietary supplements not effective in lowering LDL-C, use of low-dose statins encouraged

Rosuvastatin at a low dose outperformed various dietary supplements and placebo in decreasing low-density lipoprotein-cholesterol (LDL-C), total cholesterol and triglycerides. Furthermore, no dietary supplement was superior to placebo in lowering LDL-C.

"We all see patients that have their medication list littered with dietary supplements and, in fact, over 3 quarters of Americans take a dietary supplement, and 18% of those individuals take a supplement to promote *heart health*," Dr Luke Laffin (Cleveland Clinic, OH, USA) explained [1]. The presented SPORT trial (NCT04846231) evaluated the effect of low-dose statin treatment of 5 mg rosuvastatin on lipids and inflammatory biomarkers compared with six widely used dietary supplements (fish oil, cinnamon, garlic, turmeric, plant sterols or red yeast rice) and placebo. Within the prospective, randomised, single-blinded trial, 199 participants were equally allocated to 1 of the 8 study arms. Laboratory testing (days 0 and 28) included analysis of a lipid and comprehensive metabolic panel, and highly sensitive (hs)CRP levels. The primary endpoint was the proportion of change in LDL-C.

"Study participants were in their mid-60s, we enrolled 60% women, the median 10-year atherosclerotic cardiovascular disease (ASCVD) risk was 7.9%, mean LDL-C was 128 mg/dL, and most people had relatively normal or low CRP," Dr Laffin described the SPORT cohort. Analysis of the change in LDL-C showed a -37.86% reduction in LDL-C for rosuvastatin, a significantly greater reduction than was reported for placebo (-2.63%) or any of the supplements (ranging between -6.55 and +5.13; P<0.001 for all comparisons). The results for change in total cholesterol (P<0.001) and triglycerides (P<0.05) were similarly superior in the rosuvastatin arm for all evaluations. HsCRP levels did not differ between the statin arm and the other groups.

"None of the supplements decreased LDL-C compared with placebo and the garlic supplement even increased LDL-C by almost 8% (P=0.01)," Dr Laffin commented on the values for biomarker results of the supplement arms versus the placebo group. Plant sterols significantly decreased HDL-C versus placebo (-7.1%; P=0.02). Additional comparisons did not yield significant results for change in total cholesterol, triglycerides or hsCRP.

"Adverse events were numerically similar across all study groups, and slightly higher with some of the supplements, particularly for plant sterols and red yeast rice," Dr Laffin indicated, emphasising that no musculoskeletal events were reported in the rosuvastatin arm.

"We should use these results to engage in evidence-based discussions with patients about the benefits of low dose statin and the lack of benefit that we see for these *heart health* supplements," Dr Laffin reviewed the public health importance of the trial.

1. Laffin L. Effect of low-dose statin compared with placebo and six dietary supplements on lipid and inflammatory biomarkers: The SPORT randomised clinical trial. LBS.05, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

No sex differences in lipid-lowering effect and treatment benefit of PCSK9 inhibitors

The use of PCSK9 inhibitors in both primary and secondary prevention has been associated with a reduced risk of major adverse cardiovascular events (MACE), non-fatal myocardial infarction (MI), and stroke. According to a new meta-analysis, this effect is similar for men and women; however, the low-density lipoprotein-cholesterol (LDL-C) lowering effect seems to be smaller in women.

PCSK9 inhibitors can reduce LDL-C, even in patients that cannot reach ideal LDL-C target levels with high-dose statin and ezetimibe. They have also been shown to reduce MACE [1]. However, it remained unclear whether potential sex differences in LDL-C reduction existed. Dr Frederick Rivera (Lincoln Medical Center, NY, USA) and colleagues hence performed a comprehensive literature search, identifying ongoing studies using ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform [2]. Included in the meta-analysis were 16 trials that passed the inclusion criteria.

Adverse cardiovascular outcomes were significantly reduced by PCSK9 inhibitor use versus placebo in both men (HR 0.85; 95% CI 0.80–0.91; P<0.0001) and women (HR 0.86; 95% CI 0.76–0.96; P=0.009). The significant reductions in LDL-C that were found with PCSK9 inhibitors compared with placebo and ezetimibe were similar for both sexes. A significant reduction in LDL-C was seen in both sexes when analysed according to the frequency of PCSK9 inhibitor administration (i.e. biweekly or monthly) and the type of PCSK9 inhibitor (i.e. evolocumab or alirocumab).

"We conclude that there is no sex difference regarding adverse cardiovascular events and LDL-C reduction among PCSK9 inhibitors. However, subgroup analysis shows greater LDL-C-lowering in men compared with women," Dr Rivera said.

1. Du H, et al. Heart 2019;105(15):1149–1159.
2. Rivera FB, et al. Sex Differences on cardiovascular outcomes of Pcsk9-inhibitors: A meta-analysis. GR.APS.P201, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

COVID-19 and the Heart

'No' to routine use of rivaroxaban in outpatients with COVID-19

In non-hospitalised patients with symptomatic COVID-19 and an increased risk for thrombosis, rivaroxaban did not outperform placebo in reducing the risk for a composite outcome of venous and arterial thrombotic events, hospitalisation, and death in the PREVENT-HD trial.

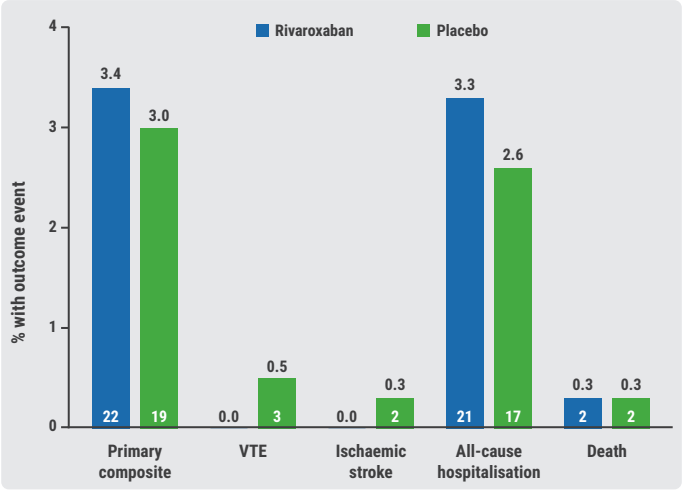
"Outpatients with COVID-19 may have an increased risk for venous and arterial thrombotic events, especially if they carry one or more risk factors," explained Dr Gregory Piazza (Brigham and Women's Hospital, MA, USA). "Moreover, evidence suggests that lung deterioration leading to hospitalisation may be partially explained by *in situ* pulmonary artery thrombosis [1,2]." Dr Piazza and colleagues designed

the PREVENT-HD trial (NCT04508023) to assess whether early initiation of thromboprophylactic dosing of rivaroxaban in outpatients with COVID-19 results in improved health outcomes [3].

The study randomised 1,284 participants with symptomatic COVID-19 and at least 1 risk factor 1:1 to rivaroxaban (10 mg, once daily) plus standard-of-care or placebo plus standard-of-care. The primary efficacy outcome was the time-to-first-occurrence of a composite endpoint of symptomatic venous thromboembolism (VTE), ischaemic stroke, acute limb ischaemia, non-central nervous system systemic embolisation, all-cause hospitalisation, and all-cause death up to day 35. Dr Piazza mentioned that enrolment ended early because the blinded pooled event rates were lower than expected, the COVID-related death and hospitalisation rates were falling nationwide, and there was a very low likelihood to reach the number of events that was required.

There was no significant difference between the intervention arm and the control arm in the rate of the primary efficacy endpoint (3.4% vs 3.0%; HR 1.16; P=0.626; see Figure). Dr Piazza noted that a post-hoc exploratory analysis did suggest a significant difference in the rate of symptomatic VTE and arterial thrombotic events in favour of the rivaroxaban arm (P=0.025). Non-major clinically relevant bleeding (1.5% vs 0.2%; P=0.01) and trivial bleeding (2.8% vs 0.8%; P=0.01) were more common in the rivaroxaban than in the placebo arm, while no differences were observed in International Society on Thrombosis and Haemostasis (ISTH) major bleeding (0.2% vs 0%) or fatal and critical site bleeding (0% in both arms).

Figure: Percentage of participants with respective outcome events at day 35 [1]



VTE, venous thromboembolism.

"Data from the PREVENT-HD trial do not support routine antithrombotic prophylaxis in non-hospitalised patients with symptomatic COVID-19," concluded Dr Piazza. Prof. Renato Lopes (Duke University Medical Center, NC, USA) added that the results of the randomised controlled trials investigating the use of anticoagulants in COVID-19 are in contrast to the observational data that has been gathered on this topic, illustrating the critical importance of randomised controlled trials as a foundation for medical guidance in clinical practice.

1. Ackermann M, et al. N Engl J Med 2020;383:120–128.
2. Piazza G & Morrow DA. JAMA. 2020;324(24):2548–2549.
3. Piazza G, et al. Rivaroxaban to reduce the risk of major venous and arterial thrombotic events, hospitalization, and death in medically ill outpatients with COVID-19: Primary results of the PREVENT-HD randomized clinical trial. LBS.07, AHA Scientific Sessions 2022, 05–07 November Chicago, USA.

COVID-19 pandemic: Older adults and those affected by the delta variant experienced increased cardiovascular morbidity and mortality

A study in hospitalised COVID-19 patients evaluated the impact of age and SARS-CoV-2 virus variant time period on major adverse cardiovascular events (MACE) and in-patient mortality. Patients presenting during the delta wave faced increased rates of MACE and mortality compared with alpha and omicron waves. Older adults exhibited higher probabilities of MACE and death than the young adults, irrespective of the variant.

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has led to significant cardiovascular morbidity and mortality. A study conducted on 45,421 patients admitted to 134 hospitals and medical centres with a diagnosis of COVID-19 assessed the impact of a patient's age and time period of virus variant on MACE (new onset heart failure, myocardial infarction, stroke, or death) and in-patient mortality.

This study included patient information from the American Heart Association's Get with the Guidelines COVID-19 cardiovascular disease registry (AHA COVID-19 CVD), which is a comprehensive national database of adult patients hospitalised with COVID-19 across the United States [1].

Dr Pratyaksh Srivastava (Department of Cardiology, Smidt Heart Institute, Cedars-Sinai, CA) and his team divided these participants into 3 groups based on the dominant variant (wild type/alpha, delta, omicron) of the SARS-CoV-2 virus at the time of hospitalisation.

They further stratified the cohort based on the age of the individuals (young adults: 18–40 years; older adults: >40 years). The majority (85.7%) were in the older age category. The median age was 63 (50–75) years, and 47% were women. "We compared rates of MACE and rates of in-patient mortality between the groups using logistic regression models adjusted for possible confounders such as age, sex, body mass index, race, payment source, and medical comorbidities," Dr Srivastava explained. The rates of MACE during hospitalisation in the alpha, delta, and omicron waves were 20.8%, 23.6%, and 15.5%, respectively. In-hospital mortality rates in these periods were 14.0%, 14.8%, and 6.0%, respectively.

Patients presenting during the delta wave had increased odds of MACE and in-hospital mortality (odds ratio [OR] 1.57; 95% CI 1.42–1.73; P<0.0001 and OR 1.49; 95% CI 1.34–1.66) compared with those in the alpha wave. Patients in the omicron wave had decreased probabilities of in-hospital mortality (OR 0.6; 95% CI 0.43–0.84; P=0.003) and similar odds of MACE when compared with the alpha wave period.
An age-based analysis of the study cohort revealed that older adults had increased odds of MACE and in-hospital mortality (OR 3.08; 95% CI 2.70–3.51 and OR 3.60; 95% CI 3.06–4.23; P<0.0001) compared with those in the young adult group.
Dr Srivastava and his team concluded that COVID-19 patients had higher probabilities of MACE and mortality during the delta wave compared with the other 2 periods, particularly when they were >40 years old.

1. Srivastava PK, et al. Impact of age and variant on cardiovascular events among patients hospitalized with COVID-19: An analysis from the AHA COVID-19 CVD registry. EP.APS.P47. AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

COVID-19 mRNA vaccination does not amplify risk of cardiovascular hospitalisation

Patients with pre-existing cardiovascular (CV) disease did not have an increased likelihood of hospitalisation after receiving an mRNA vaccination against COVID-19. However, SARS-CoV-2 infected patients with pre-existing CV disease were at substantially increased risk for CV hospitalisation compared with non-infected controls.

Does vaccination with an mRNA COVID-19 vaccine introduce a particular risk of worsening for patients with pre-existing cardiovascular (CV) diseases? That was the central question assessed by Dr Anthony Simone (Kaiser Permanente Los Angeles Medical Center, CA, USA) and his fellow researchers [1]. They evaluated CV hospitalisations of adult patients with a history of a CV condition within 30 days after their vaccination compared with the expected incidence of CV hospitalisation (control) using data obtained from the same population during the same 30-day calendar period 2 years prior (a baseline period before the COVID-19 pandemic).

Out of a cohort of 229,829 patients with CV conditions, 165,711 who had received at least 1 dose of an mRNA-based vaccination were included. 160,482 of the included patients were vaccinated at least twice (38.7% mRNA-1273 and 31.2% BNT162b2). Prior diagnoses included atrial fibrillation, myocarditis, coronary artery disease, and heart failure. The baseline findings comprised a median age of 72 years, 43% women, 52% White, 25.4% Hispanic, 10.4% Asian, and 10.2% Black.

In total, admissions for CV conditions were registered for 844 patients during the 30 days following the first dose of an mRNA COVID-19 vaccine compared with 1,012 CV hospitalisations in the historical control group (odds ratio [OR] 0.86; 95% CI 0.76–0.91). After the second dose, 812 patients were hospitalised due to CV conditions compared with 960 in the control (OR 0.85; 95% CI 0.77–0.93). Of note, there were no hospital admissions in the group of patients with prior myocarditis. Looking at the hospitalisation rate of patients with CV disease after testing positive for SARS-CoV-2, the investigators found that out of 24,282 persons, 836 had to be admitted within 1 month after confirmation of the infection. Compared with controls, this translated into a nearly 5 times higher likelihood for patients with CV disease history to be hospitalised when infected with SARS-CoV-2 (OR 4.7; 95% CI 4.0–5.6).

The authors concluded that the difference in hospitalisation risk for vaccination compared with SARS-CoV-2 infection is large and suggests that the benefit of vaccination far outweighs the risks.

1. Simone A, et al. Exacerbation of pre-existing cardiovascular disease following COVID-19 mRNA vaccination. EP.APS.P47, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Best of the Posters

Higher LDL-cholesterol levels linked to higher CVD mortality risk in the elderly

In healthy older adults not taking any lipid-lowering agents, higher low-density lipoprotein-cholesterol (LDL-C) concentrations were associated with a decreased mortality risk from non-cardiovascular causes and an increased mortality risk due to cardiovascular disease (CVD); however, the reduced risk for non-CVD mortality was likely driven by reverse causality.

The prognostic implications of cholesterol levels in older persons remain uncertain. In the absence of consistent evidence, there is a perception that low levels of total cholesterol and LDL-C might be linked to a high mortality risk in this population, as they are indicators of serious disease.

Dr Zhen Zhou (University of Tasmania, Australia) presented the results of a cohort study, which explored the longitudinal associations of LDL-C levels with all-cause mortality, CVD mortality, cancer mortality, and the combined non-CVD/non-cancer mortality in healthy, older adults [1]. It included 12,334 participants from the ASPREE (NCT01038583) trial, a double-blind, randomised, placebo-controlled trial of aspirin in the elderly. These participants had no prior CVD events, dementia, or physical disabilities at enrolment and were not taking any lipid-lowering agents. The mean age was 75 years and 54% were women. They were followed up for a median duration of 6.9 years.

Of the 12,334 participants, 1,250 (10%) died during the study period (24% due to CVD, 43% cancer, and 33% from non-CVD/non-cancer causes). The researchers calculated adjusted hazard ratios for each outcome per 1 mmol/L increment in LDL-C. To check for reverse causality (i.e. the direction of cause-and-effect contrary to a common presumption), the analysis was repeated by excluding participants who died in the 5 years after baseline. In addition, the researchers adjusted their analyses for age, sex, race/country, high-density lipoprotein-cholesterol (HDL-C), triglycerides, body mass index, smoking, alcohol use, education, hypertension, diabetes, chronic kidney disease, and frailty status.

"We noted a U-shaped relation linking LDL-C and all-cause mortality, with the lowest mortality at 3.3 mmol/L) and a curvilinear relation for other mortality outcomes," Dr Zhou described. Each 1 mmol/L higher LDL-C was associated with a lower risk of all-cause mortality (HR 0.91; 95% CI 0.84–0.98), cancer mortality (HR 0.84; 95% CI 0.74–0.94), and the combined non-CVD/non-cancer mortality (HR 0.82; 95% CI 0.72–0.93) but a higher risk of CVD mortality (HR 1.19; 95% CI 1.03–1.39). However, the reduced risks of all-cause and non-CVD/non-cancer mortality were significant only in men ($P_{sex\ interaction}$<0.05). After excluding the deaths in the first 5 years, the HRs were increased for all-cause mortality, cancer mortality, and combined non-CVD/non-cancer mortality (1.03 vs. 1.05 vs 0.91, respectively), but the HR was stable for CVD mortality (1.21, all P>0.10).

The researchers concluded that these counterintuitive findings regarding non-CVD mortality suggest reverse causality.

1. Zhou Z, et al. Low-density-lipoprotein cholesterol and mortality outcomes among healthy older adults not taking lipid-lowering agents: A cohort study with 12,334 participants. EP.APS.P327. AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

AF: Moderate alcohol intake possibly associated with a reduced mortality risk

Registry data on patients with atrial fibrillation (AF) demonstrated that light or moderate alcohol consumption is not related to higher odds of stroke or major bleeding compared with abstinence. Remarkably, low and moderate drinking seemed to be associated with a lower probability of hospitalisation for heart failure (HF) and all-cause mortality.

"You already know that AF is associated with a higher risk of adverse cardiovascular events, and alcohol drinkers are at an increased risk of recurrent AF episodes; however, the role of alcohol on hard clinical endpoints in the AF population is still uncertain," Dr Alireza Oraii (Population Health Research Institute, Canada) introduced his research [1].

The cross-sectional study analysed data from the global RE-LY AF Registry containing information from 47 different countries on 1-year outcomes of AF patients who visited emergency rooms. Data on self-reported quantities of alcohol consumption from 14,058 patients were included (mean age

66 years and 48% women). The assessment was performed according to 4 categories, i.e. abstainers, light drinkers (i.e. less than 7 standard drinks per week), moderate drinkers (i.e. 7–13 standard drinks per week), and heavy drinkers (at least 14 standard drinks per week). Endpoints after 1 year included stroke or systemic embolism, major bleeding events, hospitalisation for HF, and all-cause mortality.

Most of just over 12,000 participants did not drink any alcohol and 359 were heavy drinkers. Concerning stroke/systemic embolism, no significant differences were found when comparing each of the alcohol-drinking categories to the non-drinkers. For the 1-year odds of major bleeding, similar results were found for low, moderate, and heavy alcohol consumption versus abstinence.

"Interestingly, our data also suggested that light to moderate drinking habits were associated with significantly lower odds of HF hospitalisation and all-cause mortality," Dr Oraii added. Light and moderate alcohol intake led to an odds ratio (OR) of 0.75 (95% CI 0.59–0.95) and OR 0.57 (95% CI 0.38–0.85), respectively, compared with no alcohol consumed. Furthermore, the likelihood of all-cause mortality was significantly reduced in those who drank light and moderate versus abstainers: OR 0.42 (95% CI 0.30–0.58) and OR 0.42 (95% CI 0.26–0.68).

"The evidence suggests that alcohol intake in moderation is not associated with excess odds of thromboembolic and major bleeding events in patients with AF and may even reduce odds of mortality and HF hospitalisation. However, a randomised controlled trial will need to be performed to solidify the evidence," Dr Oraii concluded.

1. Oraii A, et al. Alcohol consumption and cardiovascular outcomes in patients with atrial fibrillation; a RE-LY AF registry analysis. EA.APS. P270, AHA Scientific Sessions 2022, 05–07 November, Chicago, USA.

Periodontitis: An independent risk factor for AF

Histological assessment of left atrial appendages in patients with periodontitis revealed an association between the degree of periodontitis and atrial fibrosis, a dominant factor for the development of atrial fibrillation (AF). The correlation of AF with periodontal inflamed surface area remained positive after adjustment for known risk factors.

Periodontitis, a common inflammatory and infectious disease of the gums, has been shown to aggravate some systemic diseases. Until now, the association of periodontitis with both atrial fibrosis, which contributes to the onset and persistence of AF, and AF remains unclear [1]. To elucidate a possible relationship between periodontitis and atrial fibrosis, Prof. Shunsuke Miyauchi (Hiroshima University, Japan) and his team studied resected left atrial appendages of 76 participants with AF following atrial appendage excision [2]. Additionally, all participants underwent an oral examination evaluating the remaining number of teeth, bleeding on probing (BOP), periodontal probing depth, and periodontal inflamed surface area (PISA). PISA depicts the sum of all the areas of bleeding in the periodontal pocket epithelium and reflects the quantification of clinical periodontal inflammation degree. In addition, the degree of left atrial appendage fibrosis was quantified histologically by Azan-Mallory staining in sections randomly resected from the distal side of each left atrial appendage.

The researchers found that 3 periodontitis-suggesting parameters were positively correlated with atrial fibrosis, namely BOP (R=0.48; P<0.0001), periodontal probing depth of >4 mm (r=0.26; P=0.02), and PISA (r=0.46; P<0.0001). Among patients with >10 remaining teeth, PISA was positively and strongly correlated with atrial fibrosis (r=0.57; P<0.0001). Also after adjusting the results for known risk factors of AF, such as age, AF duration, body mass index, mitral valve regurgitation, and $CHADS_2$ (congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack) score, PISA was still significantly associated with atrial fibrosis (P=0.0002).

The authors concluded that there is a positive association of periodontitis with atrial fibrosis, especially in the presence of distinct inflammation. Periodontitis should be considered a modifiable risk factor for AF.

1. Xintarakou A, et al. Europace. 2020;22(3):342–351
2. Miyauchi S, et al. Relationship between periodontitis and atrial fibrosis in atrial fibrillation: Histological evaluation of left atrial appendages. EA.APS.P270, AHA Scientific Sessions 2022, Chicago, USA, 05–07 November.