Medicom International Conference Series in Cardiology

AHA Scientific Sessions 2021

American Heart Association

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PEER-REVIEWED CONFERENCE REPORT

Remote Programme Improves Hypertension/Lipids

In >10K high-risk patients guided by non-physicians, 92% of the patients who completed the programme reached their guideline-recommended blood pressure. Subgroup analysis demonstrated that traditionally underserved subgroups benefit equally.

read more on PAGE 7

CHIEF-HF: Canagliflozin Improves Heart Failure Symptoms

The phase 3 CHIEF-HF trial showed that, within 2 weeks, canagliflozin improved heart failure symptoms compared with placebo, regardless of ejection fraction, diabetes, or type of heart failure.

read more on PAGE 12

Tricuspid Repair at Time of MVR

Patients undergoing concomitant tricuspid annuloplasty with mitral-valve replacement had a lower incidence of a primary endpoint event than those who underwent mitral-valve surgery alone at 2 years.

read more on PAGE 25

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

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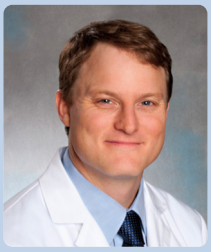
Letter from the Editor



Prof. Marc P. Bonaca

Dear colleagues,

Thank you for choosing our Medicom Conference Report of the 2021 American Heart Association Scientific Sessions. This year's meeting was rich in innovative science, late-breaking studies, and engaging virtual content.

In the following pages you will find late-breaking science on digital interventions in atrial fibrillation, remote virtual programs for population management of hypertension and hyperlipidemia, exciting data on novel anticoagulants and new evidence in heart failure, vascular disease and coronary disease.

We hope you find our peer-reviewed summaries informative, engaging and balanced. Most of all, we wish you all a safe and healthy 2022 and hope that this year brings our scientific community even closer together.

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. 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:
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Atrial Fibrillation

New developments in remote diagnostics and monitoring of AF

A novel algorithm for Fitbit wearables using photoplethysmogram (PPG) software was able to detect undiagnosed atrial fibrillation (AF) with a high positive predictive value in a large population study. Another study demonstrated that individual AF trigger testing did not lead to improved AF-related quality of life compared with symptom surveillance alone. However, fewer AF episodes were reported in the experimental arm of the study. Moreover, a significant association was observed between alcohol use and the occurrence of AF.

Dr Steven Lubitz (Massachusetts General Hospital, MA, USA) explained that early detection of AF may prevent morbidity of this condition [1]. Since smartwatches and fitness trackers are often equipped with optical PPG sensors, software algorithms that analyse PPG data can detect AF on these wearable devices. Dr Lubitz and colleagues developed a software algorithm with overlapping PPG pulse tachogram sampling and assessed its positive predictive value for undiagnosed AF in various wearable Fitbit devices.

Participants of the Fitbit Heart Study (NCT04380415) were 22 years or older, possessed a compatible Fitbit device, and did not have a known AF diagnosis. The software reported an irregular heart rhythm detection (IHRD) if the algorithm registered ≥30 minutes of irregular rhythm. Patients with an IHRD received an ECG patch to wear for 1 week. In total, 455,669 participants enrolled in the study (median age 47 years, 71% women), of whom 4,278 (1%) received an IHRD notification. Of these participants, 1,057 (24.7%) completed the 1-week ECG patch period, illustrating the limited engagement of participants in this remote clinical trial. The primary endpoint was the positive predictive value of the first IHRD for AF during ECG monitoring.

The percentage of participants receiving an IHRD was higher among men and participants ≥65 years old. The positive predictive value of IHRD for AF was 98% and similar in the predefined age and sex subgroups. IHRD showed a sensitivity of 68% for AF measurement during ECG monitoring. In addition, participants who had an IHRD notification and completed ECG patch monitoring displayed AF in 32% of the cases. This percentage was equally divided across sex and age categories. Dr Lubitz added that the ≥65 years subgroup is an important category to consider since AF in these patients is associated with an increased risk of stroke.

Dr Gregory Marcus (University of California, CA, USA) presented another study on the remote management of AF [2,3]. He argued that the risk factors for AF, such as hypertension, age, male sex, and coronary disease, are mostly chronic and immutable, and that the acute triggers of AF are less well documented. Thus, the I-STOP-Afib trial (NCT03323099) aimed to test individual AF triggers using an innovative N-of-1 study design. Eligible adult participants were randomised to a data-tracking control group (n=248) or an experimental arm (n=251) and received a KardiaMobile to track AF episodes. Participants in the experimental arm could select a presumed trigger from a menu of triggers or add a customised trigger. These participants received instructions on when to avoid or expose themselves to the selected trigger during a 6-week period. Hereafter, they received individual (N-of-1) results of the enhanced risk of AF via exposure to the selected trigger. Subsequently, participants followed a 4-week lifestyle-changing period, in which they could adjust their behaviour in response to the results. The primary outcome was the change in the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) questionnaire in the intention-to-treat population after 10 weeks. The most commonly selected triggers were caffeine (n=53), alcohol (n=43), reduced sleep (n=31), and exercise (n=30).

The average improvement on the AFEQT in the trigger-testing arm (+1.7) was not significantly larger than the average improvement in the control arm (+0.5; P=0.17). However, patients in the experimental arm documented 40% fewer self-reported AF episodes during the 4-week lifestyle-changing period compared with patients in the control arm (P<0.0001). This effect was driven by participants who selected alcohol, dehydration, or exercise as triggers. Per-protocol analysis of the N-of-1 trials displayed significant near-term effects of alcohol exposure on AF (OR 1.77) and customised triggers on AF (OR 4.09).

Discussant Dr Mina Chung (Cleveland Clinic, OH, USA) argued that conventional randomised controlled trials deliver average results for a pre-defined population, whereas the current N-of-1 study design has the potential to address individual patients. Although subgroup analyses in standard randomised controlled trials offer stratification of the results, the N-of-1 approach promises to surpass their ability to provide a truly personalised approach. According to Dr Chung, the significant secondary outcomes of the current study support the value of N-of-1 studies for individual patients.

1. Lubitz SA, et al. Detection of Atrial Fibrillation in a Large Population using Wearable Devices: the Fitbit Heart Study. LBS04, AHA Scientific Sessions 2021, 13–15 November.
2. Marcus GM, et al. The Individualized Studies of Triggers of Paroxysmal Atrial Fibrillation Trial. LBS04, AHA 2021 Scientific Sessions, 13–15 November.
3. Marcus GM, et al. JAMA Cardiol. 2021 Nov 14. Doi: 10.1001/jamacardio.2021.5010.

Head-to-head: Efficacy of dabigatran versus warfarin on cognitive impairment

Dabigatran treatment in older patients with atrial fibrillation (AF) or atrial flutter did not result in different cognitive outcomes than warfarin treatment after 2 years, as demonstrated in the phase 4 GIRAF trial [1].

AF is associated with cognitive impairment. A recent, retrospective, observational study suggested that anticoagulants may reduce cognitive impairment and dementia in patients with AF [2]. Prof. Bruno Caramelli (University of São Paulo, Brazil) and colleagues conducted a head-to-head comparison of 2 anticoagulants, dabigatran and warfarin, on cognitive outcomes in older patients with AF.

The open-label GIRAF trial (NCT01994265) included 200 patients >70 years without major cerebrovascular comorbidities, who were randomised 1:1 to dabigatran (110/150 mg, twice daily) or warfarin (target INR 2-3, once daily). The primary clinical endpoint was cognitive impairment at 2 years. Notably, the cognitive status of the included patients was extensively assessed at baseline and at 2-years follow-up, including the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), and 2 other neuropsychological test batteries.

In general, no difference was observed between the 2 treatment groups regarding cognitive status after 2 years of follow-up. The co-primary endpoint MoCA score suggested an advantage of warfarin (adjusted mean change 0.58) over dabigatran (adjusted mean change -0.39; P=0.02) regarding cognitive status, but the other co-primary measures did not did not show a statistically significant difference: MMSE (P=0.75), NTB (P=0.40), CGNT (P=0.06). In addition, comparing the treatment groups on several cognitive domains (i.e. memory, executive functions, language) did not result in statistical differences between dabigatran and warfarin.

Other randomised trials currently investigating the effects of direct oral anticoagulants on cognitive functioning in patients with AF are the CAF trial (NCT03061006) and the BRAIN-AF trial (NCT02387229).

1. Caramelli B, et al. Dabigatran versus warfarin on cognitive outcomes in nonvalvular atrial fibrillation: results of the GIRAF trial. LBS03, AHA Scientific Sessions 2021, 13–15 November.
2. Cadogan SL, et al. Heart. 2021;107(23):1854–1855.

Posterior left pericardiotomy safe and effective in reducing atrial fibrillation

Posterior left pericardiotomy significantly reduced the incidence of postoperative atrial fibrillation (AF) after cardiac surgery and appeared safe in the PALACS trial [1].

Post-operative AF is the most common complication of cardiac surgery, with an incidence of 20–40%, depending on the performed surgery [2]. The incidence of post-operative pericardial effusion is also common, with an incidence of 60–70% [3]. Dr Mario Gaudino (Weill Cornell Medical Center, NY, USA), first author of the PALACS trial (NCT02875405), argued there is evidence that post-operative pericardial effusion is associated with post-operative AF [1,4].

The PALACS study hypothesised that a 4 to 5 cm incision in the posterior pericardium, connected to the left pleural cavity, allows for drainage and, thus, reduces post-operative AF. Patients (n=420) undergoing cardiac surgery (i.e. coronary arteries, aortic valve, and/or ascending aorta) were randomised 1:1 to posterior left pericardiotomy or no additional intervention. The primary outcome was in-hospital post-operative AF, assessed by cardiac rhythm monitoring.

Participants in the pericardiotomy arm had fewer post-operative AF events (18%) than patients in the no-intervention arm (32%; RR 0.55; P<0.001). The cumulative time in AF was 1,262 hours in the intervention arm versus 2,277 hours in the no-intervention arm. In addition, the results displayed a reduction in the need for post-operative antiarrhythmic medications (RR 0.55) and systemic anticoagulation (RR 0.44) in the intervention arm. A subgroup analysis showed consistency of the primary outcome across predefined strata such as demographic and surgery

type. The safety data showed that postoperative pericardial effusion was more prevalent in the no-intervention arm (21%) than in the intervention arm (12%; RR 0.58; CI 95% 0.37–0.91). Rates of operative mortality (1% in both groups), postoperative major adverse events (2% and 3%), and postoperative left pleural effusion (30% and 32%) were comparable.

The current trial had many strengths. This is the first surgical approach to reduce post-operative AF after cardiac surgery. Moreover, the hypothesis that post-operative AF is secondary to pericardial effusion-induced inflammation is novel. Compared with other available options to reduce post-operative AF following cardiac surgery, such as pre-operative β-blocker, pre-operative amiodarone, colchicine, and intra-operative botulinum, the risk reduction of posterior pericardiotomy of approximately 45% is pronounced.

However, this trial only investigated in-hospital post-operative AF. Possible events of sub-acute AF were not captured. The study did also not include patients who were scheduled for mitral valve or tricuspid valve surgery. In addition, the absolute reduction should be interpreted in the context of the sample size and additional data will clarify the absolute and durability of effect. Although Dr Gaudino argued that there is no biologic rationale to expect a different result in these patients, it should be examined in future trials. Following these encouraging results, the next step would be to test posterior left pericardiotomy in a large, multicentre trial across the entire spectrum of cardiac surgery.

1. Gaudino M, et al. Posterior left pericardiotomy for the prevention of atrial fibrillation after cardiac surgery: an adaptive, single-centre, single-blind randomised controlled trial. LBS03, AHA 2021 Virtual Congress, 13–15 November.
2. Greenberg JW, et al. Eur J Cardiothorac Surg. 2017;52(4):665–672.
3. Pepi M, et al. Br Heart J. 1994;72(4):327–331.
4. St-Onge S, et al. Ann Thorac Surg. 2018;105(1):321–328.

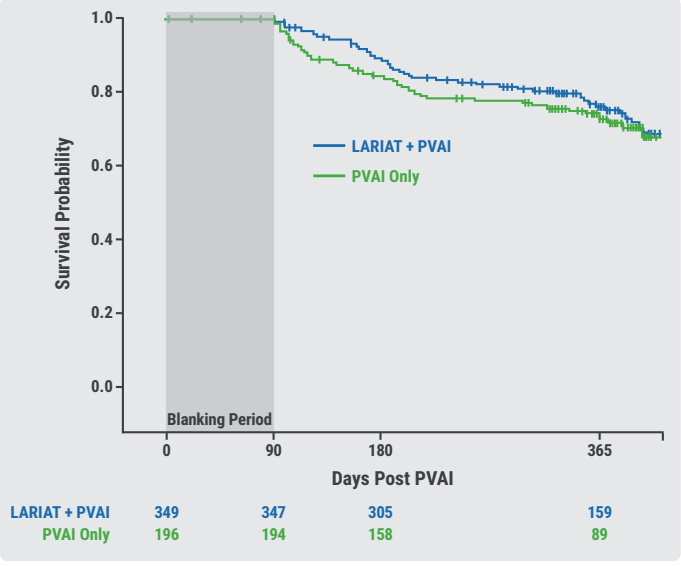
LAA ligation did not reduce recurrent atrial arrhythmias in persistent AF

Recurrent atrial arrhythmias were not reduced after adjunctive left atrial appendage (LAA) ligation compared with pulmonary vein antral isolation (PVAI) alone in patients with persistent atrial fibrillation (AF) undergoing AF ablation. Patients with early persistent AF and larger LA volumes may benefit more from adjunctive LAA ligation, exploratory analyses revealed. Future studies are needed to verify these exploratory outcomes.

Dr David Wilber (Loyola University Chicago, IL, USA) explained that ablation outcomes via PVAI alone in patients with persistent AF are often suboptimal [1]. Therefore, secondary procedures such as LAA ligation are in development. The prospective, multicentre, randomised aMAZE trial (NCT02513797) aimed to assess the efficacy of LAA ligation with the LARIAT system compared with PVAI in decreasing recurrent atrial arrhythmias. Patients with persistent AF undergoing AF ablation were randomised 2:1 to LAA ligation plus PVAI (n=404) or PVAI alone (n=206). The primary efficacy endpoint was freedom of atrial arrhythmias 12 months after surgery.

The experimental condition did not significantly outperform the control condition: 64.3% of the patients in the LAA ligation plus PVAI condition were free from atrial arrhythmias 12 months after surgery, compared with 59.9% of the patients in the PVAI alone group (see Figure). The Bayesian posterior probability of 0.835 did not meet the superiority criterion (>0.977). Notably, exploratory subgroup analysis revealed that patients with early persistent AF (7 days to 6 months) may benefit relatively more from the LARIAT device than from PVAI alone (7.5% difference in the primary endpoint; P=0.084) compared with patients with late or long-standing persistent AF. In addition, patients with larger LA volumes (≥133 cm^3) show a numerical larger relative benefit of adjunctive LAA ligation (12.4% difference; P=0.093) than patients with smaller LA volumes (<133 cm^3; 2.5% difference).

Figure: Primary endpoint – Freedom of atrial arrhythmias after 1 year [1]



The percentage of serious adverse events (AEs) 30 days after the LARIAT procedure was 3.4%, meeting the predefined <10% performance goal. Notably, 3 patients in the experimental group experienced serious injuries to cardiac

structures, requiring surgery. The 12-month post-surgery LAA ligation closure rates were high, with 100% closure in 84% of the patients.

Although adjunctive LAA ligation with the LARIAT device did not result in significantly reduced atrial arrhythmias in patients with persistent AF undergoing AF ablation, subgroups may benefit from this procedure.

1. Wilber DJ, et al. Outcomes Of Adjunctive Left Atrial Appendage Ligation Utilizing The LARIAT Compared To Pulmonary Vein Antral Isolation Alone: The aMAZE Trial. LBS03, AHA 2021 Scientific Sessions, 13–15 November.

Equal benefits of early rhythm control in AF subtypes

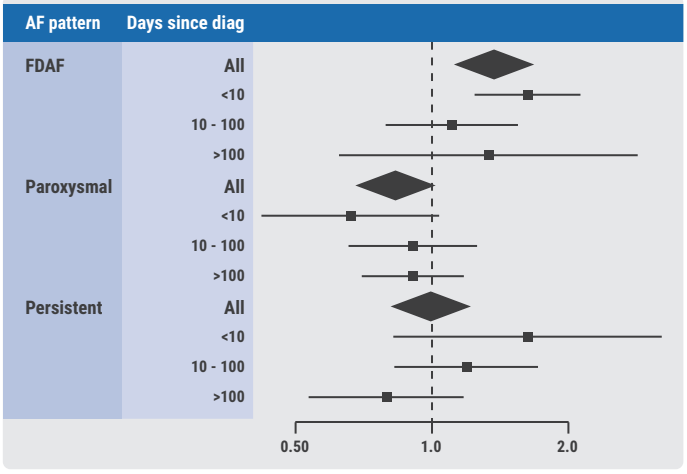
In a prespecified analysis of the EAST-AFNET 4 trial, early rhythm control showed similar clinical benefits for patients with first-diagnosed atrial fibrillation (AF), patients with persistent AF, and patients with paroxysmal AF. However, patients with first-diagnosed AF demonstrated higher hospitalisation rates than patients with paroxysmal or persistent AF when they were randomised to early rhythm-control therapy.

The multicentre, investigator-initiated EAST-AFNET 4 trial (NCT01288352) was conducted to assess the benefits of early rhythm-control therapy compared with usual care in patients with early, recently diagnosed AF [1]. Patients with a CHA₂DS₂-VASc score of ≥2 and recent onset (≤1 year) AF were eligible for randomisation. The primary outcome was a composite of cardiovascular death, stroke, heart failure worsening, or acute coronary syndrome. The previously published results displayed clinical benefits of early rhythm control compared with usual care (HR 0.79; P=0.005) [2].

Dr Andreas Goette (St. Vincenz Hospital Paderborn, Germany) presented the prespecified analysis, which divided AF patients into 3 groups: first-diagnosed AF (n=1,048), paroxysmal AF (n=994), and persistent AF (n=743). The same composite outcome was evaluated as the first primary outcome. The second primary outcome was the number of nights spent in hospital.

After 8 years of follow-up, the clinical benefits of early rhythm control were consistent amongst all 3 subgroups (first-diagnosed AF HR 0.91; paroxysmal AF HR 0.67; persistent AF HR 0.76), without significant heterogeneity of effect between groups (P-interaction=0.39). However, the nights spent in hospital in the rhythm-control group were significantly increased in patients with first-diagnosed AF (mean 1.38/year; 95% CI 1.12–1.70) compared with patients with paroxysmal AF (0.84; 95% CI 0.67-1.03) or persistent AF (1.02; 95% CI 0.80-1.30; P-interaction=0004). Additional analysis showed that this effect was mainly driven by events that occurred within the first 10 days after diagnosis (see Figure). Notably, the risk of hospitalisation due to acute coronary syndrome was significantly increased in patients with first-diagnosed AF.

Figure: Subgroup analysis across AF subtypes and time since diagnosis [1]



AF, atrial fibrillation; FDAF, first-diagnosed AF.

Furthermore, the 2-year EQ-5D scores for these subgroups displayed a decreased quality of life in patients with first-diagnosed AF (mean delta -2.16) compared with patients paroxysmal AF (+2.49) and persistent AF (+3.96; P=0.019). Dr Goette argued that the drop in quality of life of those with first-diagnosed AF may be related to the increased rates of hospitalisations or other events in this group. Moreover, he explained that these increased rates suggest that first-diagnosed AF may be a biomarker for concomitant cardiovascular disease; a pattern that could not be observed in patients with chronic types of AF. Careful monitoring of patients with first-diagnosed AF, especially during the first weeks after diagnosis is therefore recommended, according to Dr Goette.

1. Goette A, et al. Patients with first diagnosed atrial fibrillation are at high risk for cardiovascular events and suitable for early rhythm control: The EAST-AFNET 4 trial. FS05, AHA Scientific Sessions 2021, 13–15 November.
2. Kirchhof P, et al. N Engl J Med 2020;383:1305–16.

CVD Risk Reduction

Remote healthcare programme improves hypertension and lipid control

Featured interview: Dr Alexander Blood (Brigham and Women's Hospital, USA) discusses the scope of remote healthcare in hypertension and hyperlipidaemia. read the interview online >

A remote, algorithm-driven programme with over 10,000 enrolled participants was able to reduce hypertension and LDL cholesterol in patients with a high risk for cardiovascular events. The programme may reduce the need for in-person visitations and has the potential to provide equitable care across underserved populations.

Dr Alexander Blood (Brigham and Women's Hospital, MA, USA) explained that undertreatment of hypertension and hypercholesterolaemia is a serious problem, with 30–50% of patients not receiving the optimal medical treatment [1]. A remote programme was developed to improve hypertension and lipid control, with an emphasis on equal healthcare distribution across subgroups. Patient navigators, pharmacists, and digital technology were integrated into the programme's model using a remote care delivery platform. In total, 6,887 patients were included in the lipid programme and 3,367 patients entered the hypertension programme. Approximately 40% of participants in either group completed the programme. The main reasons for study discontinuation were withdrawal, referral to an MD, and not being able to reach the participant.

In all patients enrolled in the hypertension programme, systolic blood pressure (BP) was reduced at the last measurement of the study (mean 135 mmHg) compared with baseline (mean 145 mmHg; P<0.0001). This effect was more pronounced in patients who completed the programme (mean 125 mmHg vs 137 mmHg; P<0.0001). Similarly, diastolic BP was significantly decreased at the latest BP measurement of the study compared with baseline. Dr Blood added that "92% of the patients who completed the programme reached their guideline-recommended BP goals. Subgroup analysis demonstrated that the effect was consistent across ethnic groups, with equal proportions of subgroup populations achieving study completion. This result suggests that traditionally underserved subgroups benefit equally from the current programme."

The lipid programme showed a reduction of LDL cholesterol at the latest performed measurement (mean 100 mg/dL) compared with baseline (mean 145 mg/dL; P<0.0001). Again, this effect was more pronounced in patients who completed the programme (mean 70 mg/dL vs 140 mg/dL; P<0.0001). Reductions in LDL cholesterol were also similar across subgroups. The effects of the lipid-lowering programme could be explained by the significantly higher prescription rates of high-intensity statins (baseline 40% vs exit 55%), ezetimibe (baseline 9% vs exit 20%), and PCSK9i (baseline 1% vs exit 5%). In addition, the proportion of participants who did not receive any lipid-lowering therapy decreased (baseline 19% vs exit 3%). According to Dr Blood, this programme should be replicable in healthcare systems across the world, reducing the barrier of individuals to interact with the healthcare system. However, the low percentage (40%) of study completers with the majority not completing the study impacts the generalisability of the findings and reaffirms the difficulty of maintaining patients in longitudinal remote care management.

1. Blood AJ, et al. Digital Care Transformation: Report from the First 10,000 Patients Enrolled in a Remote Algorithm-based Cardiovascular Risk Management Program to Improve Lipid and Hypertension Control. LBS02, AHA Scientific Sessions 2021, 13–15 November.

Novel oral PCSK9 inhibitor shows promising results for hypercholesterolaemia

MK-0616, an oral PCSK9 inhibitor in development, was efficacious in lowering LDL cholesterol in patients with hypercholesterolaemia treated with statins and showed a favourable safety profile across two phase 1 trials. An oral PCSK9 inhibitor could help to overcome treatment barriers, providing cardiovascular risk reductions for patients with hypercholesterolaemia in an earlier phase.

Dr Douglas Johns (Merck & Co., NJ, USA) mentioned that many patients with hypercholesterolaemia do not reach their LDL cholesterol treatment goals [1]. Although injectable PCSK9 inhibitors demonstrated LDL cholesterol reductions of 50–60%, these therapies are often administered as a last resort only. An oral PCSK9 inhibitor could remove the barriers associated with injectable treatments.

A first randomised, double-blind, placebo-controlled, in-human trial assessed the safety and tolerability of single doses of MK-0616 ranging from 10 mg to 300 mg in 60 male

participants (aged 18–50 years). MK-0616 was generally safe and well tolerated in this population. No serious adverse events (AEs) were reported and only 1 treatment-related discontinuation was observed, a case of maculopapular rash. Drug-related AEs were mostly abdominal discomfort, diarrhoea, dyspepsia, and headache. Free PCSK9 was reduced by more than 80%, regardless of the administered dose of MK-0616. This effect lasted for approximately 24 hours. Free PCSK9 levels returned to baseline levels in 96 hours. In addition, the authors observed that a permeation enhancer (i.e. sodium caprate) improved the absorption of MK-0616 and noted a negative pre-dose food effect.

A second double-blind, placebo-controlled, phase 1 trial evaluated the LDL-cholesterol lowering capacities of MK-0616 in 40 men and women (aged 18–65 years) treated with statin therapy. Patients were randomised 3:1 to 1 of 3 dosing regimens of MK-0616 or placebo (see Figure). The 14-day result displayed no serious AEs, deaths, or discontinuations. Treatment-related AEs were similar to the reported AEs in the first trial, demonstrating a favourable safety profile of the agent. LDL cholesterol was reduced by a maximum of 65% in all experimental conditions, except for the pre-dose food condition (see Figure).

This result suggests that low-dose MK-0616 plus low-dose sodium caprate can achieve a major reduction in LDL cholesterol. Larger clinical trials need to confirm the safety and efficacy of MK-0616 in a diverse population.

1. Johns DG, et al. The Clinical Safety, Pharmacokinetics, and LDL-Cholesterol Lowering Efficacy of MK-0616, an Oral PCSK9 Inhibitor. LBS06, AHA Scientific Sessions 2021, 13–15 November.

REVERSE-IT: Interim analysis shows promising effect of bentracimab on ticagrelor reversal

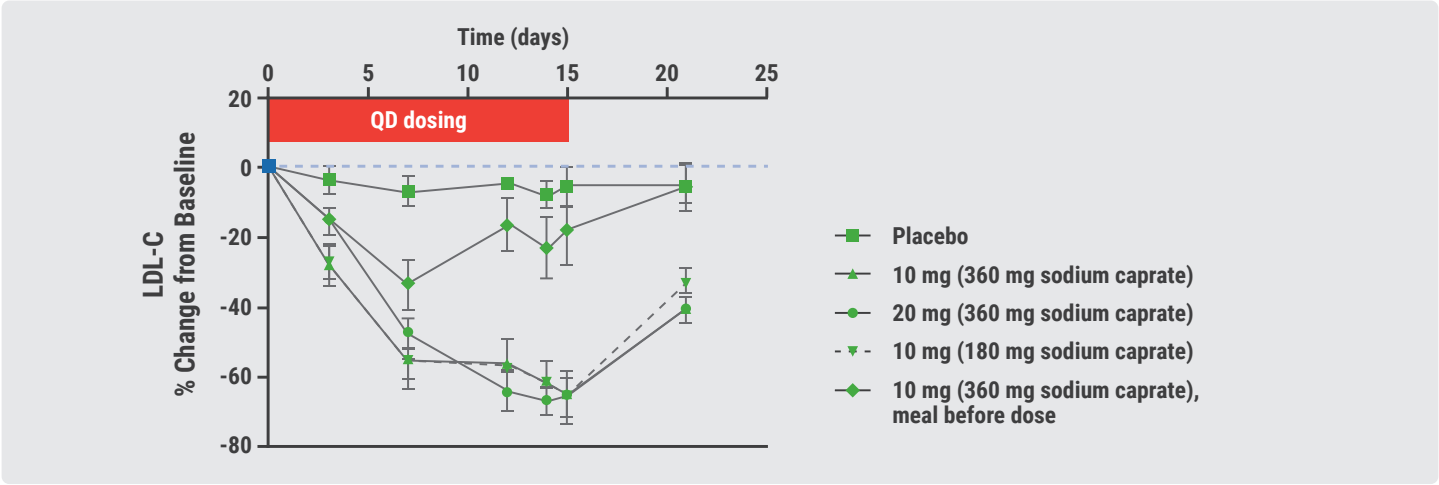
Bentracimab delivered immediate and sustained reversal of ticagrelor's antiplatelet effect in patients undergoing invasive procedures or experiencing major bleeding. In addition, effective haemostasis rates were good or excellent in >90% of participants in the REVERSE-IT trial. Thus, bentracimab appears to be a promising option for ticagrelor reversal [1].

Ticagrelor is an oral $P2Y_{12}$ inhibitor for patients with acute coronary syndromes. Dr Deepak Bhatt (Brigham and Women's Hospital, MA, USA) explained that antiplatelet drugs like ticagrelor are associated with spontaneous bleeding and surgery-related bleeding. In addition, the antiplatelet effects of ticagrelor cannot be reversed by platelet transfusion. Instead, a fast-acting reversal agent is needed to reverse ticagrelor's mechanism of action.

Bentracimab is an intravenous monoclonal antibody, which has demonstrated swift and sustained reversal of ticagrelor's antiplatelet effects in healthy individuals [2]. The multicentre, open-label, prospective, single-arm, phase 3 REVERSE-IT trial (NCT04286438) assessed the efficacy of bentracimab on reversing ticagrelor in patients who require urgent surgery or experience major bleeding. The current interim analysis' primary reversal endpoint was the minimum percentage inhibition of $P2Y_{12}$ reaction units (PRU) within 4 hours. In total, 122 surgical patients and 7 bleeding patients were included in the reversal analysis.

The minimum percentage inhibition of PRU within 4 hours after bentracimab infusion was significantly lower than pre-dose PRU inhibition levels (P<0.001). The inhibitive effect of

Figure: MK-0616 dosing and LDL-cholesterol change from baseline [1]



LDL-C, low-density lipoprotein cholesterol; PBO, placebo.

bentracimab on ticagrelor was significant as soon as 5–10 minutes after administration. The VASP platelet reactivity index (PRI) confirmed these results. The reversal effect was similar across surgical and bleeding patients. Moreover, the predefined subgroups benefitted equally from the bentracimab intervention. Adjudicated haemostasis within 24 hours was achieved in 100% of the analysed surgical patients and 77.8% of the bleeding patients. The results were consistent across subgroups. P-selectin levels or mean platelet volumes did not show platelet rebound activity. Correspondingly, none of the thrombotic events that occurred during the trial were attributed to bentracimab therapy.

Although this study did not have a control arm and the number of bleeding patients was low, the current interim analysis of the REVERSE-IT trial supported bentracimab as a promising agent for ticagrelor reversal. The enrolment of additional patients with bleeding is ongoing.

1. Bhatt DL, et al. REVERSE-IT: Effect of Bentracimab on Platelet Inhibition and Hemostasis in Patients on Ticagrelor with Major Bleeding or Requiring Urgent Procedures. LBS07, AHA 2021 Scientific Sessions, 13–15 November.
2. Bhatt DL, et al. N Engl J Med. 2019;380:1825-1833.

No significant effect of aspirin on reducing cognitive impairment

Aspirin did not significantly reduce dementia outcomes in patients from the ASCEND trial with diabetes. The results were based on 1,146 dementia events and trended towards a beneficial effect of aspirin, excluding harms >2%. Subgroup analyses could provide insight into to the extent in which certain populations may benefit from long-term aspirin use.

Prof. Jane Armitage (Oxford University, UK) explained that the effect of aspirin on cognitive impairment could be beneficial by avoiding ischaemic events in the brain [1]. However, there could be a harmful effect of aspirin on cognitive impairment via the increased risk of intracranial bleeding. Prior randomised trials have not observed a clear effect of aspirin on cognitive impairment.

In the current analysis, patients with diabetes from the ASCEND trial (NCT00135226; n=15,480; mean age 63 years) were randomised to aspirin (100 mg daily) or placebo. They were followed for 7.4 years in the trial plus an additional 1.8 years post-trial. Key outcomes were dementia, a broad and narrow definition, and a cognitive function test: the Telephone Interview for Cognitive Status and verbal fluency (TICSm) or the Healthy Minds test.

The observational analysis of the study showed an increased risk of dementia following serious vascular events (i.e. myocardial infarction, ischaemic stroke, or transient ischaemic attack; rate ratio 2.40) and intracranial bleeding (rate ratio 1.96). The randomised analysis did not show a significant effect of aspirin on dementia (aspirin 7.1% vs placebo 7.8%; rate ratio 0.91) or cognitive function (mean z-score aspirin 0.004 vs placebo -0.002; rate ratio 0.012).

"The results of this study are relevant since individuals with diabetes have a higher risk of dementia," said discussant Prof. Amytis Towfighi (University of Southern California, CA, USA). "Another large trial investigating the effect of aspirin on cognitive impairment, the ASPREE trial (NCT01038583), did not demonstrate a difference between aspirin and placebo regarding the incidence of dementia. However, the JPAD trial (NCT00110448), with approximately 2,500 enrolled patients with type 2 diabetes showed a protective effect of aspirin on dementia for women (HR 0.56). Therefore, future studies may consider subgroup analyses to evaluate which groups may benefit from long-term aspirin use. We could also assess other antiplatelet therapies, with more favourable bleeding profiles," concluded Prof. Towfighi.

1. Parish S, et al. Effects of aspirin on dementia and cognitive impairment in the ASCEND trial. LBS07, AHA Scientific Sessions 2021, 13–15 November.

Milvexian phase 2 data supports safety and efficacy for VTE prevention after total knee replacement

Milvexian, a novel factor XIa inhibitor, was associated with a reduced risk of post-operative venous thrombo-embolism (VTE) after total knee replacement surgery in the phase 2 AXIOMATIC-TKR trial. Moreover, the associated risk of bleeding was low for this treatment. The promising results of this trial confirm the emerging role of factor XI inhibition in anticoagulation.

Milvexian is an oral, small molecule, factor XIa inhibitor. "Factor XI is an exciting target for anticoagulant therapies since there is mounting evidence that factor XI is important for thrombosis but mostly dispensable for haemostasis," said Prof. Jeffrey Weitz (McMaster University, Canada) [1]. "Therefore, factor-XI inhibitors are potentially safer than downstream inhibitors, such as agents targeting factor Xa."

The prospective, randomised, phase 2 AXIOMATIC-TKR trial (NCT03891524) aimed to assess the efficacy and safety of milvexian regarding postoperative VTE [2]. The primary efficacy

outcome was VTE (i.e. asymptomatic deep vein thrombosis, symptomatic VTE, or death). The principal safety outcome was any bleeding. In total, 1,242 participants were randomised over 7 milvexian arms (i.e. 25 mg, 50 mg, 200 mg once daily, or 25 mg, 50 mg, 100 mg, 200 mg twice daily) or enoxaparin (40 mg once daily).

After 14 days of therapy, the combined milvexian twice-daily doses were associated with significantly fewer VTE events (12.2%) compared with the prespecified benchmark of 30% (P<0.0001). Moreover, a significant dose-response was observed with the twice-daily doses (P=0.0004). The rates of VTE events were significantly lower in the 200 mg twice daily group (8%), 100 mg twice daily group (9%), 50 mg twice daily group (11%), and the 200 mg once daily group (7%) compared with enoxaparin receivers (21%).

Similar rates of any bleedings occurred in patients receiving milvexian and patients receiving enoxaparin (both 4%). Clinically relevant bleeding was reported in 1% of the milvexian receivers. No major bleeding was observed in the milvexian arms. Any adverse events were equally divided across enoxaparin (38%) and milvexian (39%) receivers.

In conclusion, the results of AXIOMATIC-TXR supported the efficacy of the oral factor XIa inhibitor milvexian and showed a favourable bleeding profile.

1. Weitz JI, et al. Milvexian for prevention of venous thromboembolism after elective knee arthroplasty: The AXIOMATIC-TKR Study. LBS07, AHA Scientific Sessions 2021, 13–15 November.
2. Weitz JI, et al. N Engl J Med 2021;385:2161–2172.

Network meta-analysis observes no clear effect of eicosapentaenoic acid on CV outcomes

Eicosapentaenoic acid (EPA) displayed cardiovascular benefits over mineral oil but not compared with other placebo oils or standard-of-care. Moreover, the applicability of mineral oil as a placebo oil is questionable. Thus, the benefits of EPA supplementation are not conclusive.

Dr Yujiro Yokoyama (St. Luke's University Health Network, PA, USA) explained that most randomised clinical trials evaluating the effect of omega-3 fatty acid supplementation on cardiovascular risk reduction have shown neutral results [1]. Although a recent trial did show benefits of an EPA supplement in the secondary prevention of cardiovascular events, the suitability of the used placebo oil is a topic of discussion [2,3]. A network meta-analysis was conducted to examine the effect of EPA, docosahexaenoic acid (DHA), or EPA plus DHA on cardiovascular death, myocardial infarction, stroke, coronary revascularisation, and all-cause death. In total, 17 randomised controlled trials investigating 141,009 participants were included in the analysis.

In reducing cardiovascular death, the findings showed that EPA was more effective than mineral oil in (HR 0.80) in 1 analysis: a regimen of EPA plus DHA showed superiority in the prevention of cardiovascular death compared with olive oil (HR 0.93) and controls (HR 0.83). EPA versus placebo demonstrated neutral results in 6 other comparisons.

In reducing myocardial infarction, EPA was overall more effective than mineral oil regarding the reduction (HR 0.73). Eight comparisons demonstrated neutral results. Similarly, the occurrence of stroke was reduced in patients receiving EPA compared with patients receiving mineral oil (HR 0.74). Only 1 analysis found a reducing effect of EPA on stroke occurrence, whereas 8 other comparisons between EPA and placebo oils displayed neutral findings.

In reducing coronary revascularisation, EPA was more effective than EPA plus DHA (HR 0.67), corn oil (HR 0.63), mineral oil (HR 0.65), and olive oil (HR 0.66). Five analyses showed neutral results. Finally, no significant effect was found of EPA or EPA plus DHA on all-cause death versus placebo.

Although EPA outperformed a mineral oil placebo in the reduction of cardiovascular death, myocardial infarction, and stroke, the use of mineral oil as a placebo oil is questionable as mineral oil has been associated with increased apolipoprotein B, LDL cholesterol, and hs-CRP levels, and coronary artery plaque progression [2,4].

The observed effects of EPA on cardiovascular events are mostly neutral. Small beneficial effects of EPA have been observed for certain cardiovascular outcomes. However, the authors were unable to analyse participants with a low cardiovascular risk. Also, different regimens and doses of omega-3 fatty acids and placebo oils and heterogeneity in follow-up periods were reported. Therefore, a definite conclusion regarding the impact of EPA on cardiovascular outcomes cannot be made.

1. Yokoyama Y, et al. Network Meta-Analysis of Randomized Controlled Trials of Eicosapentaenoic Acid for Cardiovascular Events Reduction. LF.RFO.13, AHA 2021 Scientific Sessions, 13–15 November.
2. Bhatt DL, et al. N Engl J Med 2019;380(1):11–22.
3. Sharma G, et al. JAMA. 2020;324(22):2262–2264.
4. Budoff MJ, et al. Eur Heart J. 2020;41(40)3925–2932.

Heart Failure

Empagliflozin efficacious in HF patients with preserved ejection fractions ≥50%

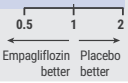
The EMPEROR-Preserved is the first large-scale trial that showed meaningful improvements of a drug therapy in patients with preserved ejection fraction. In a subanalysis of the trial, empagliflozin also demonstrated clinical benefits for heart failure (HF) in patients with left ventricular ejection fraction (LVEF) ≥50%. This result extended to health-related quality of life and symptoms.

EMPEROR-Preserved (NCT03057951) evaluated the efficacy and safety of the sodium-glucose co-transporter 2 (SGLT2) inhibitor empagliflozin compared with placebo in patients with HF with preserved ejection fraction (HFpEF) [1,2]. The trial included 5,988 patients with an LVEF >40%. Dr Stefan Anker (Charité University Berlin, Germany) presented the current analysis, which assessed the subset of included patients with truly preserved EF (≥50%) (n=4,005), in line with the recently updated ESC Guidelines on HF [3]. This analysis is relevant for trial comparisons and guideline recommendations. The primary outcome was a composite score of time to cardiovascular death or HF hospitalisation.

At 52 weeks, the primary endpoint of empagliflozin was met for patients with LVEF ≥50% (HR 0.83; P=0.024). The effect was driven by first HF hospitalisation (HR 0.78; P=0.013). No significant effect of empagliflozin was found on cardiovascular death, all-cause mortality, or cumulative HF hospitalisation (see Figure).

Figure: Primary and secondary outcomes for LVEF ≥50% [1]

Endpoint	Events		Events/100 patient-years			
	Placebo (n=2,003)	Empagliflozin (n=2,002)	Placebo	Empagliflozin	P-value	HR (95% CI)
Primary endpoint						
LVEF ≥50%	318	270	8.0	6.7	0.83 (0.71-0.98)	
First HHF						
LVEF ≥50%	226	182	5.7	4.5	0.78 (0.64-0.95)	
CV death						
LVEF ≥50%	144	126	3.4	3.0	0.89 (0.70-1.13)	
All-cause mortality						
LVEF ≥50%	260	259	6.1	6.1	1.02 (0.86-1.21)	
Total HHF*						
LVEF ≥50%	332	285	7.9	6.8	0.83 (0.66-1.04)	



CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

The effect of empagliflozin on the primary endpoint in patients with an LVEF between 41% and 49% was numerically more pronounced (HR 0.71; P=0.002). Nonetheless, no interaction effect was observed between patients with LVEF ≥50% and patients with an LVEF ranging from 41% to 49% (P=0.27) regarding the primary outcome. A trend analysis did not reveal a significant trend of the effect of empagliflozin across 5% LVEF margins (50–55%, 55–60%, and so on up to >70%). The Kansas City Cardiomyopathy Questionnaire (KCCQ) demonstrated quality-of-life benefits of empagliflozin for patients with LVEF ≥50% (adjusted mean difference 4.24) compared with placebo (adjusted mean difference 2.78). Finally, empagliflozin receivers showed a significant and ongoing improvement on the New York Heart Association (NYHA) functional class score.

Dr Anker highlighted that the 17% reduction on the primary clinical endpoint in this study is remarkable compared with other pharmaceutical interventions for patients with HFpEF assessed in previous clinical trials. "Prior clinical trials showed efficacy rates between 4–8%. Thus, empagliflozin is the first agent to demonstrate a meaningful effect in HF patients with truly preserved EF in a large-scale trial."

1. Anker SD, et al. Empagliflozin in Heart Failure With a Preserved Ejection Fraction ≥50% – Results From the EMPEROR-Preserved Clinical Trial. LBS05, AHA Scientific Sessions 2021, 13–15 November.
2. Anker SD, et al. N Engl J Med 2021;385:1451–1461.
3. McDonagh TA, et al. Eur Heart J 2021;42(36):3599–3726.

EMPULSE: Empagliflozin improves outcomes of acute heart failure

Patients hospitalised for acute heart failure (HF) who were treated with empagliflozin showed significant clinical benefits over patients who were treated with placebo in the phase 3 EMPULSE trial. Empagliflozin therapy was associated with fewer deaths and HF events. Moreover, the agent showed a favourable safety profile in this vulnerable population [1].

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that has demonstrated efficacy in the treatment of patients with chronic HF [2,3]. The randomised, double-blind, placebo-controlled, phase 3 EMPULSE trial (NCT04157751) aimed to assess the efficacy and safety of empagliflozin in hospitalised patients with acute HF. *De novo* or decompensated

hospitalised patients with a primary diagnosis of acute HF were eligible for inclusion, regardless of ejection fraction or diabetes status. After stabilisation, patients were randomised to 10 mg empagliflozin once daily (n=265) or placebo (n=265). Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) at baseline was approximately 38, indicating severe disease in the study population. The primary endpoint was a composite of death, number of HF events, time to first HF event, and change from baseline KCCQ-TSS, assessed by stratified win ratio following the aforementioned sequence. The 90-day results were presented by Prof. Adriaan Voors (University of Groningen, the Netherlands).

Participants receiving empagliflozin demonstrated an increased probability of experiencing clinical benefit (53.0%) compared with patients receiving placebo (39.7%; P=0.0054). Death was observed in 4.2% and 8.3% of the patients in the empagliflozin arm and placebo arm, respectively. Moreover, HF events were more common among placebo receivers (14.7%) than in empagliflozin receivers (10.6%). Subgroup analyses displayed consistency over the predefined strata, in particular regarding HF status (*de novo* or decompensated chronic), diabetes status, and ejection fraction (≤40% and >40%). In addition, the quality of life after 90 days was enhanced in patients receiving empagliflozin, which was reflected by a mean 4.5-point difference in KCCQ-TSS between the empagliflozin arm and the placebo arm (P=0.0347).

The safety profile of empagliflozin was favourable. Any adverse events were reported in 70.0% of the patients in the empagliflozin arm and in 77.3% of the patients in the placebo arm. Serious adverse events were less common among empagliflozin receivers (32.3%) than in placebo receivers (43.6%). Acute renal failure was observed in 7.7% and 12.1% of the patients in the experimental arm and placebo arm, respectively.

Discussant Dr Nancy Sweitzer (University of Arizona, AZ, USA) added that empagliflozin was efficacious in this population, regardless of background therapy. "*De novo* patients were not treated with guideline-recommended therapies but experienced equal benefits from treatment with empagliflozin. Therefore, I think we should not withhold this agent while other drug classes are being initiated and optimised. However, it is interesting to investigate how empagliflozin interacts with other drug classes, for example with regard to renal function, in future studies."

1. Voors AA, et al. Empagliflozin in patients hospitalized for acute heart failure: the EMPULSE trial. LBS05, AHA 2021 Scientific Sessions, 13–15 November.
2. Anker SD, et al. N Engl J Med 2021;385:1451–1461.
3. Packer M, et al. N Engl J Med 2020;383:1413–1424.

CHIEF-HF: Canagliflozin improves health status in heart failure

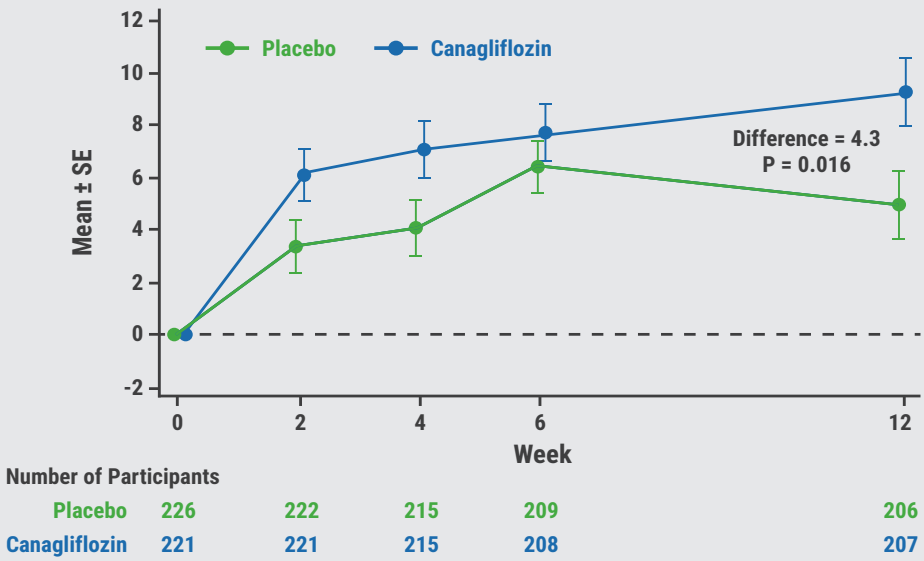
Canagliflozin improved heart failure (HF) symptoms compared with placebo, regardless of ejection fraction or diabetes status in patients with any type of HF. Moreover, the effects were observed as early as 2 weeks from treatment initiation. The phase 3 CHIEF-HF trial was conducted without in-person visitations, which resulted in a diverse study population and a high completion rate.

Prof. John Spertus (University of Missouri-Kansas City, MO, USA) explained that canagliflozin has been shown to reduce HF outcomes and improve renal protection in patients with type 2 diabetes [1]. However, the agent has not yet been approved for a primary HF indication. The randomised, double-blind, placebo-controlled, phase 3 CHIEF-HF trial (NCT04252287) assessed the efficacy of canagliflozin on symptom improvement in patients with any type of HF. Participants could register for the trial via a smartphone application, after which the study medication and Fitbit devices were delivered. In total, 448 participants (mean age 63; 45% women) were randomised 1:1 to 100 mg canagliflozin once daily or placebo. The primary outcome was the 12-week change on the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS).

After 12 weeks, canagliflozin treatment evoked a mean 4.3-point increased change in KCCQ-TSS versus placebo (P=0.016). Notably, the effect was observed as early as 2 weeks after treatment initiation (see Figure). The number needed to treat to avoid a large deterioration in KCCQ-TSS (≥10-point decrease) was 15, and 27 patients needed to be treated to achieve a large improvement on this instrument. The results were similar across ejection fractions and type 2 diabetes status. No new safety issues of canagliflozin emerged during this study.

Discussant Dr Eldrin Lewis (Stanford University, CA, USA) put the results of the CHIEF-HF trial in perspective. "We have seen a remarkable improvement in mortality rates of HF patients due to therapeutic advances in recent years. Up to 60% reductions in mortality rates can be achieved in these patients if they follow combination therapies. The SGLT2 inhibitors are the latest drug class to add to the progress in HF management. In addition, the current completely decentralised trial recruited a diverse treatment population (14% Black, 45% women, 59% preserved ejection fraction) and established excellent follow-up rates (98%). Therefore,

Figure: 12-week KCCQ-TSS improvement for canagliflozin [1]



the CHIEF-HF trial design shows benefits over standard randomised controlled trials. I am curious to see the long-term follow-up data of this trial regarding the persistence of established improvements in health-related quality of life."

1. Spertus J, et al. Canagliflozin: Impact on Symptoms, Physical Limitations and Quality of Life in Heart Failure (CHIEF-HF) Trial. LBS05, AHA 2021 Scientific Sessions, 13–15 November.

DREAM-HF: MPC therapy for HFrEF did not meet primary endpoint

Transendocardial delivery of mesenchymal precursor cells (MPCs) did not reduce cumulative recurrent non-fatal decompensated heart failure (HF) events in HF patients with a reduced ejection fraction (HFrEF). However, a single dose of MCPs was associated with lower rates of non-fatal myocardial infarction, non-fatal stroke, and cardiac death. These effects were more pronounced in patients with baseline inflammation.

Dr Emerson Perin (Texas Heart Institute, TX, USA) argued that MPCs may decrease cardiac inflammation, reduce heart muscle death, induce a microvascular network in heart muscle, and reverse endothelial dysfunction [1]. In a recent phase 2 trial, MPCs showed promising results in reducing HF-associated events in patients with high-risk, persistent HFrEF [2]. The multicentre, double-blind, sham-controlled, phase 3 DREAM-HF trial (NCT02032004) randomised 537 patients with HFrEF (New York Heart Association [NYHA] functional class II–III) 1:1 to MPC therapy or sham control. Patients in the MPC condition underwent left ventricular electronic mapping to scan for viable but inflamed myocardium. Subsequently, transendocardial injections were administered in the selected myocardial areas. The primary endpoint was the mean cumulative rate of recurrent non-fatal decompensated HF events per 100 patients.

After a mean follow-up of 30 months, the primary endpoint of MPC therapy was not met (HR 1.2; P=0.406). However, predefined secondary endpoints did show benefits of MPC therapy: the risk of non-fatal myocardial infarction or non-fatal stroke was decreased in the MPC group (HR 0.35; P=0.001) and the risk of cardiac death was reduced in NYHA class II patients within the treatment arm (HR 0.43; P=0.044).

In addition, a post-hoc analysis showed that MPC therapy was able to reduce a composite outcome of cardiac death, non-fatal myocardial infarction, or non-fatal stroke in patients with elevated inflammatory markers (hsCRP ≥2 mg/L; HR 0.551; P=0.012) but not in patients without inflammation (hs-CRP <2 mg/L; HR 0.843; P=0.519). Compared with the sham control, MPC therapy was not associated with an increased risk of adverse events. Nor did MPC administration evoke clinically meaningful immune-related responses.

1. Perin EC, et al. Randomized trial of targeted transendocardial delivery of mesenchymal precursor cells in high-risk chronic heart failure patients with reduced ejection fraction – the DREAM-HF trial. LBS05, AHA Scientific Sessions 2021, 13–15 November.
2. Perin EC, et al. Circ Res. 2015;117:576–584.

Therapeutic approaches in heart failure with diabetes

The new therapeutic options for patients with heart failure (HF) offer physicians a growing number of choices in finding the right integrated approach in the treatment of HF patients with diabetes mellitus. Key considerations, according to Prof. Lynne Stevenson (Vanderbilt University Medical Center, TN, USA) are the robustness or frailty of the patient, the stage of disease, and the patient's financial resources and accessibility to healthcare facilities [1].

HFrEF

The 3 fundamental therapies for patients with HF with reduced ejection fraction (HFrEF) are angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and β-blockers. The first choice of therapy depends on heart rate, blood pressure, and renal function. "For example, in patients with an increased heart rate, β-blockers would be the first therapy of choice. If we want to expand from our fundamental therapies, angiotensin receptor-neprilysin inhibitor (ARNIs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors are the available options. Although ARNIs provide a clear additional benefit for our patients, we have to consider blood pressure and tolerance of ACE inhibitors or ARBs." An analysis of the PARADIGM-HF trial (NCT01035255) showed that patients on the ARNI sacubitril/valsartan with a baseline systolic blood pressure ≤110 mmHg experienced hypotensive events in 25% of the cases [2]. "Therefore, patients with a blood pressure <100 mmHg, in general, do not qualify for this expansion option." On the other hand, SGLT2 inhibitors do not display much blood pressure lowering [3]. In addition, SGLT2 inhibitors may have an added benefit for renal function. Since half of the patients with HF have chronic kidney disease and the mortality in patients with HF increases when renal function drops (RR of 1.4 when eGFR <60), this is an important factor to consider [4,5]. "In summary, SGLT2 inhibitors might be favoured over ARNIs in less robust patients with HFrEF."

HFpEF

"In patients with a preserved EF (HFpEF), there is no recommended routine neurohormonal therapy," Prof. Stevenson continued. "Controversial indications for ARBs and MRAs, β-blockers for arrhythmias or ischaemia, and perhaps SGLT2 inhibitors for renal preservation are the options we currently have. In addition, although SGLT2 inhibitors show benefits in patients with HFpEF, the benefits may be limited to the lower EFs within this population [6]."

Obesity

"Importantly, we need to tackle obesity as a cause and aggravator of the disease. The prevalence of obesity is >30% in most [US] states. If we do not address this problem, the treatment effect of emerging therapies will remain limited. Semaglutide, a GLP-1 antagonist, showed a remarkable 18% weight reduction in overweight or obese adults in 2 recent studies. However, the tolerance of this agent is problematic in many patients [7,8].

In conclusion, therapy design in patients with HF and diabetes is challenging. The robustness, disease stage, and resources of the patients are important decision criteria, and the therapy effectiveness will remain limited in this population if obesity is not adequately addressed.

1. Stevenson LW. An Abundance of Therapeutics: An Integrated Approach to Managing HF with DM. PR.ME.461, AHA 2021 Scientific Sessions, 13–15 November.
2. Böhm M, et al. Eur Heart J. 2017;38(15):1132–1143.
3. Böhm M, et al. J Am Coll Cardiol. 2021;78(13):1337–1348.
4. Dries DL, et al. J Am Coll Cardiol. 2000;35(3):681–689.
5. McGuire DK, et al. J Am Coll Cardiol. 2021;6(2):148–158.
6. Packer M, et al. Circulation. 2021;144:1193–1195.
7. Wilding JHP, et al. N Engl J Med 2021;384:989–1002.
8. Rubino D, et al. J Am Coll Cardiol. 2021;325(14):1414–1425.

Acute Coronary Syndrome

Ticagrelor cessation: early CABG non-inferior to delayed surgery

Early surgery, 2–3 days after the termination of ticagrelor treatment, was non-inferior to delayed surgery by 5–7 days regarding severe or massive bleeding in patients with acute coronary syndrome (ACS). The RAPID CABG trial was the first randomised controlled study assessing an early coronary artery bypass graft (CABG) surgery strategy in this population [1].

The previous phase 3 PLATO trial (NCT00391872) showed that patients with ACS undergoing CABG surgery within 1 day of ticagrelor termination had higher mortality rates, mostly caused by perioperative bleeding, than patients who had a longer period of ticagrelor cessation before surgery [2]. The current North American guidelines recommend a minimum of 5–7 days between termination of ticagrelor and non-urgent CABG surgery, whereas the ESC supports a minimum waiting period of 3 days for this procedure. Thus, the multicentre, randomised RAPID CABG trial (NCT02668562) assessed the non-inferiority of a 2–3 day ticagrelor cessation period (i.e. early CABG) to a 5–7 day period (i.e. delayed CABG) for perioperative bleeding in patients with ACS.

Participants were randomised 1:1 to early (n=72) or delayed surgery (n=71). The primary outcome was severe or massive perioperative bleeding by Universal Definition of Perioperative Bleeding (UDPB), class 3 or 4. Dr Derek So (University of Ottowa Heart Institute, Canada) presented the 6-month results.

A pre-surgery test demonstrated lower $P2Y_{12}$ reaction unit (PRU) rates for participants in the early surgery arm compared with the delayed surgery arm (P<0.001). Severe or massive perioperative bleeding occurred in 4.6% and 5.2% of the participants in the early and delayed surgery group, respectively, demonstrating non-inferiority of an early surgery strategy (P=0.025). In addition, other bleeding outcomes, such as TIMI CABG bleeding, BARC 4, or BARC 5, did not feature significant differences between the 2 treatment conditions. Moreover, bleeding and transfusion parameters displayed no differences between the early and delayed surgery strategies. The median length of stay until hospital discharge was 3 days longer in the delayed CABG group (12 days) than in the early CABG group (9 days).

Discussant Prof. Roxanne Mehran (Icahn School of Medicine at Mount Sinai, NY, USA) argued that "the results are important and encouraging. Since the guidelines regarding the timing of $P2Y_{12}$ antagonist discontinuation before CABG are mostly based on observational studies, this first randomised, well-conducted study addressed an unmet need. However, the small sample size, small number of events, and non-inferiority margin of 8% call for larger trials to verify these results."

1. So DYF, et al. A Randomized Study of Early vs. Delayed Coronary Artery Bypass among Patients with Acute Coronary Syndromes Treated with Ticagrelor: The RAPID CABG Study. LBS01, AHA Scientific Sessions 2021, 13–15 November.
2. Held C, et al. J Am Coll Cardiol. 2011;57(6):672–684.

Distinguishing patients before AMI based on plaque morphology

Patients with and without pre-infarction angina (PIA) could be distinguished based on culprit plaque morphology imaged by intracoronary optical coherence tomography (OCT). Patients with PIA displayed higher rates of intact fibrous cap (IFC) and plaque healing, and lower rates of thrombus burden. These results provide insights into the association between plaque morphology and the clinical presentation of acute myocardial infarction (AMI).

"It has been established that destabilisation in plaque morphology evolution is an important coronary thrombosis mechanism," explained Dr Alfredo Ricchiuto (Università Cattolica del Sacro Cuore, Italy) [1]. "However, the association between culprit plaque morphology, healed culprit plaque prevalence, and the clinical presentation of AMI is mostly unexplored." The current retrospective, observational study aimed to evaluate the differences in plaque morphology and healing capacity in patients with (n=50) and without PIA (n=52), who were assessed via intracoronary OCT.

Patients without PIA displayed higher rates of plaques rupture than patients with PIA (63.5% vs 42.0%) and lower rates of intact fibrous cap compared to patients with PIA (36.5% vs 58.0%). In addition, patients with PIA demonstrated higher rates of plaque rupture with macrophages (71.4%) than patients without PIA (27.3%). The thrombus burden was numerically lower in patients with PIA, although this result was not significant (P=0.145). Several plaque phenotypes (i.e. fibrous, lipid, thin cap fibroatheroma) did not show significant differences between patients with or without PIA. Furthermore, patients without PIA featured diffuse calcification more frequently (40.4%) than patients with PIA (22.0%). Finally, patients with PIA showed higher rates of healed plaques (66.0%) than patients without PIA (25.0%).

In conclusion, this study showed that patients with and without PIA have different plaque morphologies; thus, adding to the understanding of the clinical presentation of AMI and the underlying pathophysiological mechanisms.

1. Ricchiuto A, et al. Culprit plaque morphology and healing capacity in patients with and without pre-infarction angina: an optical coherence tomography imaging study. AC.AOS.483, AHA 2021 Scientific Sessions, 13–15 November.

Vascular Diseases: PVD

Rivaroxaban regimen beneficial after revascularisation for claudication

A regimen of rivaroxaban plus low-dose aspirin showed consistent benefits for patients with claudication who underwent lower-extremity revascularisation (LER) and patients with critical limb-threatening ischaemia (CLTI) that were subjected to LER. Thus, rivaroxaban plus aspirin is a valid adjunctive therapy option for patients with claudication after LER [1].

The VOYAGER PAD trial (NCT02504216) showed a significant reduction of major cardiovascular events in patients with CLTI or claudication after LER who were treated with rivaroxaban compared with placebo (HR 0.86; P=0.0086) [2]. The current sub-analysis analysed the consistency of these results across the different patient conditions (i.e. claudication or CLTI). Furthermore, the study described haemodynamic and patient-reported outcomes, and the risk profile of major adverse events in patients with claudication after LER. In total, 5,031 patients with claudication were assessed. The primary outcome was a composite score of major cardiovascular events, and the 3-year results were presented by Prof. Marc Bonaca (University of Colorado, CO, USA).

The primary endpoint was met: there was a significant risk reduction of major cardiovascular events in patients with claudication who were treated with rivaroxaban after LER (HR 0.86) compared with placebo. In addition, no interaction effect was observed between patients with claudication and patients with CLTI who underwent LER (P=0.94; see Figure).

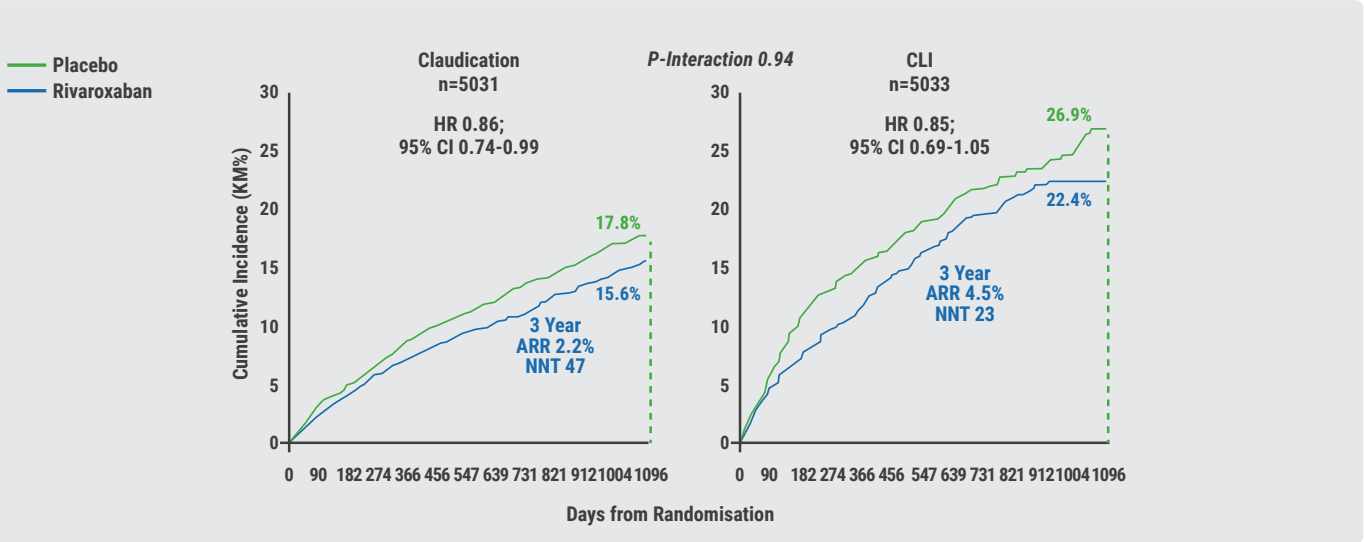
Patients with claudication (both rivaroxaban and placebo pooled) showed an improved walking function 1 month after LER. Pre-LER, 38% of participants indicated in the Walking Impairment Questionnaire that they were able to walk 2 blocks compared with 82% of participants post-LER. This effect was durable over approximately 2–3 years regardless of surgical approach.

At 3 years after LER, the unplanned index limb revascularisation rate was 22%. In addition, major adverse limb events occurred with a rate of 8.5% per 3 years, and thus a high risk in patients with claudication following LER. Rivaroxaban consistently reduced these risks in those with claudication and CLI.

A risk-benefit analysis of rivaroxaban after LER for patients with claudication showed that a net value of 22 major cardiovascular events was prevented by the treatment at the expense of 5 major bleeding events. Moreover, a net value of 16 unplanned limb revascularisations was prevented by the treatment.

1. Bonaca MP, et al. Efficacy and Safety of Rivaroxaban in Patients with PAD Undergoing Lower Extremity Revascularization for Claudication. FS06, AHA Scientific Sessions 2021, 13–15 November.
2. Bonaca MP, et al. N Engl J Med 2020;382:1994–2004.

Figure: Primary efficacy endpoint of rivaroxaban in claudication and CLTI



ARR, absolute risk reduction; CI, confidence interval; CLI, critical limb-threatening ischaemia; HR, hazard ratio; NNT number needed to treat.

LIBERTY 360 shows quality-of-life improvements after peripheral vascular intervention

Quality of life (QoL) improved significantly and sustainably in patients with peripheral artery disease (PAD) after lower extremity endovascular intervention. Moreover, the prospective, observational, multicentre LIBERTY 360 study demonstrated that baseline health status and disease severity were the strongest predictors for QoL improvement after the intervention [1].

QoL improvement is a valid indication for peripheral vascular intervention in patients with PAD [2]. However, Dr Mohsin Chowdhury (Harvard Medical School, MA, USA) pointed out that evidence was lacking regarding the long-term QoL improvements and predictors of QoL improvement after peripheral vascular intervention. The multicentre, prospective LIBERTY 360 study (NCT01855412) hypothesised that surgical intervention is related to significant and sustained improvement in QoL. Furthermore, the authors predicted an inverse association between disease severity and QoL improvements. In total, 1,204 patients who underwent lower extremity endovascular intervention were followed for up to 5 years. The European Quality of Life Scale (EuroQoL) EQ-5D-5L and the Vascular Quality of Life Questionnaire (VascuQol-25) were assessed. For the analysis, participants were categorised as patients with claudication (Rutherford classification 2–3) or patients with critical limb ischaemia (Rutherford classification 4–6).

In patients with claudication, EuroQol scores displayed an improved and mostly sustained QoL at 30 days (mean delta EQ-VAS +6.3), 12 months (+5.4), and 36 months (+3.4) after surgery, compared with baseline QoL (mean EQ-VAS 68.8). A similar pattern was observed in patients with critical limb ischaemia: mean baseline EQ-VAS 64.2 and at 30 days (+4.6), 12 months (+6.5), and 36 months (+3.5). The VascuQoL-25 scores (see Figure) demonstrated that surgery resulted in a minimal important difference in QoL in 56.7% of the patients with claudication after 30 days. Respectively, 52.9% and 53.5% of the patients displayed a minimal important difference in QoL after 12 months and 36 months. In patients with critical limb ischaemia, the corresponding percentages were 50.8% (30 days), 59.1% (12 months), and 57.7% (36 months).

The authors reported that patients with no/slight QoL problems at baseline were more likely to experience QoL improvements after surgery than patients with moderate/severe QoL problems at baseline (OR 4.81; P<0.0001). In addition, critical limb ischaemia (OR 0.61; P=0.0021), female sex (OR 0.64; P=0.0081), a history of renal disease (OR 0.56; P=0.0006), or a history of previous lower limb endovascular treatment (OR 0.70; P=0.0286) were associated with fewer QoL improvements after surgery.

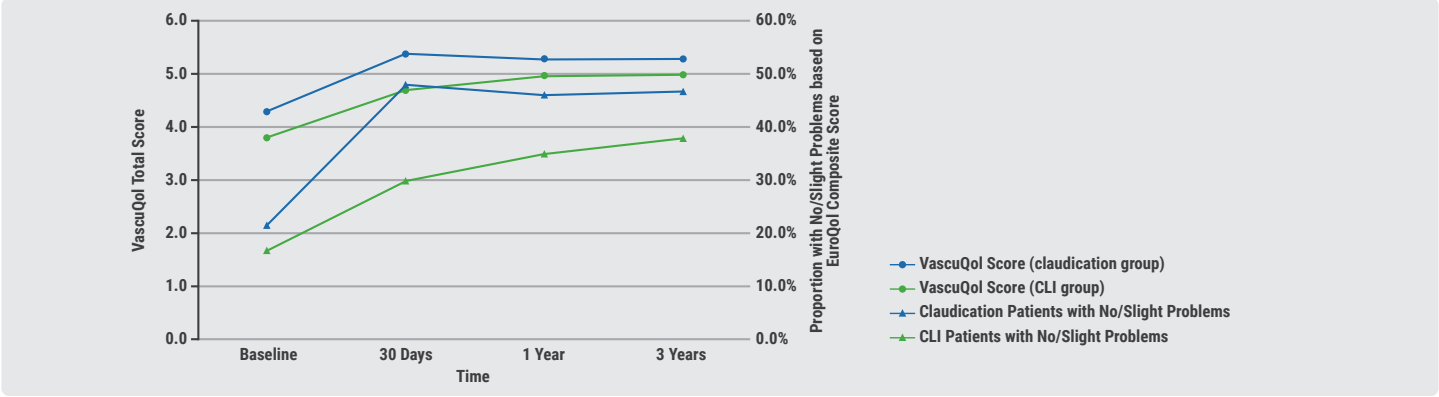
1. Chowdhury M, et al. Long term quality of life improvement after peripheral vascular intervention: insights from the LIBERTY 360 study. VA.AOS.427, AHA 2021 Scientific Sessions, 13–15 November.
2. Gerhard-Herman MD, et al. Circulation. 2017;135(12):e726-e779.

Deficient treatment outcomes after PVI in Black and low-income adults with PAD

The risk of undergoing femoropopliteal peripheral vascular intervention (PVI) was higher in Black or low-income adults with peripheral artery disease (PAD) than in White or high-income adults with PAD, respectively. In addition, health outcomes after PVI were worse in low-income adults or Black adults. This effect may be mediated by a higher burden of comorbidities. Targeted efforts should be made to improve the reported disparities between subpopulations [1].

Previous research has shown that Black adults demonstrate a higher prevalence of PAD than White adults and that low-income adults show a higher prevalence of PAD than high-

Figure: Quality of life improvements in claudication and critical limb ischaemia [1]



income adults. In addition, Black or low-income adults show higher amputation rates [2]. In the current study, Dr Anna Krawisz (Beth Israel Deaconess Medical Center, MA, USA) and colleagues aimed to investigate the possible association of race and income on PVI occurrence and associated outcomes [1]. Between 2016 and 2018, data was collected from 'fee for service' Medicare beneficiaries ≥66 years of age. The risk of death and amputation was assessed within 1 year after PVI, stratified by income and race.

Black adults demonstrated higher PVI rates than White adults (risk ratio 1.75; P<0.01). In addition, a higher proportion of Black patients was treated for chronic limb-threatening ischaemia (CLTI) (62%) compared with White patients (50%), indicating more advanced disease in Black patients at the time of intervention. A similar pattern was observed in low-income versus high-income patients: low-income patients were more at risk of receiving PVI compared with high-income patients (risk ratio 2.02; P<0.01) and were more frequently treated for CLTI (62% vs 49%, respectively). These results were consistent across all regions of the US.

The occurrence of death or amputation after PVI was more prevalent in Black patients (17.6%) than in White patients (15.2%; risk ratio 1.16; P<0.01). Similarly, low-income patients had a higher risk of experiencing amputation or death after PVI (19.3%) than high-income patients (14.4%; risk ratio 1.34; P<0.01). The increased risk of death and amputation after PVI in Black adults and low-income adults disappeared when the analysis was adjusted for comorbidities. This indicates that comorbidities may mediate the relationship between race or income and the composite outcome of death and amputation.

Dr Krawisz argued that these data reveal disparities in care in patients with PAD. "Risk factor monitoring, early disease identification, and treatment optimisation in Black adults and low-income adults are needed to reduce these inequalities in care."

1. Krawisz AK, et al. Disparities in the Prevalence of and Outcomes associated with PVI by Race and Income. VA.RFO.19, AHA 2021 Scientific Sessions, 13–15 November.
2. Allison MA, et al. Am J Prev Med. 2007;32(4):328-333

REDUCE-IT: Cardiovascular risk reduction with icosapent ethyl in PAD

Icosapent ethyl was associated with cardiovascular risk reduction in patients with prior peripheral artery disease (PAD) in a post-hoc analysis of the REDUCE-IT trial. A significant 32% reduction in total ischaemic events was demonstrated over approximately 5 years in patients with PAD treated with icosapent ethyl. The results in this subpopulation are consistent with the overall trial results [1].

The randomised, phase 3 REDUCE-IT trial (NCT01492361) was conducted to investigate the safety and efficacy of icosapent ethyl in patients at high risk for cardiovascular events [2]. For the primary analysis, 8,179 patients who were treated with statins were randomised 1:1 to 4 g icosapent ethyl once daily or placebo. After approximately 5 years of follow-up, a relative risk reduction in cardiovascular events of 24.8% was observed in participants receiving icosapent ethyl compared with those receiving placebo. The current subgroup analysis, presented by Dr Deepak Bhatt (Brigham and Women's Hospital, Boston, MA, USA), examined whether this benefit extends to patients with prior PAD (n=688).

The subpopulation of patients with prior PAD was demonstrated to be a very high-risk cohort in the REDUCE-IT study: 41.7% of the patients with PAD showed a first ischaemic cardiovascular event in the 5-year follow-up period versus 31.1% of the patients with atherosclerosis but without PAD (P=0.0004). The cumulative event rate was 98.2% in patients with PAD versus 61.4% in patients without prior PAD (P<0.0001).

The risk reduction of icosapent ethyl on total cardiovascular events in patients with prior PAD after approximately 5 years of follow-up was 32% (P=0.03) and displayed a non-significant 22% risk reduction in first cardiovascular events (P=0.08). A similar effect was observed in patients with atherosclerosis but without PAD.

The safety profile of icosapent ethyl in patients with PAD was consistent with the overall trial population. Tolerability and adverse events of placebo receivers and icosapent ethyl receivers were mostly comparable. Atrial fibrillation was reported numerically more frequently in the icosapent ethyl arm (5.2%) than in the placebo arm (2.6%; P=0.07). No differences in bleeding were found. However, Dr Bhatt added that this last finding could be related to the limited sample size of the PAD subpopulation.

In conclusion, icosapent ethyl provided significant risk reduction in cardiovascular events in the very high-risk sub-population of patients with prior PAD of the REDUCE-IT trial. The effect sizes were similar to the overall trial results.

1. Bhatt DL, et al. Benefits of Icosapent Ethyl in Patients with Prior Peripheral Artery Disease: REDUCE-IT PAD. VA.RFO.19, AHA 2021 Scientific Sessions, 13–15 November.
2. Bhatt DL, et al. N Engl J Med 2019;380:11–22.

Vascular Diseases: CAD

Long-term reduced risk of CV events with ticagrelor plus aspirin after CABG

Ticagrelor plus aspirin significantly reduced the risk of cardiovascular events up to 5 years following coronary artery bypass graft (CABG) surgery compared with ticagrelor or aspirin alone. The benefits were mainly associated with a risk reduction of myocardial infarction and ischaemic stroke.

"Antiplatelet therapy is guideline-recommended after CABG in patients with acute coronary syndrome," explained Dr Qiang Zhao (Shanghai Jiao Tong University, China) [1]. "However, there is less evidence on the effect of antiplatelet therapies in patients with chronic coronary syndrome." The randomised, multicentre, open-label, phase 4 DACAB trial (NCT02201771) showed an improvement in vein graft patency in patients who received ticagrelor (90 mg twice daily) plus aspirin (100 mg once daily; n=168) compared with either one of these therapies alone (n=166 each arm), 1 year after CABG [2].

The current follow-up extension of this trial, DACAB-FE (NCT03987373), assessed the 5-year outcomes of the study population [1]. The 5-year post-CABG follow-up extension was completed by 477 participants. The primary outcome was the incidence of major adverse cardiac events (MACE)-4 (i.e. death, myocardial infarction, stroke, repeated revascularisation). Silent myocardial infarctions were included.

After 5 years, the incidence of MACE-4 was significantly reduced in participants receiving the combination therapy versus those who received aspirin alone (HR 0.63; P=0.03) or ticagrelor alone (HR 0.64; P=0.03). A landmark analysis, separating the effect of 0–12 months post-CABG from 12–60 months post-CABG, demonstrated that the long-term effect was largely a maintained effect of the first post-operative year. The secondary MACE-5 and MACE-3 outcome measures displayed similar effectiveness of the aspirin plus ticagrelor regimen.

Considering the components of MACE-4, no significant differences were observed between treatment conditions for the time to all-cause death and cardiovascular death. In contrast, myocardial infarctions were reduced in the combination therapy arm versus the aspirin monotherapy arm (HR 0.49; P=0.02) and the ticagrelor monotherapy arm (HR 0.43; P=0.01). Participants in the combination group had a decreased risk of stroke compared with participants receiving aspirin alone (HR 0.38; P=0.05). However, ticagrelor plus aspirin was not associated with a significant reduction in the risk of stroke compared with ticagrelor alone (HR 0.83; P=0.75). The time to repeat revascularisation and hospitalisation for unstable angina did not display benefits of the combination regimen over the monotherapies. Additional data on the safety of this regimen will be needed to assess the overall risk benefit of this approach.

1. Zhao Q, et al. Five-Year Clinical Outcomes After Ticagrelor Plus Aspirin, Ticagrelor Alone, or Aspirin Alone After Coronary Artery Bypass Grafting: Follow-Up Extension of the DACAB Trial. FS06, AHA Scientific Sessions 2021, 13–15 November.
2. Zhao Q, et al. JAMA. 2018;319(16):1677–1686.

Early surgery outperforms conservative management in asymptomatic severe aortic stenosis

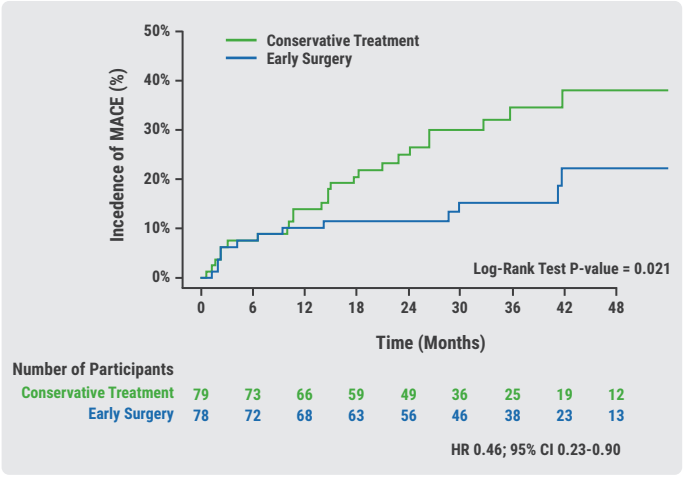
The AVATAR trial demonstrated benefits of early surgical aortic valve replacement compared with conservative management in patients with asymptomatic severe aortic stenosis with a normal left ventricular function. These results show that surgery is indicated when aortic stenosis is significant, albeit asymptomatic [1].

A recent randomised trial suggested that early surgery outperforms conservative management in a population of patients with very severe aortic stenosis [2]. However, surgery in asymptomatic patients with severe aortic stenosis remained a topic of debate. Thus, the prospective, multicentre, randomised, open-label AVATAR study (NCT02436655) assessed the efficacy and safety of early surgical valve replacement in a population of patients with asymptomatic severe aortic stenosis with a normal left ventricular function. Eligible patients underwent a mandatory exercise test to control for the onset of aortic stenosis-related symptoms. The primary endpoint was the incidence of major adverse cardiac events (MACE). The event-driven design targeted 35 events for the analysis. Prof. Marko Banovic (University Clinical Centre of Serbia, Serbia) presented the findings of the study.

The pre-specified number of events was achieved at a median follow-up of 32 months, with 157 patients randomised 1:1 to the early surgery arm or the conservative management arm. Participants in the early surgery arm demonstrated

fewer MACE events (13 events) than participants in the conservative management arm (26 events). A log-rank test showed a corresponding hazard ratio of 0.46 (P=0.021) over 48 months for the primary endpoint (see Figure).

Figure: 48-week trajectory of cardiovascular events [1]



In addition, a numerical advantage of early surgery over conservative treatment was displayed for all-cause death (HR 0.56; P=0.16) and heart failure hospitalisation (HR 0.32; P=0.075). A composite endpoint of all-cause death and heart failure hospitalisation, conducted post-hoc, showed significant benefits of early surgery over watchful waiting (HR 0.40; 0.013). The intraoperative mortality rate in the early surgery arm (1.4%) did not exceed the expectations of the authors, according to Dr Banovic.

The results of the AVATAR trial are consistent with the findings of Kang et al. [2]. However, long-term follow-up is required to assess potential safety issues, such as valve durability, endocarditis, and thromboembolic complications.

1. Banovic M, et al. Aortic Valve Replacement versus Watchful Waiting in Asymptomatic Severe Aortic Stenosis: The Avatar Trial. LBS01, AHA Scientific Sessions 2021, 13–15 November.
2. Kang DH, et al. N Engl J Med 2020;382:111–119.

External support device for SVG grafts in CABG surgery shows promise

No significant difference in intimal hyperplasia was reported between supported and unsupported saphenous vein grafts (SVGs) in patients who underwent coronary artery bypass graft (CABG) surgery in the VEST trial. However, the additional sensitivity analysis did show benefits of the externally supported SVG. Further investigation of external graft support devices is warranted.

Prof. John Puskas (Mount Sinai Hospital, Israel) explained that 50% of all SVGs fail within 10 years, mostly due to proliferative intimal hyperplasia of the grafts [1]. This process causes graft atherosclerosis and occlusion, leading to unwanted clinical events. According to Prof. Puskas, external support of SVGs may prevent SVG dilatation and reduce intimal hyperplasia. In addition, an external support device could improve long-term vein patency by reducing SVG wall tension, decreasing lumen irregularities, and improving haemodynamics and shear stress.

The current VEST Pivotal trial (NCT03209609) assessed the efficacy and safety of an external support device for SVGs in reducing intimal hyperplasia. The randomised, within-patient-controlled study design included 224 patients with multi-vessel coronary artery disease who were scheduled for CABG surgery. One SVG bypass was randomised to be externally supported, whereas another served as control. The primary endpoint was intimal hyperplasia at 1-year follow-up, evaluated by intravascular ultrasound (IVUS).

No statistical difference was observed between the area of intimal hyperplasia in $mm^{\wedge 2}$ of supported (5.11) and unsupported SVGs (5.79; P=0.072). However, the primary analysis was performed with imputation of missing data. An additional sensitivity analysis that was executed on patients who had IVUS of both grafts (n=113) showed a significant reducing effect of the supported graft on the area of intimal hyperplasia (4.58 vs 5.12; P=0.043). In 59.5% of the supported grafts, there were no reported irregularities in lumen diameter compared with 53.5% in the unsupported grafts. The safety analysis did not reveal worrisome safety signals of the external support device after 12 months.

Prof. Puskas mentioned that the rate of compromised vessels was higher than expected. This had an impact on the primary analysis. Since the PREVENT IV trial (NCT00042081) showed similar vein graft failure rates, this could have been foreseen, admitted Prof. Puskas. He explained that arterial grafts are qualitatively better and more durable than vein grafts and that the 'no-touch' technique of saphenous vein preparation for CABG could increase graft patency. However, this procedure was not performed in the current study. "Future studies should investigate the long-term value of external support devices for vein grafts and develop novel tools and measures to prevent early vein graft failure," concluded Prof. Puskas.

1. Puskas JD, et al. Efficacy and Safety of an External Support Device for Saphenous Vein Coronary Bypass Graft: The VEST Trial. LBS01, AHA Scientific Sessions 2021, 13–15 November.

COVID-19 & the Heart

Blood pressure control disrupted during the pandemic

Blood pressure (BP) control was reduced during the COVID-19 pandemic and has not returned to pre-pandemic levels. A large-scale observational study, conducted by the Mayo Clinic, followed over 1.7 million patients with hypertension in pre-pandemic and pandemic years. Future studies are needed to investigate whether this disruption in BP control will lead to an increase in cardiovascular events.

Epidemiologist Dr Alanna Chamberlain (Mayo Clinic, MN, USA) and colleagues assessed the changes in BP control between pre-pandemic and pandemic periods [1]. Included in the analysis were 24 US health systems (18 academic). The extracted data was standardised to the PCORnet common data model. The study compared 3 qualitative measures of BP control and improvement, and 6 process metrics relevant to clinical management and treatment practice for BP control between 2019 (pre-pandemic year) and 2020 (pandemic year).

In 2019, 1.77 million patients with hypertension had a combined 8.30 million healthcare encounters. In 2020, a similar number of patients (1.73 million) was followed but fewer encounters (6.59 million) were reported. The percentage of hypertensive patients who demonstrated BP control (<140/<90 mmHg) at an ambulatory care visitation had dropped from 60.5% in 2019 to 53.3% in 2020, displaying a difference in weighted averages of 7.2%. A similar trend was observed in the <130/<80 mmHg category, featuring a 4.6% reduction in BP control.

Achieved improvements in BP control, defined as a systolic BP reduction of 10 mmHg or a systolic BP<140 mmHg, declined from 29.7% in 2019 to 23.8% in 2020. The number of repeat visits among patients with uncontrolled hypertension dropped from 36.7% in the pre-pandemic year to 31.7% in the pandemic year. The proportion of patients who was prescribed an intensification of medication remained stable. Dr Chamberlain mentioned that they observed a large variance in BP control metrics across health systems, suggesting an opportunity for improvement.

1. Chamberlain AM, et al. Disruption in Blood Pressure Control with the COVID-19 Pandemic: A Study of 24 US Health Systems in the PCORnet Blood Pressure Control Laboratory. LBS02, AHA Scientific Sessions 2021, 13–15 November.

Icosapent ethyl did not reduce the risk of hospitalisation in COVID-19

Icosapent ethyl did not significantly influence hospital outcomes in an outpatient COVID-19 population. However, all clinical outcome measures trended towards a benefit of icosapent ethyl in the PREPARE-IT 2 trial. The agent was well tolerated and did not inflict notable safety issues [1].

Icosapent ethyl is an oral form of eicosapentaenoic acid (EPA) that has been associated with a risk reduction of cardiovascular events in the phase 3 REDUCE-IT trial (NCT01492361) [2]. Moreover, the phase 2 Cardiolink-9 trial (NCT04412018) displayed symptom-reducing and inflammation-reducing qualities of icosapent ethyl in patients with COVID-19 [3]. The current PREPARE IT-2 trial, presented by Dr Rafael Díaz (Estudios Clínicos Latinoamérica, Argentina), investigated the efficacy and safety of icosapent ethyl in non-hospitalised patients with COVID-19. Enrolled were 2,052 patients with recently diagnosed COVID-19, who were older than 40 years, and without a clear indication for hospitalisation. They were randomised 1:1 to oral icosapent ethyl (8 g daily for the first 3 days, then 4 g daily) or placebo. The primary outcome was COVID-19- related hospitalisation (indication or actual) or death. Dr Díaz presented the 4-week outcomes of the study.

The proportion of COVID-19 related hospitalisations or death was not significantly different for patients receiving icosapent ethyl (11.2%) compared with patients receiving placebo (13.7%; HR 084; P=0.17). Similarly, secondary outcomes did not display significant differences between the active arm and the placebo arm of the study. Dr Díaz explained that all outcome measures trended towards a benefit of icosapent ethyl. "If we conduct an even larger trial, we could establish whether icosapent ethyl has a role in the outpatient management of patients with COVID-19," argued Dr Díaz. Adverse events were equally divided across the study groups. However, more discontinuations were observed in the icosapent ethyl group (7.1%) than in the placebo group (3.8%).

1. Díaz R, et al. PREPARE IT-2: a pragmatic trial evaluating icosapent ethyl (IPE) in non-hospitalized patients with a positive diagnosis of COVID-19 to reduce hospitalization rates and complications. LBS06, AHA Scientific Sessions 2021, 13–15 November.
2. Bhatt DL, et al. N Engl J Med 2019;380:11–22.
3. Kosmopoulos A, et al. iScience 2021;24(9):103040.

Neutral effect of $P2Y_{12}$ inhibitors in non-critical COVID-19 hospitalisations

Treatment with $P2Y_{12}$ inhibitors for non-critically ill hospitalised patients with COVID-19 was not associated with a reduced number of organ support-free days or deaths in the phase 4 ACTIV-4A trial. The incidence of major bleeding events was low. $P2Y_{12}$ inhibitors are currently being evaluated in critically ill hospitalised patients with COVID-19 [1].

Prof. Jeffrey Berger (New York University Langone, NY, USA) highlighted that approximately 1 out of 4 non-critically ill hospitalised patients with COVID-19 treated with therapeutic-dose heparin dies or needs intensive care level support, demonstrating a clear need for additional therapies in this population. In addition, there is evidence that platelets are associated with thrombotic events, organ failure, and death in patients with COVID-19 [2–4]. Thus, the randomised, open-label ACTIV-4A trial (NCT04505774) investigated the efficacy and safety of $P2Y_{12}$ inhibitors in non-critically ill hospitalised patients with COVID-19. The study randomised 576 patients 1:1 to $P2Y_{12}$ inhibitors in addition to usual standard-of-care anticoagulation or standard-of-care anticoagulation alone, before the futility criterion was met. Participants in the experimental condition received either ticagrelor (60 mg twice daily) or clopidogrel (300 mg load, followed by 75 mg once daily). The primary endpoint was 21-day organ support-free days.

Participants in the $P2Y_{12}$ inhibitor condition showed numerically, but not significantly, lower rates of 21-day organ support-free days than patients in the control condition (OR 0.83). The calculated probabilities of futility and inferiority of additional $P2Y_{12}$ treatment were 96.2% and 81.4%, respectively. The results were consistent across pre-defined subgroups. In addition, there was a numerically higher proportion of participants with major thrombotic events or in-hospital deaths in the $P2Y_{12}$ inhibitor arm (6.1%) than in the standard-of-care arm (4.5%). The key safety endpoint analysis showed low major bleeding rates in participants treated with $P2Y_{12}$inhibitors (2.0%) and in those treated with usual care (0.7%).

Notably, there was a relatively long off-treatment period, due to the median 6-day treatment period and the 21-day endpoint. Moreover, participants received full-dose anticoagulation background therapies. This could explain why there was no (added) benefit observed for $P2Y_{12}$ inhibition in these patients. The evaluation of $P2Y_{12}$ inhibitors in critically ill hospitalised patients with COVID-19 is ongoing.

1. Berger JS, et al. P2Y12 Inhibitors in Non-Critically Ill Hospitalized Patients with COVID-19: A Randomized Clinical Trial. LBS07, AHA 2021 Scientific Sessions, 13–15 November.
2. Manne BK, et al. Blood. 2020;136(11):1317–1329.
3. Barrett TJ, et al. Science Advances. 2021;7(37).
4. Barrett TJ, et al. J Throb Hemost. 2021.

COVID-19 mRNA vaccination benefits outweigh the risk for myocarditis

COVID-19 mRNA vaccines are linked to an increased risk of myocarditis, especially in young males. However, the risk is small and mRNA vaccine-related myocarditis is predominantly mild and self-limited. The evidence to date shows that the benefits of vaccination outweigh the risks.

Prof. Biykem Bozkurt (Baylor College of Medicine Houston, TX, USA) discussed the evidence to date regarding COVID-19 vaccination and the occurrence of myocarditis [1]. Each year, 10–20 per 100,000 individuals are diagnosed with myocarditis, mostly affecting young males. Post-vaccination myocarditis has been reported as a rare event following smallpox, influenza, or other vaccinations [2].

Initial reports of myocarditis after COVID-19 mRNA vaccination demonstrated myocarditis rates of 1 in 100,000 vaccinated individuals [3]. The reported risk in young individuals (16–30 years) is higher, with approximately 1 case of myocarditis in 20,000 vaccinated individuals. Young males between 12 and 17 years appeared to have the highest risk of myocarditis after mRNA vaccination. Most cases occurred after administration of the second vaccine dose. Although most individuals needed hospitalisation, the symptoms were predominantly mild [2]. Notably, an analysis of data from the largest healthcare organisation in Israel found that the risk of acquiring myocarditis after vaccination (2.7/100,000) is smaller compared with the risk of SARS-CoV-2-related myocarditis (11/100,000) [4]. Moreover, other cardiac events, such as deep-vein thrombosis, myocardial infarction, pericarditis, and pulmonary embolism are increased in COVID-19. On 23 June 2021, the US Centers for Disease Control and Prevention (CDC) concluded that the benefits of vaccination outweigh the risks in all populations, including young males.

The suggested mechanisms underlying vaccine-related myocarditis include molecular mimicry between spike protein and self-antigens, a dysregulated immune response, auto-antibody production against cardiac proteins, and immunogenicity of RNA in certain individuals [2]. In clinical practice, most cases of post-vaccination myocarditis presented with chest pain 2–3 days after the second dose

was administered. They did not show particular comorbidities or a history of COVID-19. Elevated cardiac troponin and CRP levels were observed in most patients. Furthermore, ECGs and cardiac MR were often abnormal. Physicians should consider using ECG, cardiac troponin measurement, and cardiac MR if an individual presents with chest pain after COVID-19 vaccination. The medical treatment of mild post-vaccination myocarditis cases includes non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, steroids, and intravenous immunoglobulin [2].

In conclusion, the benefits of vaccination against SARS-CoV-2 outweigh the risks. Although there is a slightly increased risk of myocarditis after vaccination, especially in young males, the symptoms usually resolve in 4–5 days.

1. Bozkurt B. COVID-19 Vaccination and Cardiovascular Disease – Assessing the Evidence to Date. CS.ME.496, AHA 2021 Scientific Sessions, 13–15 November.
2. Bozkurt B, et al. Circulation. 2021;144(6):471–484.
3. Montgomery J, et al. JAMA Cardiol. 2021.
4. Barda N, et al. N Engl J Med. 2021;385:1078–1090.

Other

2021 Guideline for Chest Pain: Top 10 takeaways

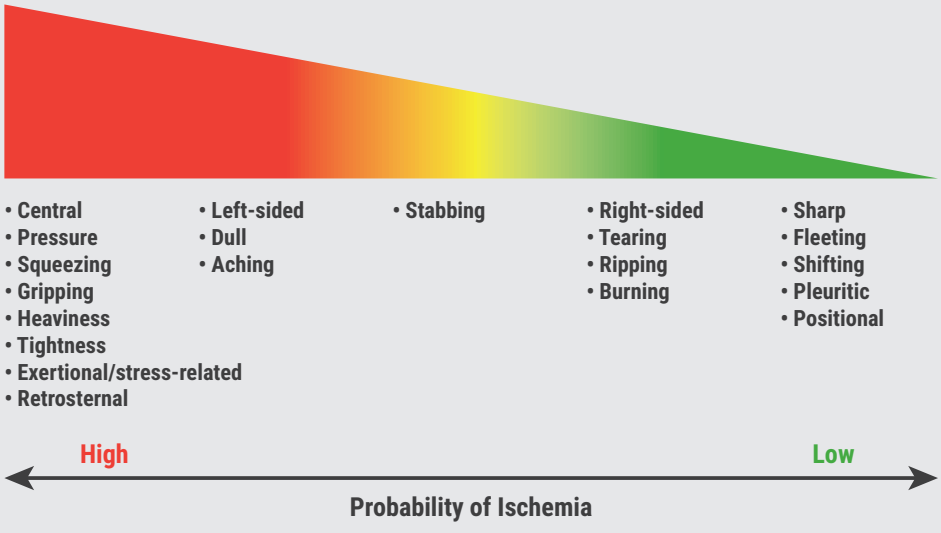
The top 10 takeaways of the new 2021 Guideline for the Evaluation and Diagnosis of Chest Pain were presented by Prof. Martha Gulati (University of Arizona, AZ, USA) [1]. "Since chest pain accounts for 6.5 million visits to the emergency department (ED) in the US each year, guidelines to manage chest pain are essential," Prof. Gulati stated. "Although only 5% of the chest pain is cardiac in nature, cardiac chest pain could entail life-threatening underlying disease. Therefore, cardiac chest pain is not to be missed during diagnosis."

Top 10 takeaways

1. Chest pain is more than pain in the chest. The shoulder area, jaw, epigastric area, neck, or back are included in the chest pain spectrum. Physicians should perform an initial assessment of chest pain to estimate the likelihood of symptoms being related to myocardial ischaemia (class 1) (see Figure).

2. High-sensitivity cardiac troponin (hs-cTn) enables swift detection or exclusion of myocardial injury. Thus, hs-cTn is the preferred biomarker in patients presenting with acute

Figure: Symptom presentation and probability of ischaemia [1]



chest pain (class 1). In addition, physicians need to be acquainted with the analytical performance and the 99th percentile upper reference limit that defines myocardial injury for the cTn assay at their facility (class 1).

3. Patients presenting with symptoms of life-threatening causes of acute chest pain need to be transported to the ED with urgency, ideally by emergency medical services (class 1). Patients with stable chest pain should receive an ECG, unless a non-cardiac cause is apparent (class 1).

4. In patients with acute chest pain and possible acute coronary syndrome (ACS) who have a low-risk profile, shared decision-making facilitates risk communication and increases understanding (class 1). Moreover, shared decision-making does not hamper outcomes.

5. Patients who present with acute or stable chest pain and have a low-risk profile do not need to be tested routinely (class 1). Prof. Gulati emphasised this recommendation as the most important one in the new guideline.

6. Patients with acute chest pain and possible ACS should be categorised in low-, intermediate-, and high-risk profiles by means of clinical decision pathways (CDPs) (class 1). Available clinical test results should be incorporated into the CDPs (class 1).
7. Women with chest pain are at risk for underdiagnosis. Thus, it is recommended to assess for accompanying symptoms that are more prevalent in women with ACS, such as shortness of breath and nausea (class 1).

8. Patients who are most likely to benefit from (further) testing should be identified. The chest guideline included CDPs to aid clinicians in the decision-making.

9. The description of chest pain as 'atypical' is not helpful. Instead, chest pain should be classified as cardiac, possibly cardiac, or non-cardiac, since these terms are more specific to the underlying diagnosis (class 1).

10. Finally, evidence-based diagnostic protocols should be used for the assessment of coronary artery disease and adverse events in patients with acute or stable chest pain, establishing a structured risk assessment.

1. Gulati M, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain. CS.ME.495, AHA 2021 Scientific Sessions, 13–15 November.

Accurate ejection fraction assessment in paediatric patients via artificial intelligence

A video-based, deep-learning model for the automated assessment of ejection fractions (EF) in paediatric cardiac patients neared human accuracy. Notably, the model delivered different results when trained on adults or paediatric patients, demonstrating the significant differences in EF assessment between these populations. Future efforts should be directed at clinical implementation and validation of the model in a broad paediatric population.

"Left ventricular function is assessed for diagnosis, screening, and treatment management in all of our paediatric patients," said Dr Charitha Reddy (Stanford Children's Health, CA, USA) [1]. She explained that human assessment of EF measurement is limited. "Since the guideline-recommended 3 separate cardiac cycles, that are needed to average the EF, are rarely measured in clinical practice due to time constraints, we need an alternative." According to Dr Reddy, deep-learning models have been developed to assess EF in adults but not in paediatric patients. "EF evaluation is different in young patients, due to increased frame rates, increased heart rates, and a wider range of body surface area in these patients," argued Dr Reddy.

The EchoNet-Dynamic, video-based, deep-learning model has been developed to assess EF in adult patients [2]. The current study investigated the assessment of EF in paediatric patients via this model. In total, 4,400 ECGs were collected from 1,923 cardiac patients under 18 years of age with structurally normal hearts. The training phase used 80% of the ECG, whereas 10% was utilised for validation, and 10% for testing. The input for the model consisted of apical 4 chamber (A4C) videos, parasternal short axis view (PSAX) videos, and a combination of both.

The EchoNet-Dynamic model showed excellent overlap with human measurement. The authors used a dice similarity coefficient to measure the similarity of 2 data sets, with values ranging from 0, no overlap, to 1, complete overlap. In this study, the values were 0.901 for A4C videos and 0.887 for PSAX videos. The model showed an R^{*2} of 0.78 in the prediction of EF for the combined input (A4C plus PSAX videos) in paediatric patients if the model used a paediatric dataset in the training phase. When the model used a paediatric dataset in assessing the EF in adult patients, it resulted in an R^{*2} of 0.33. This reflects the distinction between

assessing paediatric patients and adult patients. Notably, the model could estimate an EF 5/6 area length based on the input of only A4C or PSAX video.

Dr Reddy argued that the model should be validated in a broader paediatric dataset. Moreover, to protect the privacy of patients when applying deep-learning models in clinical practice, the utilisation of edge servers and federated models should be addressed.

1. He B, et al. Video-Based Deep Learning Model for Automated Assessment of Ejection Fraction in Pediatric Patients. CH.AOS.466, AHA 2021 Scientific Sessions, 13–15 November.
2. Ouyang D, et al. Nature. 2020;580:252–256.

Concomitant tricuspid annuloplasty reduces treatment failure in moderate tricuspid regurgitation

Tricuspid annuloplasty during mitral valve surgery (MVS) in patients with moderate or mild tricuspid regurgitation resulted in a decreased treatment failure compared with patients who did not receive tricuspid repair during MVS. However, an increased risk of permanent pacemaker implantation was observed in patients receiving tricuspid annuloplasty during MVS.

"It is common to perform tricuspid repair during MVS in patients with mitral regurgitation and severe TR. However, there is a large variability in clinical practice regarding the threshold for performing surgery in patients with mild or moderate tricuspid regurgitation," argued Prof. James Gammie (University of Maryland, MD, USA) [1]. Thus, the current trial investigated concomitant, undersized, rigid, non-planar tricuspid annuloplasty during MVS in patients with less than severe tricuspid regurgitation. Participants were randomised 1:1 to MVS alone (n=203) or MVS plus tricuspid annuloplasty (n=198). The primary endpoint was treatment failure at 2 years, defined as the composite of death, re-operation for tricuspid regurgitation, or tricuspid regurgitation progression from baseline.

At 2 years, treatment failure was reduced in the MVS plus tricuspid annuloplasty arm (3.9%) compared with the MVS alone arm (10.2%; RR 0.37; P=0.02). Subgroup analysis revealed that the difference in treatment failure between surgery groups was more pronounced in patients with moderate tricuspid regurgitation (18.1% vs 4.5%; RR 0.25; 95% CI 0.07–0.83) than in patients with less than moderate tricuspid regurgitation (6.1% vs 3.4%; RR 0.56; 95% CI 0.17–1.87). In addition, the effect was driven by tricuspid regurgitation progression from baseline and not by death or re-operation for tricuspid regurgitation. The proportion of participants with moderate or severe tricuspid regurgitation after 2 years of follow-up was higher in the MVS group (25.1%) than in the MVS plus tricuspid annuloplasty group (3.4%; RR 0.13; 95% CI 0.06-0.30). Notably, the risk of permanent pacemaker implantation was increased in the MVS plus tricuspid annuloplasty arm (14.1%) versus the MVS alone arm (2.5%). No difference was observed in all-cause mortality, quality of life, or major adverse cardiovascular or cerebrovascular events (MACCE).

Dr Gammie added that the 2-year endpoint may be too short to determine the long-term effects of tricuspid annuloplasty in this population. Thus, long-term follow-up is being performed to weigh the clinical benefits of this procedure against the cost of an increased risk of permanent pacemaker implantation.

1. Gammie JS, et al. Evaluating the benefit of concomitant tricuspid repair during mitral valve surgery. LBS01, AHA Scientific Session 2021, 13–15 November.