Medicom International Conference Series in Cardiology

AHA Scientific Sessions 2023

American Heart Association

11–13 NOVEMBER 2023 • PHILADELPHIA • USA

PEER-REVIEWED CONFERENCE REPORT

Gene editing and hypercholesterolaemia

VERVE-101, a CRISPR base editing medicine, inactivated hepatic PCSK9 in the liver by changing a single DNA base pair and reduced LDL-C in patients with heterozygous familial hypercholesterolaemia.

read more on PAGE 9

Abelacimab significantly reduces bleeding

In the AZALEA-TIMI 71 trial, the factor XI inhibitor abelacimab significantly reduced bleeding events compared with rivaroxaban in patients with atrial fibrillation.

read more on PAGE 11

Semaglutide successful in SELECT trial

Semaglutide successfully reduced adverse cardiovascular outcomes in patients with cardiovascular disease who are overweight but without diabetes. No unexpected safety issues emerged in this population.

read more on PAGE 16

MEDICOM MEDICAL PUBLISHERS

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

COLOPHON

Editor	Prof. Marc Bonaca University of Colorado, USA
Reviewer	Prof. Stefan Stortecky Bern University Hospital, Switzerland
Reviewer	Prof. Christian Ruff Brigham and Women's Hospital, USA
Reviewer	Dr Manan Pareek Copenhagen University Hospital – Rigshospitalet, Denmark
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 Writer	Robert van den Heuvel
Production Manager	Anouk Neijenhoff
Graphic Design	MOOZ grafisch ontwerp
Graphics	Wim Kempink
Printing	GVO drukkers & vormgevers B.V.
Cover Photo	Catherine Kerr, Unsplash
ISSN	2468-8762 24:01

MEDICOM
MEDICAL PUBLISHERS

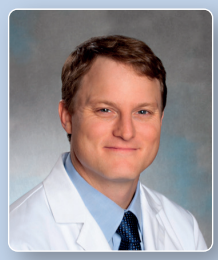
Head Office
Medicom Medische Uitgeverij B.V.
Laarderhoogtweg 25
1101 EB Amsterdam
The Netherlands

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 Reader,

The American Heart Association's (AHA) Scientific Sessions 2023, held in Philadelphia, PA offered a wide array of topics, from cutting-edge treatments in coronary artery disease (CAD) and peripheral artery disease (PAD) to promising strides in managing hypertension and lipid disorders. This Conference Report aims to contribute to the dissemination of these new insights.

Notably, the MINT trial shed light on transfusion strategies in myocardial infarction with anaemia, suggesting that a liberal approach may offer benefits. The ORBITA-2 trial results confirm the effectiveness of PCI for symptom relief in stable angina patients, marking a significant advancement in patient care.

The hypertension session brought forward intriguing insights, particularly the comparison of edoxaban versus warfarin in chronic thromboembolic pulmonary hypertension and the implications of sodium intake on blood pressure control. The lipid-lowering therapies chapter, with discussions on innovative treatments like lepodisiran and the potential of gene editing, signals a promising future in managing hypercholesterolemia.

The exploration of atrial fibrillation treatments, including the promising results of abelacimab in the AZALEA-TIMI 71 trial, and the discussions on anticoagulation in subclinical atrial fibrillation, exemplify the strides being made in this critical area. Moreover, semaglutide showed successful results in the highly anticipated SELECT trial for patients with cardiovascular disease who are overweight but do not have diabetes.

Special thanks to the series Editor, Prof. Marc Bonaca, and to Prof. Stefan Stortecky, Dr Manan Pareek and Prof. Christian Ruff for reviewing this edition.

We hope you enjoy the Report!

Medicom Medical Publishers

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

Hot Topics in CAD/PAD

MINT: Liberal or restrictive transfusion strategy in MI with anaemia?

Although a liberal transfusion strategy did not significantly outperform a restrictive transfusion strategy in patients with myocardial infarction (MI) and anaemia, the authors of the MINT study as well as the members of the late-breaking science session panel agreed that a liberal transfusion strategy is potentially a beneficial strategy in this patient population.

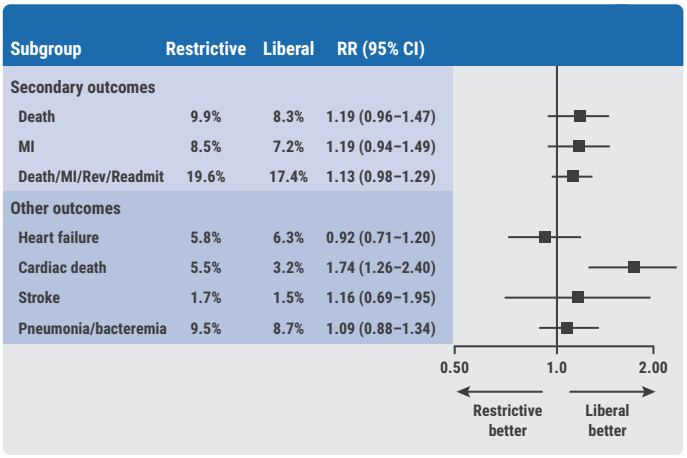
"Anaemia is a common feature in patients with MI," said Dr Jeffrey Carson (Rutgers University, NJ, USA) [1,2]. "So far, 3 trials have compared transfusion thresholds in patients with MI (n=820) with inconsistent results." The large, randomised-controlled, phase 3 MINT trial (NCT02981407) compared a restrictive transfusion strategy (i.e. starting transfusions at a haemoglobin level ≤7–8 g/dL) with a liberal transfusion strategy (i.e. targeting a haemoglobin level ≥10 g/dL) in patients with an acute MI and anaemia (defined as haemoglobin level <10 g/dL). The primary outcome was the risk of death or MI through 30 days. The 3,506 participants were randomised 1:1 to one of the treatment strategies.

On day 1, the haemoglobin levels increased in both groups from a mean 8.6 g/dL at baseline to 8.8 g/dL and 10.1 g/dL in the restrictive and liberal arms, respectively. Dr Carson mentioned that 66.3% of the participants in the restrictive group had received no blood units, compared with 5.1% in the liberal group. "For the primary outcome of death or MI through day 30, we observed rates of 16.9% and 14.5% in the study arms, achieving borderline significance in the liberal transfusion strategy arm (RR 1.16; 95% CI 0.99–1.34; P=0.07)," according to Dr Carson.

The effect appeared to be somewhat more pronounced in patients with type 1 MI compared with patients with type 2 MI (RR 1.32 vs RR 1.05), although there was no significant interaction. "Importantly, there was no significant increase in heart failure events, with rates of 5.8% and 6.3% in the restrictive and liberal arm, respectively (RR 0.92; 95% CI 0.71–1.20)," stressed Dr Carson.

Although the MINT trial did not demonstrate that a liberal transfusion strategy was significantly superior to a restrictive transfusion strategy in patients with MI and anaemia, the totality of the data (see Figure) suggests that a liberal transfusion strategy has the potential to deliver a clinical benefit.

Figure: MINT outcome measures within 30 days [1]



"Given the lack of acute harm associated with liberal transfusion and the preponderance of evidence favouring liberal transfusion in the largest trial to date, liberal transfusion appears to be a viable management strategy among patients with non-ST-elevation MI and type 1 MI," decided Prof. C. Michael Gibson (Harvard University, MA, USA), discussant of the trial.

1. Carson JL, et al. MINT: Restrictive versus liberal blood transfusion in patients with myocardial infarction and anaemia: results of the MINT trial. LB02, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.
2. Carson JL, et al. N Engl J Med 2023; 389:2446–2456.

ORBITA-2 confirms PCI effective for symptom relief in patients with stable angina

Percutaneous coronary intervention (PCI) improved the angina symptom score, increased exercise capacity, and improved quality-of-life in patients with stable angina and evidence of ischaemia who were not using anti-anginal medication. The effect occurred immediately, was sustained over 12 weeks, and was consistent across endpoints.

"Despite guidelines recommending revascularisation as add-on therapy for symptom relief in patients with stable coronary artery disease (CAD) on maximally tolerated anti-anginal medical therapy, evidence suggests that up to half

of all patients undergoing elective cardiac catheterisation do so on 0 or 1 anti-anginal agents," outlined Dr Christopher Rajkumar (Imperial College London, UK) [1,2].

The double-blind, randomised, placebo-controlled ORBITA-2 trial (NCT03742050) included 301 participants with stable angina, either due to single-vessel or multivessel disease, with evidence of ischaemia who were not on anti-anginal medication at baseline [3,4]. The primary endpoint was the novel daily angina symptom score, including the measurement of episodes of angina, the use of anti-anginal agents, and adverse cardiovascular outcomes, i.e. unacceptable angina, acute coronary syndrome, and death. The lowest score (0) represented the best outcome, whereas the highest score (79) represented death.

"PCI improved the angina symptom score compared with placebo," said Dr Rajkumar (OR 2.21; 95% CI 1.41–3.47; P<0.001) [3]. This effect was driven by a reduction in angina frequency (OR 3.44; 95% CI 2.00–5.91; P<0.001) but not by anti-anginal use (OR 1.21; 95% CI 0.70–2.10; P=0.5). The rates of unacceptable angina, acute coronary syndrome, or death were low and comparable between groups.

"Physicians now have a choice of 2 first-line, evidence-based pathways, either anti-anginal medication or PCI," concluded Dr Rajkumar. Referring to the non-significant results of the previous ORBITA trial, assessing PCI in patients with MI on anti-anginal medication, Dr Rajkumar argued that current guidelines that reserve PCI to patients on optimal anti-anginal medication may systematically select patients with the least to gain [5].

Discussant of the trial Dr Connie Hess (University of Colorado, CO, USA) added that future research should investigate the cost-effectiveness of PCI as anti-anginal monotherapy, should address the understanding of residual symptoms, and needs to focus on longer term outcomes.

1. Lawton JS, et al. Circulation. 2022;145:e18–e114.
2. Shen L, et al. Clin Cardiol. 2016;39:721–727.
3. Rajkumar CA, et al. Percutaneous coronary intervention for stable angina (ORBITA-2): a randomised, placebo-controlled trial. LB02, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.
4. Rajkumar CA, et al. N Engl J Med 2023;389:2319–2330.
5. Al-Lamee R, et al. Lancet. 2018;391(10115):31–40.

Nicotinamide riboside shows promising trend for walking function in PAD

Nicotinamide riboside was associated with a trend of improved walking function in patients with peripheral artery disease (PAD) compared with placebo. This effect was not further enhanced by additional treatment with resveratrol.

The phase 2 randomised NICE trial (NCT03743636) assessed the effect of nicotinamide riboside, a B3 vitamin and precursor to nicotinamide adenine dinucleotide (NAD+), on walking function in patients with PAD (n=90). "NAD+ is an essential co-factor and enzyme to increase mitochondrial activity, reduce oxidative stress, and increase nitric oxide to improve blood flow and help people with PAD walk better," explained Prof. Mary McDermott (Northwestern University, IL, USA) [1]. The participants of NICE were randomised to nicotinamide riboside alone (500 mg twice daily), nicotinamide riboside plus resveratrol (125 mg once daily), or a placebo. "Resveratrol increases SIRT1 affinity for NAD+, whereas nicotinamide riboside increases NAD+ abundance. The combination of these 2 agents may, therefore, have a potent effect on SIRT1 activity," Prof. McDermott outlined the rationale for combining these 2 drugs. The primary outcome was the change in 6-minute walking distance at 6 months.

At 6 months, the 6-minute walking distance showed a non-significant increase of 7.00 meters in the monotherapy arm (P=0.078 vs placebo), decreased by 6.93 meters in the combination therapy arm (P=0.376 vs placebo) and decreased by 10.58 meters in the placebo arm. In a sensitivity analysis selecting only drug-adherent participants (i.e. ≥75% adherence), both experimental arms were associated with improvements in walking distance compared with placebo. In the monotherapy arm with a mean difference of +35.4 meters (P=0.014), and in the combination therapy arm with a mean difference of +30.2 meters (P=0.028).

In summary, there was a favourable trend for monotherapy, which appeared more favourable in a post-hoc analysis limited to drug-adherent participants with PAD. "However, due to the limited sample size, there is a need to confirm these findings in larger clinical trials," concluded Prof. McDermott. "NAD boosters are not yet ready for prime time," commented Dr Naomi Hamburg (Boston University, MA, USA), discussant of the trial. She emphasised that we need to improve access to supervised and home-based programmes and that patients with PAD should be identified as early as possible.

1. McDermott MM, et al. Nicotinamide riboside for peripheral artery disease: the NICE randomised clinical trial. FS07, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

Pemafibrate reduces microvascular complications of PAD and T2D

Participants from the PROMINENT trial with type 2 diabetes (T2D) and mixed dyslipidaemia who were treated with pemafibrate had a mean 37% reduction in ischaemic

ulcerations or gangrene related to peripheral artery disease (PAD). According to the authors of this post-hoc analysis, these findings are in line with prior studies indicating that PPAR-α agonists have a positive effect on distal small vessel complications in T2D and PAD.

"Prior studies indicate that PPAR-α agonists may reduce diabetic limb vascular complications in patients with T2D," according to Dr Aruna Pradhan (Brigham and Women's Hospital, MA, USA) [1]. In the previously published, randomised-controlled, phase 3 PROMINENT trial, the PPAR-α agonist pemafibrate did not outperform placebo in reducing cardiovascular events in a population of patients with T2D and mixed hyperlipidaemia [2]. "We did see an interesting, but non-significant, trend concerning new or worsening PAD," added Dr Pradhan. The current post-hoc analysis hypothesised that pemafibrate reduced clinical ischaemic ulceration and gangrene, which are considered microvascular and micro-organ complications of PAD [2].

In the subpopulation of PROMINENT participants with ulcers or gangrene (n=91), pemafibrate was associated with significantly lower rates of ulcers and gangrene as compared with placebo (HR 0.63; 95% CI 0.41–0.96; P=0.03) after a median follow-up of 3.4 years. Both ulcers (HR 0.65; 95% CI 0.38–1.11) and gangrene (HR 0.49; 95% CI 0.27–0.87) were lower with pemafibrate treatment, whereas other PAD outcomes, such as PAD admission, revascularisation, or major amputation, were not significantly lower (HR 0.89; 95% CI 0.70–1.13).

"Reducing the risk of amputation (due to ulcers or gangrene) is complicated because there is a very heterogeneous biology," said Prof. Marc Bonaca (University of Colorado, CO, USA), who discussed the trial outcomes. Different mechanisms are at play in large artery ischaemia and microvascular disease. "In microvascular disease, we do not really understand the biology, particularly in the context of diabetes. There are no therapeutic options." However, promising data is emerging for several agents. Prof. Bonaca mentioned the GLP-1 agonist liraglutide and the PPAR-α agonist fenofibrate. "The current results are a confirmation of the findings that we saw for fenofibrate," he said. Other studies are needed to further unravel the mechanisms that are behind the effects of these agents.

1. Marinho LL, et al. Pemafibrate reduces incidence of lower extremity ischaemic ulcer and gangrene: evidence from PROMINENT. FS07, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.
2. Pradhan AD, et al. N Engl J Med 2022;387:1923–1934.

Dapagliflozin improves cardiometabolic outcomes in myocardial infarction

Dapagliflozin reduced a win ratio outcome of cardio-metabolic disease in patients with acute myocardial infarction (MI) and impaired left ventricular (LV) systolic function who did not have diabetes or chronic heart failure (HF). No differences were seen in cardiovascular outcomes.

"Since SGLT2 inhibitors have positive effects on almost all cardiometabolic parameters, dapagliflozin could be an effective secondary prevention medication for patients who have had an MI," argued Prof. Stefan James (Uppsala University, Sweden) [1]. The registry-based, double-blind, randomised, phase 3 DAPA-MI trial (NCT04564742) aimed to test the effect of dapagliflozin on cardiometabolic and cardiovascular outcomes in patients with acute MI but without diabetes or chronic HF [2]. Patients who had had a non-STEMI or STEMI in the last 10 days were eligible for enrollment in the trial.

The 4,017 participants were randomised 1:1 to the SGLT2 inhibitor dapagliflozin (10 mg once daily) or placebo. The composite of cardiovascular death and hospitalisation for HF was the initial primary outcome. "It became evident that the number of primary composite outcome events was much lower than expected," expressed Prof. James [1]. "Therefore, the primary endpoint was changed." The novel primary endpoint was a hierarchical composite outcome (win ratio) of death, hospitalisation for HF, non-fatal MI, atrial fibrillation, new diagnosis of type 2 diabetes, NYHA functional class status, and body weight decrease of at least 5%. "Importantly, this study population was very well treated according to guideline recommendations," emphasised Prof. James.

The primary outcome showed a win ratio of 1.34 in favour of participants in the dapagliflozin arm (95% CI 1.20–1.50; P<0.001). The corresponding win percentages were 32.9% in favour of dapagliflozin, 24.6% in favour of placebo, and 42.5% ties. "When we look more closely at the components of the primary outcome, we can see that the effect is driven by cardiometabolic outcomes, such as diabetes diagnosis and body weight reduction, rather than cardiovascular outcomes," added Prof. James.

In conclusion, dapagliflozin, on top of guideline-directed medical therapy, offered benefits for patients with acute MI and impaired LV systolic function who did not have

diabetes or chronic HF. "The current trial was underpowered to evaluate hard cardiovascular endpoints," said Prof. Stephen Wiviott (Brigham and Women's Hospital, MA, USA). "From my standpoint, DAPA-MI does not suggest a new mandate to expand SGLT2 inhibitor use to an isolated MI population without other SGLT2 inhibitor indications but does support the safety of use among patients with acute coronary syndromes.

1. James S, et al. Dapagliflozin in myocardial infarction without diabetes or heart failure. LB02, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.
2. James S, et al. NEJM Evid. 2023; Nov 11. DOI: 10.1056/EVIDoa2300286.

Optimising Hypertension Outcomes

Edoxaban versus warfarin in chronic thromboembolic pulmonary hypertension

In patients with chronic thromboembolic pulmonary hypertension (CTEPH) who had received re-perfusion treatment, edoxaban showed non-inferiority to warfarin for preventing the worsening of pulmonary haemodynamics.

"Direct oral anticoagulants (DOACs) are first-line anti-coagulants for the treatment of acute pulmonary embolism and the prevention of recurrent pulmonary embolism," said Dr Kazuya Hosokawa (Kyushu University, Japan) [1,2]. "It has, however, not been established whether DOACs are safe and effective in patients with CTEPH."

The multicentre, single-blind, non-inferiority, warfarin-controlled, phase 3 KABUKI trial (NCT04730037) compared edoxaban with warfarin in patients with CTEPH [2]. Participants (n=74) were randomised 1:1 and the primary endpoint was the ratio of pulmonary vascular resistance (PVR) at 48 weeks to the PVR at baseline.

The PVR ratio was non-inferior with edoxaban (treatment effect 0.92; 95% CI 0.82–1.03), reaching the non-inferiority threshold, which was an upper limit of the confidence interval of 1.19 ($P_{non\text{-}inferiority}$<0.001). Clinically relevant bleeding occurred in 2.7% of the edoxaban-treated participants and in 5.4% of the warfarin-treated participants (P=1.00).

One serious adverse event was observed in the edoxaban arm, a case of worsening pulmonary hypertension, and 3 serious adverse events were reported in the warfarin arm, being 1 tooth extraction, a haemorrhagic duodenal ulcer, and a case of urothelial transitional cell carcinoma.

"The trial was not designed to assess the effects of edoxaban on clinical outcomes," Dr Hosokawa mentioned as a study limitation. "Also, the small sample size and single-country design limit the generalisability of the findings." According to Dr Teresa Carman (University Hospitals, OH, USA), a discussant of the trial, some questions remain: "Will DOACs do as well in patients prior to reperfusion or in patients with underlying chronic vascular changes?" she wondered. "And can we extrapolate these findings to patients with more severe WHO class III disease?" Further studies are needed to address these issues.

1. Stevens SM, et al. Chest. 2021;160(6):e545–e608.
2. Hosokawa K, et al. A multicenter, randomised, warfarin-controlled trial of edoxaban in patients with chronic thromboembolic pulmonary hypertension: KABUKI trial. FS07, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

Sodium intake and blood pressure: new insights

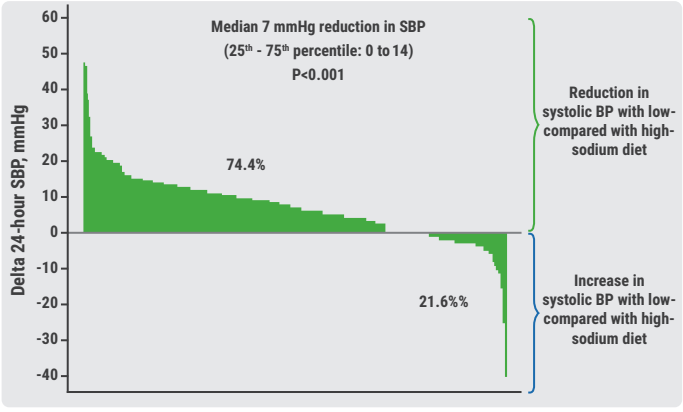
Low dietary sodium intake reduced systolic blood pressure (BP) irrespective of the use of anti-hypertensive agents or hypertension status in the CARDIA-SSBP trial. However, the BP-reducing effect of low sodium intake appears to be higher in individuals with diabetes or higher baseline BP.

"Compared with a standard Western diet, with a daily dietary sodium intake of about 3,500 mg, a low-sodium diet with an intake of 1,150 mg per day resulted in a systolic BP reduction of 6.7 mmHg," stated Dr Deepak Gupta (Vanderbilt University Medical Centre, TN, USA) [1]. "Since the publication of these results in 2001, sodium intake has not changed much. There are, however, still gaps in our understanding of the relation between dietary sodium and BP." For example, Dr Gupta mentioned the association between anti-hypertensive medication and salt sensitivity, and the extent to which lowering dietary sodium affects BP among patients with diabetes.

The CARDIA-SSBP study (NCT04258332) included 228 participants between 50–75 years with systolic BP between 90–160 mmHg and diastolic BP between 50–100 mmHg [1,2]. The investigators used a cross-over design in which participants were randomised to a high-sodium diet, comprising their usual diet plus 2,200 mg sodium per day, or a low-sodium diet (i.e. 500 mg sodium/day). After 7 days, participants switched to the other study group.

After 1 week, participants in the low-sodium group had a mean reduction of 8 mmHg in 24-hour ambulatory systolic BP compared with participants in the high-sodium group (95% CI 4–11 mmHg; P<0.0001). "These results were irrespective of anti-hypertensive medication use or whether participants had controlled or uncontrolled hypertension," added Dr Gupta. "We did see greater reductions in participants with higher baseline BP and in those with diabetes." An analysis of the within-individual salt sensitivity showed that systolic BP was reduced with low-sodium intake in 74.4% of the participants, and that systolic BP was increased in 21.6% of the participants taking the low-sodium diet as compared with the high-sodium diet (see Figure).

Figure: 24-hour change in systolic BP calculated as high minus low-sodium diet per individual [2]



BP, blood pressure; SBP systolic blood pressure.

Delta 24-hour BP was calculated as high minus low-sodium diet.

In summary, dietary sodium reductions were associated with reductions in systolic BP, whereas the addition of sodium to a standard Western diet had no clear effect on systolic BP. A meaningful BP reduction was achieved in most individuals in this middle-aged to elderly population within 1 week. "The effect of this intervention is comparable with a first-line anti-hypertensive medication," according to Dr Gupta.

1. Sacks FM, et al. N Engl J Med 2001;344(1):3–10.
2. Gupta DK, et al. Effects of dietary sodium on systolic blood pressure in middle-aged individuals: a randomised order cross-over trial. LB04, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, PA, USA.

Intensive BP intervention reduces risk of dementia

An intensive blood pressure (BP) intervention outperformed usual care in reducing the risk of dementia in patients (n=33,995) with hypertension living in rural Chinese villages. "The proven-effective intervention should be scaled up widely to reduce the global burden of dementia," stated Dr Jiang He (Tulane University, LA, USA), who presented the main results of the study.

Dr He and colleagues compared the effectiveness of an intensive BP intervention to usual care on the risk reduction of dementia in patients with hypertension in a cluster-randomised trial [1]. The 33,995 participants with hypertension from 326 rural Chinese villages were randomised 1:1. The experimental BP intervention included doctor-initiated titration of anti-hypertensive drugs, the delivery of discounted and free medications to patients, lifestyle interventions, education on BP monitoring, and medication adherence instructions. The primary outcome was all-cause dementia at 48 months.

"In the usual-care arm, the systolic BP had dropped by a mean of 7.2 mmHg, and this measure was by a mean of 29.2 mmHg in the experimental arm," said Dr He. For diastolic BP, the corresponding rates were -6.1 mmHg and -15.4 mmHg. In addition, 67.7% of the participants in the intervention arm were normotensive at 48 months compared with 15.0% in the usual-care arm (P<0.0001). Not surprisingly, those in the intervention arm were on a higher number of anti-hypertensive agents (mean 3.0 vs 1.2; P<0.0001). "Importantly, the primary outcome was met, with an annual rate of 1.12% of all-cause dementia in the intervention arm and a rate of 1.31% in the usual-care arm, representing a 15% reduction," said Dr He (RR 0.85; 95% CI 0.76–0.95; P=0.0035).

"This is the first definitive evidence from a randomised-controlled trial showing the effect of a BP-lowering intervention on dementia risk reduction," Dr Daniel Jones (University of Mississippi, MS, USA) congratulated the study authors. "Next, we have to investigate whether intensive BP reduction decreases the risk for all forms of dementia. Also, the role of BP in the pathophysiology of Alzheimer's disease, vascular dementia, and other forms of dementia needs to be studied." Finally, Dr Jones expressed that it would be interesting to investigate whether earlier intervention offers more protection.

1. He J, et al. Effectiveness of blood pressure lowering intervention on risk of total dementia among patients with hypertension: a cluster-randomised effectiveness trial. LB04, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

Biannual zilebesiran associated with substantial BP reductions

In the phase 2 KARDIA-1 study, a single subcutaneous dose of zilebesiran demonstrated encouraging reductions in systolic blood pressure (BP) in hypertensive patients at 3 and 6 months of follow-up compared with placebo.

"Despite the availability of effective therapies to reduce hypertension, many patients remain untreated or have uncontrolled disease," said Prof. George Bakris (University of Chicago, IL, USA) [1]. The subcutaneously administered investigational agent zilebesiran delivered promising efficacy data at 24 weeks after 1 infusion of this agent in a phase 1 study [2].

Prof. Bakris presented the results of the phase 2 KARDIA-1 study (NCT04936035), which randomised 394 participants with mild-to-moderate hypertension 1:1:1:1:1 to 1 of 4 dose-levels of the RNA-interference therapeutic zilebesiran (ranging from 150 mg once every 6 months to 600 mg once every 6 months) or a placebo [1,2]. The primary endpoint was the change in 24-hour mean ambulatory systolic BP from baseline to 3 months.

"At 3 months, all zilebesiran dose levels were associated with significantly larger reductions in 24-hour mean ambulatory systolic BP than placebo," said Prof. Bakris. In the lowest-dose group, the reduction was -14.1 mmHg compared with placebo (P<0.0001), and the reduction was -15.7 mmHg compared with placebo in the highest-dose group (P<0.0001). These reductions appeared to be maintained at 6 months, with corresponding reductions of -11.1 mmHg for the lowest-dose group and -14.2 for the highest-dose group.

"The agent also displayed a favourable safety profile," according to Prof. Bakris. No serious or severe drug-related adverse events were reported. However, the rates of hyperkalaemia and hypotension were higher in the zilebesiran groups (6% vs 3%; 4% vs 1%); although these cases were mostly mild or moderate and did not lead to treatment discontinuations.

These results support the quarterly or biannual dosing of subcutaneous zilebesiran to reduce the BP of patients with hypertension. The investigational agent zilebesiran is further assessed as an add-on therapy for patients with hypertension in the KARDIA-2 trial.

1. Bakris G, et al. Sustained blood pressure reduction with the RNA interference therapeutic zilebesiran: primary results from Kardia-1, a phase 2 study in patients with hypertension. LB04, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.
2. Desai AS, et al. N Engl J Med 2023;389:228–238.

Post-partum intervention lowers BP after hypertensive pregnancy

The POP-HT study demonstrated that blood pressure (BP) interventions in the first weeks after pregnancy have the potential to yield long-term benefits following a hypertensive pregnancy. Improving post-partum BP control has a positive influence on the mid-long term, which appears to persist after medication is stopped.

"Although hypertensive disorders of pregnancy are associated with an increased risk of cardiovascular disease, there are no proven therapies to reduce the post-partum risk," according to Dr Jamie Kitt (University of Oxford, UK) [1]. The POP-HT study (NCT04273854) randomised 220 women with gestational hypertension or pre-eclampsia 1:1 to standard NHS care in the control group or the intervention arm, in which self-monitored BP readings were sent to a physician who subsequently optimised BP medication for the respective participants [1,2]. The primary endpoint was the 24-hour mean diastolic BP at approximately 9 months post-partum.

At 9 months post-partum, the between-group difference in 24-hour mean diastolic BP was -5.8, favouring the intervention arm over the control arm (95% CI -4.2 to -7.4). Likewise, the difference in 24-hour mean systolic BP was -6.5 mmHg, favouring the intervention arm (95% CI -4.2 to -8.8). "Furthermore, there were 29 BP-related re-admissions in the control arm versus 8 in the intervention arm, meaning that we need to treat 5 individuals to avoid 1 BP-related post-natal re-admission," added Dr Kitt.

According to Dr Kitt, the results of this trial are clinically meaningful. "A 5 mmHg improvement in BP would result in a 20% reduction in lifetime cardiovascular risk if this improvement is maintained in the long-term," he concluded [1,2].

1. Kitt J, et al. Physician optimized postpartum hypertension treatment (POP-HT) randomised trial. LB04, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.
2. Kitt J, et al. J. Am. Med. Assoc. 2023;330(20):1991–1999.

Future of Lipid-Lowering Therapies

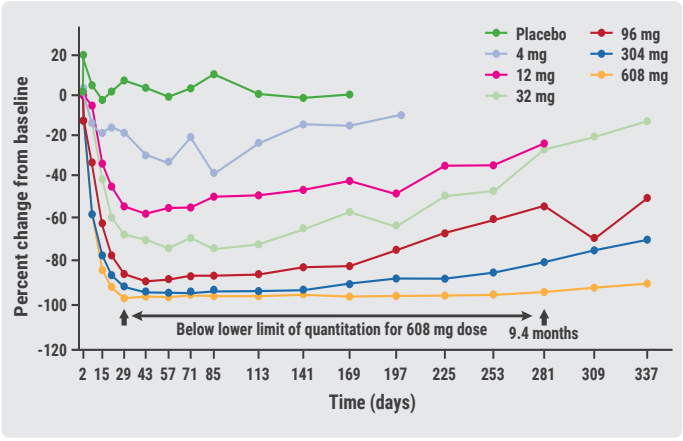
Encouraging data for lepodisiran as Lp(a) lowering therapy

A substantial reduction in lipoprotein(a) was achieved with a single subcutaneous injection of lepodisiran, a siRNA-targeting mRNA for the *LPA* gene. Together with the favourable safety profile of this agent, the results support the further development of lepodisiran.

"Lepodisiran is a siRNA designed to degrade the mRNA coding for apolipoprotein(a), thereby reducing translation of the *LPA* gene," explained Dr Steven Nissen (Cleveland Clinic, OH, USA) [1]. The current phase 1 trial (NCT04914546) evaluated the safety and efficacy of lepodisiran in 48 participants with Lp(a) serum concentrations of ≥75 nmol/L who did not have known cardiovascular disease at enrolment. "Participants were randomised to 1 of 6 single-dose levels of lepodisiran, ranging from 4 mg to 608 mg, or to a placebo, all subcutaneously administered," outlined Dr Nissen. The primary outcome measures were safety and Lp(a) serum concentrations through 48 weeks.

At 48 weeks, the mean reduction in Lp(a) was 94% in the highest dose group, showing a long duration of effect on Lp(a) levels (see Figure). The rate of adverse events (AEs) was overall low, and no dose-related trend could be observed in the occurrence of AEs. Headache, COVID-19, rhinorrhoea, and ECG patch erythema were the most common AEs. Injection-site reactions were reported as well but not more frequently in the active arms than in the placebo arm.

Figure: Median percentage reduction in lipoprotein(a) over time [1]



Lepodisiran was cleared from the plasma rapidly. "Even in the highest dose level, the drug was essentially gone from the plasma at 48 hours, reducing systemic exposure," mentioned Dr Nissen. "This is a major advantage of this approach."

Thus, lepodisiran delivered promising results as an Lp(a)-lowering agent in the current phase 1 study, supporting further development of the drug. "Nucleic acid therapeutics offer a highly promising approach to treat this previously untreatable disorder," concluded Dr Nissen. "Cardiovascular outcomes trials will determine whether these therapies can reduce the incidence of major adverse cardiovascular events."

1. Nissen SE, et al. Lepodisiran: an extended-duration siRNA targeting lipoprotein(a). LB06, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

Gene editing may change the treatment landscape of hypercholesterolaemia

The first-in-human study to investigate VERVE-101, a novel CRISPR base editing medicine, showed successful inactivation of hepatic PCSK9 in the liver by changing a single DNA base pair. Furthermore, durable, dose-dependent reductions of LDL-cholesterol profile were observed in the first assessed patients with heterozygous familial hypercholesterolaemia (HeFH).

"Patients with HeFH need daily pills or intermittent injections over decades," said Dr Andrew Bellinger (Verve Therapeutics, MA, USA) [1]. "This is a heavy burden on patients, providers, and the healthcare system." Dr Bellinger and colleagues wondered whether a single-course treatment that mimics PCSK9 variants protecting against atherosclerotic cardiovascular disease can be developed.

The phase 1b heart-1 study (NCT05398029) tested the CRISPR base editing medicine VERVE-101 for patients with HeFH and a high risk of cardiovascular events. The first 10 participants (8 men and 2 women; mean age 54 years) were allocated to 4 single-infusion dose groups: 0.1 mg/kg (n=3), 0.3 mg/kg (n=3), 0.45 mg/kg (n=3), and 0.6 mg/kg (n=1). "The patients had severe atherosclerotic cardiovascular disease (ASCVD) and a high risk for cardiovascular events," added Dr Bellinger. The primary endpoint was the safety and tolerability of the agent.

"In the higher dose cohorts, we saw blood PCSK9 protein level reductions of 47%, 59%, and 84%," noted Dr Bellinger. Also, blood LDL-cholesterol level reductions of 39%, 48%, and 55% were reported in 3 participants in the higher dose groups. "The patient in the highest dose group had the 55% reduction and this reduction was maintained up to day 180," added Dr Bellinger.

As for safety, 4 infusion-site reactions were noted and some transient, reversible increases in ALT levels in the higher dose groups. "Mean bilirubin levels remained below the upper limit of normal," according to Dr Bellinger. Finally, there was 1 serious cardiovascular event, a myocardial infarction, that may have been related to treatment.

The heart-1 trial will keep enrolling patients in the 2 highest dose groups for an expansion cohort planned for 2024 to complete the dose-escalation phase. A phase 2 trial is scheduled for 2025. "These preliminary results suggest that single-course gene editing medicines may become an option in patients who require deep LDL-cholesterol reductions over decades," decided Dr Bellinger.

1. Bellinger AM, et al. Safety and pharmacodynamic effects of VERVE-101: an investigational DNA base editing medicine designed to durably inactivate the PCSK9 gene and lower LDL cholesterol - interim results of the phase 1b heart-1 trial. LB05, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

REPRIEVE: Mechanisms behind MACE reduction in HIV population on pitavastatin

A mechanistic substudy of the REPRIEVE trial, investigating the effects of pitavastatin on coronary artery disease (CAD) in patients with HIV, showed a risk reduction in non-calcified plaque volume, a decreased risk of plaque progression, and less evidence of lipid oxidation and arterial inflammation in patients on pitavastatin. According to the investigators, these effects could explain the reduction in major cardiovascular events (MACE) that was observed in the parent trial.

"We know that patients with HIV have an increased risk of cardiovascular disease," stated Dr Michael Lu (Massachusetts General Hospital, MA, USA) [1]. "Also, the moderate-intensity statin pitavastatin has minimal interaction with the antiretroviral therapy that is used by patients with HIV." The phase 3 REPRIEVE trial (NCT02344290) randomised 7,769 participants with HIV on antiretroviral therapy with a low-to-moderate 10-year atherosclerotic cardiovascular disease risk (ASCVD) to pitavastatin calcium or placebo [2]. The primary analysis at 5.1 years showed a reduction of 35% in MACE in participants on pitavastatin compared with those who were treated with a placebo. The current analysis, presented by Dr Lu, evaluated the effect of pitavastatin on non-calcified coronary plaque formation and inflammatory and immune biomarkers in 804 participants.

At 24 months, the authors observed a reduction of 7% in non-calcified coronary plaque volume in participants on pitavastatin compared with those on placebo (95% CI -8.6 to -0.1; P=0.044). In participants with plaques at baseline, the corresponding difference was 12%. Furthermore, the risk of non-calcified plaque progression was 33% lower in the pitavastatin group than in the placebo group (95% CI 0.52–0.88; P=0.003).

"We also noted significant reductions in Lp-PLA2 and oxidised LDL levels in pitavastatin-treated individuals compared with placebo-treated individuals," added Dr Lu. Changes in other biomarkers, such as MCP-1, sCD14, and IL-6, did not significantly differ between the 2 study groups at 24 months. "The results of REPRIEVE are in a similar ballpark with respect to plaque changes as other trials investigating LDL-reducing agents in higher-risk populations," according to Dr Lu.

In conclusion, in a primary prevention population of patients with HIV and a low-to-moderate ASCVD risk, 2 years of pitavastatin treatment was associated with reduced non-calcified plaque volumes, a lower risk of plaque progression, and a reduction in relevant biomarkers of lipid oxidation and arterial inflammation, potentially explaining the reduction in MACE that was reported in the primary analysis of this trial.

1. Lu MT, et al. Effects of pitavastatin on coronary artery disease and inflammatory biomarkers: mechanistic substudy of the REPRIEVE primary prevention trial in HIV. LB06, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.
2. Grinspoon SK, et al. N Engl J Med 2023;389:687–699.

Recaticimab may offer a solution for uncontrolled hypercholesterolaemia

Recaticimab demonstrated to be a promising add-on therapy for patients with hypercholesterolaemia and mixed hyperlipidaemia who were inadequately controlled on statins. The drug allowed for infrequent dosing and no substantial safety issues emerged in the REMAIN-2 study.

"Although anti-PCSK9 antibodies are efficacious as add-on therapy for patients with non-familial hypercholesterolaemia (non-FH) and mixed hyperlipidaemia, adherence in the real world is compromised due to frequent dosing," explained Dr

Xin Du (Beijing Anzhen Hospital, China) [1–3]. "Recaticimab is a long-acting anti-PCSK9 antibody, designed to overcome this matter" [3]. This new PCK9 inhibitor can be injected every 1 to 3 months.

The randomised, double-blind, placebo-controlled, phase 3 REMAIN-2 study (NCT04885218) randomised 692 participants with hypercholesterolemia and mixed hyperlipidaemia who were not known to have FH 2:1 to one of three recaticimab arms (150 mg every 4 weeks, 300 mg every 8 weeks, or 450 mg every 12 weeks, subcutaneously administered) or a matched placebo. The primary endpoint was the percentage change in LDL-cholesterol from baseline to week 24.

At week 24, recaticimab reduced LDL-cholesterol by 53.4–62.2% compared with placebo, irrespective of dose level (P<0.0001 for all dose levels). These reductions were sustained through week 48. "LDL-cholesterol control goals were achieved by 85.8–94.5% of the participants treated with recaticimab and by 9.8–33.3% of the participants on placebo," added Dr Du.

Furthermore, recaticimab outperformed placebo in reducing other lipid parameters, such as non-HDL-cholesterol, ApoB, and Lp(a). According to Dr Du, the incidence and severity of treatment-related adverse events were comparable across treatment groups. Increased alanine transaminase (ALT), increased blood creatine phosphokinase (CPK), and hyperuricaemia were the most common adverse events in both groups.

Prof. Stephen Nicholls (Monash University, Australia), a discussant of the trial, commented that longer studies are required to determine whether this agent can evoke durable reductions in LDL-cholesterol and cardiovascular adverse events cost-effectively.

1. Blom DJ, et al. N Engl J Med 2014;370(19):1809–1819.
2. Robinson JG, et al. N Engl J Med 2015;372(16):1489–1499.
3. Du X, et al. Recaticimab add-on therapy in patients with non-familial hypercholesterolaemia and mixed hyperlipidemia (REMAIN-2): a multicenter, randomized, double-blind, placebo-controlled phase 3 trial. LB06, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

Atrial Fibrillation and Sudden Cardiac Death

Abelacimab substantially lowers bleeding risk compared with rivaroxaban

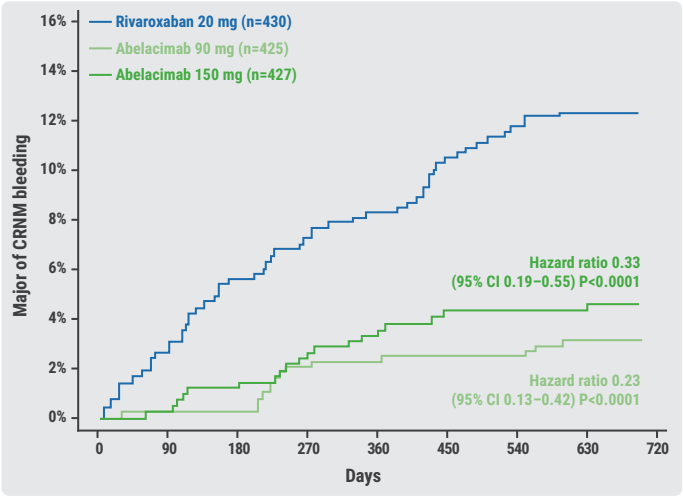
In the phase 2b AZALEA-TIMI 71 trial, abelacimab significantly reduced bleeding events compared with rivaroxaban in patients with atrial fibrillation (AF). Furthermore, the agent showed potent inhibition of factor XI. Whether this novel agent also reduces the risk of ischaemic events compared with other anticoagulants requires further study.

The multicentre, randomised, active-controlled AZALEA-TIMI 71 trial (NCT04755283) compared the bleeding profile of the factor XI inhibitor abelacimab with the direct oral anticoagulant (DOAC) rivaroxaban in patients with AF and a moderate-to-high risk of stroke. The participants (n=1,287) were randomised in a 1:1:1 fashion to receive 90 mg or 150 mg abelacimab, subcutaneously administered once per month, or 20 mg rivaroxaban, orally administered once daily. The primary endpoint was major or clinically relevant non-major (CRNM) bleeding. Dr Christian Ruff (Brigham and Women's Hospital, MA, USA) presented the key findings [1].

"The trial was terminated early because the data-monitoring committee reported that abelacimab yielded a larger than anticipated reduction in the primary endpoint compared with the active comparator," announced Dr Ruff. At the time of termination, abelacimab displayed a factor XI inhibition of >95% in both dose groups. Further, the occurrence of major or CRNM bleeding was significantly lower in the 90 mg group (HR 0.23; 95% CI 0.13–0.42; P<0.0001) and the 150 mg group (HR 0.33; 95% CI 0.19–0.55; P<0.0001) than in the rivaroxaban group (see Figure on the next page).

No significant difference was observed in the risk of stroke or systemic embolism between the rivaroxaban group and either the 90 mg abelacimab group (HR 1.13; 95% CI 0.41–3.12; P=0.81) or the 150 mg group (HR 1.45; 95% CI 0.55–3.80; P=0.45). "However, the rates of these events

Figure: Primary endpoint of major or CRNM bleeding in the AZALEA-TIMI 71 trial [1]



CRNM, clinically relevant non-major.

were low and were only evaluated as exploratory endpoints," commented Dr Ruff. Finally, there were no substantial differences between the safety profiles of the 2 agents.

In summary, abelacimab 150 mg (i.e. the dose being investigated in phase 3 trials) was associated with a 67% reduction in major or CRNM bleeding compared with rivaroxaban, a decrease of 74% in major bleeding, and a reduction of 93% in major gastrointestinal bleeding. "A phase 3 trial testing abelacimab for the primary endpoint of ischaemic stroke or systemic embolism in a population of patients with AF deemed ineligible for currently available anticoagulants is underway," Dr Ruff ended his presentation.

1. Ruff CT, et al. A multicentre randomised active-controlled study to evaluate the safety and tolerability of two blinded doses of abelacimab compared with open-label rivaroxaban in patients with atrial fibrillation. LB05, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

Liraglutide may improve post-ablation outcomes in obese patients with AF

The GLP-1 agonist liraglutide may be a useful additional therapy to a risk factor modification (RFM) programme in obese patients with atrial fibrillation (AF) in terms of reducing AF or atrial flutter after ablation. However, larger studies are needed to further explore the potential benefits of liraglutide in this patient population.

"We know that the success rate of AF ablation is lower in obese patients," claimed Dr Jeffrey Goldberger (University of Miami, FL, USA) [1]. "Therefore, weight loss and RFM were added as a Class 1 recommendation for obese or overweight patients with AF" [1,2]. The current, phase 4 LEAF study (NCT03856632) compared RFM alone with RFM plus treatment with the GLP-1 agonist liraglutide as therapy before ablation for AF in obese patients [1,3]. "The RFM programme included diabetes, hypertension, and hyperlipidemia control, as well as exercise prescription, dietary interventions, sleep apnoea assessment, and alcohol reduction strategies," said Dr Goldberger [1].

The participants (n=65) were randomised 1:1 to the 2 treatment options. After 3 months of therapy, 59 participants (mean age of 62 years; 27% women; BMI ≥27 kg/m^2) underwent ablation, after which the therapy was continued for another 6 months. Subsequently, all participants received RFM for another 6 months.

"At the time of ablation, there was significant weight loss in both groups, but the difference in weight loss between the study arms was not statistically significant (P=0.09)," noted Dr Goldberger. Similarly, both arms showed a significant reduction in epicardial adipose tissue from baseline to the time of ablation (mean 9.0 mm vs 8.2 mm; P<0.001), but no significant difference was reported between the groups (P=0.23). The 1-year freedom from AF or atrial flutter was higher in the liraglutide arm than in the RFM alone arm (83% vs 57%; P=0.036).

Dr Goldberger mentioned that this was a single-centre study with a small sample size. "Although further follow-up is ongoing and additional analyses are pending, larger studies are needed to confirm these findings," he decided.

1. Goldberger JJ, et al. Liraglutide effect on atrial fibrillation (LEAF) study. FS06, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.
2. Hindricks G, et al. Eur Heart J. 2021;42(5):373–498.
3. Goldberger JJ, et al. Heart Rhythm 2023;20(7): 1079.

Single or dual cardioversion in patients with obesity and AF?

Obese patients undergoing electrical cardioversion for atrial fibrillation (AF) appeared to benefit more from dual direct current (DC) than from single DC cardioversion, without an increased risk for complications.

"By 2030, an estimated 1 out of 4 adults will have a BMI ≥35 kg/m^2 and 6–16 million people in the USA will have AF," outlined Dr Joshua Aymond (Ochsner Health, LA, USA) [1–3]. "These 2 conditions are strongly linked to one another." Electrical cardioversion is the treatment of choice, but failure to restore sinus rhythm is seen in 20–35% of patients with obesity and <10% of patients without obesity [4]. However,

higher shock energy may lead to a higher success rate in patients with obesity [5].

The current multicentre, randomised, patient-blinded study compared single DC cardioversion (with an energy of 200 J) with dual DC cardioversion (with an energy of 400 J) in patients with obesity and AF (n=200) [1]. The primary outcome was the restoration of sinus rhythm, regardless of duration, immediately following cardioversion.

The failure rate was 14% in the single DC cardioversion arm compared with 2% in the dual DC cardioversion arm (P=0.002). In addition, a multivariable analysis showed that the OR of failure was 12.6, disfavouring the single DC cardioversion arm. "Of the 14 patients that had failed single cardioversion, 12 succeeded on the first subsequent dual cardioversion," said Dr Aymond. Finally, there were no differences in post-procedure chest discomfort between the study groups and no procedure-related adverse events.

Dr Jose Joglar (UT Southwestern Medical Center, TX, USA), a discussant of the trial, concluded that, although some unanswered questions remain, the results of the current trial suggest that cardiologists should be more liberal with the use of high energies for DC cardioversion and that an initial energy of 400 J has its place in clinical practice.

1. Aymond JD, et al. Efficacy and safety of dual direct current cardioversion versus single direct current cardioversion as an initial treatment strategy in obese patients with atrial fibrillation. LB05, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.
2. Ward ZJ, et al. N Engl J Med 2019;381(25):2440–2450.
3. Myasaka Y, et al. Circulation. 2006;114(2):119–125.
4. Gardner MW, et al. J Cardiovasc Electrophysiol. 2019;30(9):1636–1643.
5. Glover BM, et al. Heart. 2008;94(7):884–887.

NOAH-AFNET 6: Does the duration of AHRE influence response to edoxaban?

A subanalysis of the NOAH-AFNET 6 trial did not reveal interactions between the duration of atrial high-rate episodes (AHRE) and the use of the direct oral anticoagulant (DOAC) edoxaban on key safety and efficacy endpoints in patients with AHRE and stroke risk factors.

The previously published, double-blind, double-dummy NOAH-AFNET 6 study (NCT02618577) showed that the DOAC edoxaban did not substantially decrease a composite outcome of stroke, systemic embolism, or cardiovascular death compared with placebo in patients with AHRE and stroke risk factors [1]. However, major bleeding was more common in the edoxaban group. "Observational studies suggest a higher stroke risk associated with AHRE that last 24 hours or longer," said Dr Nina Becher (University of Hamburg, Germany) [2–4]. "Randomised data evaluating anticoagulation in patients with long AHRE are, however, lacking."

In the current sub-analysis of the NOAH-AFNET 6 trial, Dr Becher and her team compared the efficacy and safety of edoxaban between participants with AHRE lasting ≥24 hours (n=259) and participants with shorter duration AHRE (n=2,130) [2]. The primary efficacy endpoint was a composite of stroke, systemic embolism, or cardiovascular death, and the primary safety outcome was a composite of International Society on Thrombosis and Haemostasis (ISTH) major bleeding and all-cause death.

No significant interaction effect was found between treatment allocation and the duration of AHRE on the primary efficacy outcome ($P_{interaction}$=0.65). Similarly, no interaction was observed between treatment randomisation and the duration of AHRE on the main safety outcome ($P_{interaction}$=0.96). "These results were consistent using AHRE as a continuous variable or using median AHRE duration," added Dr Becher. Finally, participants with long-duration AHRE had a higher ECG-diagnosed atrial fibrillation rate per patient-year than those with short-duration AHRE (17.0% vs 8.2%; HR 2.20; 95% CI 1.71–2.84; P<0.001). According to Dr Becher, regular ECGs are thus warranted in patients with AHRE lasting ≥24 hours.

"This was the first randomised comparison of oral anticoagulation and placebo in patients with AHRE lasting ≥24 hours. The number of ischaemic events was too small to rule out effects of anticoagulation on stroke prevention," concluded Dr Becher.

1. Kirchhof P, et al. N Engl J Med 2023;389:1167–1179.
2. Becher N, et al. Efficacy and safety of anticoagulation with edoxaban in patients with atrial high rate episodes (AHRE) durations ≥ 24 hours: the NOAH-AFNET 6 trial. LB05, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, PA, USA.
3. Uittenbogaart SB, et al. Europace. 2018;20(9):1420–1427.
4. Van Gelder IC, et al. Eur Heart J. 2017;38(17):1339–1344.

ARTESIA: How useful is anticoagulation in subclinical AF?

Compared with aspirin, apixaban was associated with a reduced risk of stroke or systemic embolism in patients with subclinical atrial fibrillation (AF). However, an increased risk for major bleeding was observed in the phase 4 ARTESIA study.

The randomised, double-blind, active-controlled ARTESIA trial (NCT01938248) compared the efficacy and safety of the direct oral anticoagulant (DOAC) apixaban with aspirin in patients with subclinical AF and a risk factor for ischaemic events [1,2]. The participants (n=4,012) were randomised 1:1 to apixaban (either 2.5 mg or 5 mg twice daily) or aspirin (81 mg once daily). The primary endpoint was the rate of stroke or systemic embolism. Prof. Jeff Healey (McMaster University, Canada) presented the main results [1].

After a mean of 3.5 years of follow-up, "the risk of stroke or systemic embolism was significantly reduced in the apixaban arm as compared with the aspirin arm," said Prof. Healey (HR 0.63; 95% CI 0.45–0.88; P=0.007). However, major bleedings occurred more frequently in the apixaban arm than in the aspirin arm (1.71% per year vs 0.94% per year; HR 1.80; P<0.001). Shared decision-making regarding the initiation of anticoagulation in this patient population should be tailored to patient-specific risk stratification for thromboembolism and bleeding with consideration of patient-specific values and preferences.

Prof. Christine Albert (Cedars-Sinai Medical Center, CA, USA) explained that the number needed to treat is 47 in clinical AF, but 250 in subclinical AF. On the other hand, the number needed to harm is 130 in the apixaban arm and only 210 in the aspirin arm. "Given the benefit-to-risk ratio, there should be a pause and further consideration by expert guideline committees before implementing DOACs in patients with subclinical AF and a risk factor for ischaemic events," she reasoned. If a decision is made to defer anticoagulation, it should be recognised that a substantial proportion of patients with device-detected AF go on to develop clinically overt AF. Accordingly, such patients merit close surveillance, as the development of clinical AF warrants reconsideration of anticoagulation.

1. Healey JS, et al. The ARTESIA trial: apixaban for stroke prevention in subclinical atrial fibrillation. LB05, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.
2. Healey JS, et al. N Engl J Med 2023;Nov 12. DOI: 10.1056/NEJMoa2310234.

Jewel IDE: High compliance rates for novel patch wearable cardioverter defibrillator

The patch-based wearable cardioverter defibrillator named JEWEL appeared safe and effective in patients with a risk of sudden cardiac arrest who were indicated for a wearable cardioverter defibrillator. With a low number of inappropriate shocks, no deaths or serious adverse events, and high patient compliance rates, JEWEL met the clinical trial's endpoints.

"Patients who actually wear their wearable cardioverter defibrillator have a survival benefit," stated Dr John Hummel (Ohio State University, OH, USA) [1]. Thus, a wearable with a high adherence rate may be a fruitful solution for patients at risk for sudden cardiac death. The multicentre, prospective, single-arm Jewel IDE study (NCT05201495) evaluated the safety and efficacy of JEWEL in 290 participants at risk for sudden cardiac arrest with an indication for a wearable cardioverter defibrillator. The primary efficacy endpoint was fewer than 2 inappropriate shocks per 100 patient-months, whereas the primary safety endpoint was fewer than 15% of participants with clinically significant cutaneous adverse device effects. Dr Hummel presented the key results.

The observed inappropriate shock rate was low, at 0.36 per 100 patient-months (upper 98% CI 1.53). Sinus tachycardia and supraventricular tachycardia with underlying left bundle branch block were reported as the causes for inappropriate shocks. Next, the clinically significant adverse device effect rate was 2.30% (upper one-sided 98% CI 4.80), meeting the primary safety endpoint. "Importantly, the median wear time of JEWEL was 23.5 hours, indicating that JEWEL is comfortable enough to wear for most patients," argued Dr Hummel.

"The key statistic of this trial is the median wear time of 23.5 hours," expressed Dr Gregory Marcus (University of California San Francisco, CA, USA). He further raised some considerations: "Would some of the observed ventricular tachyarrhythmias have spontaneously terminated? And do we need randomised trials for specific populations to prove superiority in mortality?"

1. Hummel JD, et al. Safety and efficacy of the JEWEL, a novel patch wearable cardioverter defibrillator: results from the JEWEL IDE study. FS06, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

Sudden cardiac death in athletes: incidence, causes, and trends over 20 years

Although the incidence of sudden cardiac death (SCD) among American college athletes has decreased in the last 20 years, a significantly higher rate was observed in certain subgroups. Male basketball and male football players appeared to have the highest risk of SCD, according to the findings of a large observational study.

Dr Bradley Petek (Oregon Health and Science University, OR, USA) and co-investigators conducted a study to explore the incidence and causes of SCD among National Collegiate

Athletic Association (NCAA) athletes [1]. The retrospective/prospective cohort study ran for 20 years (from 2002 through 2022) and registered over 9 million years of athletic participation.

Over those 20 years, 1,102 athletes died and 143 of these cases were reported as SCDs. The average age of those who died due to SCD was 20 years, 83% of them were men, 59% were White, and 36% were Black. Also, most SCD cases were division 1 athletes (45%), whereas 29% and 26% of the SCD cases were participating in division 2 and 3, respectively. In terms of sports, the highest absolute numbers of SCD cases were seen among American football players (30%), basketball players (25%), and track-and-field athletes (13%).

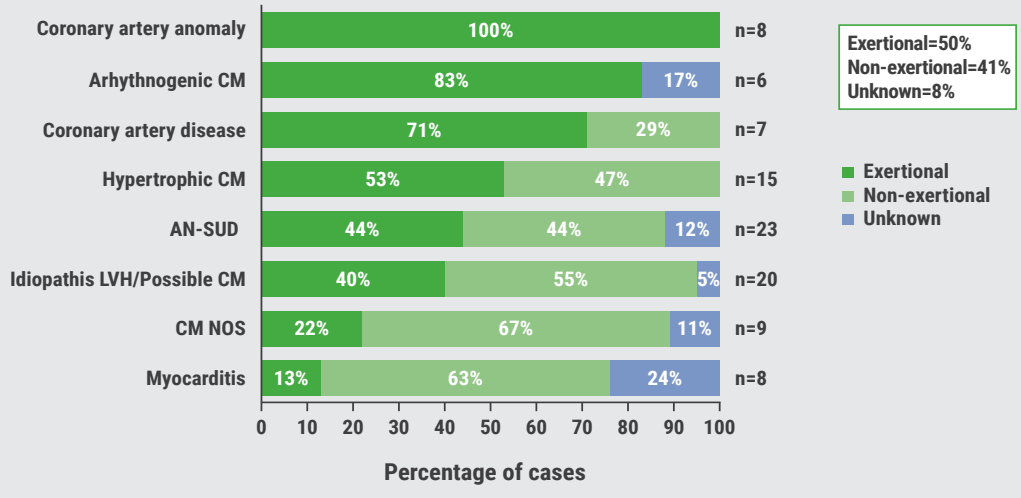
The overall incidence of SCD was 1 case in 63,682 athlete-years. The risk of SCD appeared to be higher among men, with 1 case in 43,348 athlete-years. This risk was 1 case in 164,504 athlete-years among women. Furthermore, the incidence of SCD was higher among Black athletes than among White athletes, with 1 case per 27,217 athlete-years and 1 case per 74,581 athlete-years, respectively. Next, division 1 and 2 athletes may be at higher risk, with approximately 1 case of SCD per 50,000 athlete-years compared with 1 case in 95,313 athlete-years in division 3 athletes. The highest rates were found among basketball players (1 per 19,164 athlete-years) and American football players (1 per 31,743 athlete-years).

"It becomes even more interesting when we look at the individual levels," expressed Dr Petek. The incidence of SCD was 1 per 5,848 athlete-years among division 1 basketball players who were men and White and 1 per 7,696 athlete-years among division 1 basketball players who were men and Black. Among women athletes, the highest incidence rates were observed among division 2 track-and-field athletes who were Black (1 per 24,942 athlete-years) and division 2 basketball players who were Black (1 per 30,880 athlete-years). "When we looked at SCD over the 20-year timeframe, there was a decrease in SCD with a 5-year IRR of 0.71 (95% CI 0.61–0.82)," noted Dr Petek. He further outlined that autopsy-negative sudden unexplained death (19.5%), idiopathic left ventricular hypertrophy/possible cardiomyopathy (16.9%), and hypertrophic cardiomyopathy (12.7%) were the most common causes of SCD. Finally, Dr Petek mentioned the exertional status at the time of SCD for the various causes of SCD (see Figure).

"Continual efforts to improve cardiopulmonary resuscitation training, AED access, emergency action planning, and pre-participation cardiovascular screening are imperative to improve outcomes," Dr Petek concluded.

1. Petek B, et al. Incidence and causes of sudden cardiac death in NCAA athletes: a 20-year study. FS06, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

Figure: Exertional status at the time of SCD [1]



AN-SUD, autopsy-negative sudden unexplained death; CM, cardiomyopathy; NOS, nitric oxide synthases; SCD, sudden cardiac death.

Miscellaneous Trials

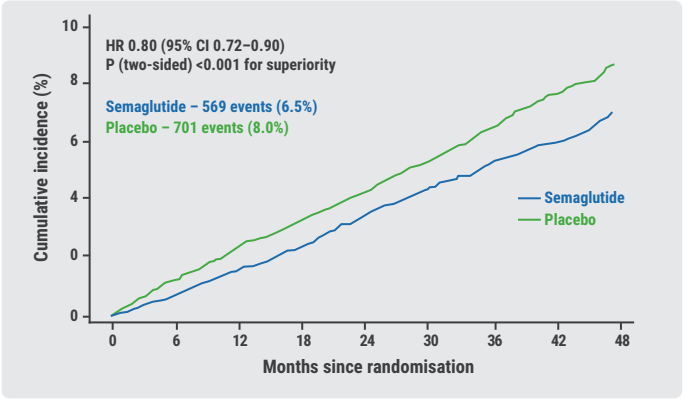
Successful results for semaglutide in the highly anticipated SELECT trial

Semaglutide successfully reduced adverse cardiovascular outcomes in patients with cardiovascular disease (CVD) who are overweight but without diabetes. No unexpected safety issues emerged with semaglutide in this population.

The randomised, double-blind, placebo-controlled, phase 3 SELECT trial (NCT03574597) assessed the safety and efficacy of the GLP-1 receptor agonist semaglutide, added to standard-of-care, in patients with pre-existing CVD and overweight or obesity but without diabetes [1]. The 17,604 participants were randomised 1:1 to 2.4 mg semaglutide (subcutaneously administered once weekly) or a placebo. Of note, the dosing of semaglutide was titrated, starting at a dose of 0.24 mg and increasing to the anticipated dose of 2.4 mg at week 16. The primary outcome was a composite of cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke, measured at week 48.

"Semaglutide met its primary endpoint in this trial," expressed Dr Michael Lincoff (Cleveland Clinic, OH, USA) (see Figure). The event rate was 8.0% in the placebo arm and 6.5% in the semaglutide arm, with a corresponding hazard ratio of 0.80 (95% CI 0.72–0.90; P<0.001). Further, the primary outcome result was consistent across pre-defined subgroups.

Figure: Primary cardiovascular composite endpoint at 48 weeks [1]



The first confirmatory secondary endpoint of cardiovascular death was numerically but not significantly in favour of the semaglutide arm (HR 0.85; 95% CI 0.71–1.01; P=0.065). The second and third confirmatory secondary endpoints, which were a heart failure composite and death from any cause, showed benefits for participants randomised to semaglutide over those randomised to placebo (HR 0.82; 95% CI 0.71–0.96; HR 0.81; 95% CI 0.71–0.93).

Finally, no unexpected safety issues were encountered. The rate of gastrointestinal adverse events was higher in the semaglutide arm than in the placebo arm (10.0% vs 2.0%; P<0.001). However, the rates of serious gastrointestinal events were similar between the groups.

1. Lincoff AM, et al. Semaglutide and cardiovascular outcomes in patients with overweight or obesity and cardiovascular disease who do not have diabetes: the SELECT trial. LB01, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

Can a walking intervention improve functional status and quality of life in HFrEF?

For patients with heart failure with reduced ejection fraction (HFrEF), a walking intervention may increase the number of daily steps taken. However, this improved walking activity level did not appear to be related to functional improvements in this patient population.

Dr Tomas Vetrovsky (Charles University, Czechia) and colleagues performed a multicentre, randomised, controlled study to assess the effect of a 6-month lifestyle walking intervention on functional capacity in patients with HFrEF [1]. The 202 participants were randomised 1:1 to usual care or the walking intervention. The intervention included behaviour change techniques, self-monitoring of daily step count with a wrist-worn wearable device, recording daily steps in a paper diary, goal setting, and phone counselling sessions. The primary outcome was the difference in walking distance, measured by a 6-minute walk test at 6 months.

At 6 months, no significant difference was observed between the control group and the experimental group in the primary outcome, with an adjusted between-group difference of 7.4 meters, numerically favouring the experimental group (95% CI -8.0 to 22.7; P=0.35). "Nonetheless, from baseline, the average daily step count was increased in the intervention group (+790 steps) and decreased in the control group (-667

steps). This difference was significant," according to Dr Vetrovsky (difference 1,420 steps; 95% CI 749–2,091).

Similarly, the number of daily minutes of moderate to vigorous physical activity was increased in the intervention arm compared with the control arm (adjusted difference 8.2 minutes; 95% CI 3.0–13.3). Moreover, participants in the intervention arm reported an improvement in SF-36 'general health' score, assessing health-related quality of life, compared with those in the control arm (adjusted difference 4.5; 95% CI 0.7–8.4). Other areas of the SF-36 and other secondary outcomes did not reveal differences between the 2 groups at 6 months.

"The increased walking activity that we observed in the intervention arm was not associated with an improvement in functional capacity," concluded Dr Vetrovsky. "Further research is needed to understand why increased physical activity does not lead to improved functional outcomes in this population."

1. Vetrovsky T, et al. Lifestyle walking intervention in patients with HFrEF: the WATCHFUL trial. FS06, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, USA.

Head-to-head: Surgical embolectomy versus ultrasound-assisted thrombolysis in high-risk pulmonary embolism

Surgical pulmonary embolectomy (SPE) yielded better health outcomes than ultrasound-assisted thrombolysis (USAT) in patients with intermediate-high or high-risk pulmonary embolism in the phase 2 SPECIAL trial.

"To date, no randomised trials have been conducted comparing USAT and SPE as reperfusion strategies in patients with intermediate-high or high-risk pulmonary embolism," said Dr Stefan Stortecky (University of Bern, Switzerland) [1]. The single-centre, randomised-controlled, non-inferiority, phase 2 SPECIAL trial investigated this matter. The primary endpoint was the difference in right to left ventricular dimension ratio (RV/LV ratio), assessed by contrast-enhanced chest CT from baseline to 72 hours. "The trial was ended prematurely due to the difficulty of enrolling patients in the emerging era of less-invasive endovascular techniques," added Dr Stortecky. Thus, the trial included 27 instead of the planned 60 participants.

Both treatment options resulted in significant mean changes in RV/LV ratio from baseline to 72 hours: for USAT 1.43 to 1.09 ($P<0.001$) and for SPE 1.47 to 0.94 ($P<0.001$). However, USAT was not non-inferior to SPE (mean change 0.34 vs 0.53; $P_{non\text{-}inferiority}=0.80$). In addition, the P-value for superiority was 0.013 in favour of the SPE arm. Other endpoints, such as the Qanadli Obstruction Index and the total number of fully and partially occluded segments also indicated that SPE led to better treatment results than USAT.

Finally, there were no significant differences in safety outcomes, including the rate of recurrent VTE (SPE vs USAT, 14% vs 0%) and any bleeding (SPE vs USAT, 14% vs 23%). No deaths or strokes were reported in the current trial.

Dr Sahil Parikh (Columbia University Irving Medical Center, NY, USA) commented that there are several catheter-based treatment options effective in reducing the RV/LV ratio in 2023 and that the remaining role of SPE in this era still needs to be determined. "We see a movement towards mechanical thrombectomy and because this approach delivers more rapid clinical improvement, it offers the opportunity to avoid thrombolytics and may result in less need for an ICU stay," he decided.

1. Stortecky S, et al. Ultrasound-assisted catheter-directed thrombolysis versus surgical pulmonary embolectomy for intermediate-high or high-risk pulmonary embolism: a randomised phase 2 non-inferiority study. FS07, AHA Scientific Sessions 2023, 11–13 November, Philadelphia, PA, USA.