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PEER-REVIEWED CONFERENCE REPORT

STELLAR results for sotatercept in PAH

Adding the first-in-class sotatercept to standard pulmonary arterial hypertension (PAH) therapy led to significant improvements in exercise capacity and other endpoints in the placebo-controlled, phase 3 STELLAR trial.

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TAVR benefits durable versus surgical aortic valve replacement

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Bempedoic acid benefits statin-intolerant patients

The CLEAR Outcomes trial reports that treatment with bempedoic acid effectively reduced LDL and the risk of major adverse cardiovascular events among statin-intolerant patients.

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

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Letter from the Editor

Dear colleagues,

Thank you for your interest in this edition of Medicom's Conference Report covering the American College of Cardiology Scientific Session occurring in New Orleans, USA, in March of 2023. This year's meeting was filled with late-breaking clinical trials, innovative science and new developments in structural cardiology.

In the following pages, you can read about outcomes from latest clinical trials, including new advances in lipid lowering therapy such as improved outcomes with bempedoic acid in the landmark CLEAR OUTCOMES trial and new encouraging data for oral PCSK9 inhibitors. Late-breaking data were also presented for sotatercept showing improved outcomes in patients with pulmonary hypertension. In addition, new data regarding catheter-based therapies for mitral and tricuspid valve disease as well as data on the durability of TAVR were presented. As always, our summaries are written independently and are peer-reviewed for balance. We hope you find this edition informative, engaging, and balanced and thank you again for your readership.

Sincerely,
Marc 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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Pulmonary Arterial Hypertension

Sotatercept improves exercise capacity in patients with PAH

Adding the novel, first-in-class sotatercept to background pulmonary arterial hypertension (PAH) therapy led to significant and clinically relevant improvements in exercise capacity and other endpoints in the placebo-controlled, phase 3 STELLAR trial.

Sotatercept is a fusion protein that traps activins and growth differentiation factors involved in PAH. The first of 3 phase 3 trials evaluating this novel agent is the multicentre, randomised, double-blind, parallel-group STELLAR study (NCT04576988) [1,2]. The study, presented by Prof. Marius Hoeper (Hannover Medical School, Germany), included adults with PAH (WHO functional class II or III) on stable background therapy. Their mean age was 48 years, and 79% were women. They were randomised 1:1 to subcutaneous sotatercept (starting dose 0.3 mg/kg; target dose 0.7 mg/kg; n=163) or placebo (n=160) every 3 weeks. The primary endpoint was the median change from baseline at week 24 in the 6-minute walk distance (6MWD) test.

At 24 weeks, the observed change in the placebo group was -1.4 metres (95% CI -13.2 to 10.3) and 40.1 metres (95% CI 29.9–50.2) in the sotatercept group. The Hodges–Lehmann estimate of the difference between the 2 groups was 40.8 metres (95% CI 27.5–54.1; P<0.001). This exceeded the minimum of 33 metres that, according to earlier research, patients experienced as a noticeable improvement in their walking capacity, Prof. Hoeper said. From the 9 secondary endpoints, ranging from pulmonary vascular resistance to patient-reported symptoms, 8 were significantly improved with sotatercept versus placebo, including 2 of 3 domain scores of the Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) questionnaire. Prof. Hoeper stressed: "We also saw a decline in the exploratory endpoint of least-squares mean pulmonary artery pressure of 13.9 mmHg, which we have never seen before with any add-on therapy used for PAH."

After a mean follow-up of 32.7 weeks, the number of patients who died or experienced at least 1 clinical worsening event was 42 (32.9%) in the placebo group and 9 (5.5%) in the sotatercept group, which equals a relative risk reduction of 84% (95% CI 0.08–0.35; P<0.001). Sotatercept was generally well-tolerated. Adverse events, such as bleeding events (31.9% vs 15.6%), telangiectasia (14.1% vs 3.8%), increased haemoglobin levels (6.1% vs 0%), and epistaxis (20.2% vs 1.9%), were more common in the sotatercept group.

"These results establish the clinical utility of sotatercept as a new approach to the treatment of PAH in combination with existing approved therapies," Prof. Hoeper concluded. He expects these results to cause a paradigm shift in the treatment of PAH.

1. Hoeper MM, et al. The STELLAR Phase III Trial: A Study Of Sotatercept In Combination With Background Therapy For The Treatment Of Pulmonary Arterial Hypertension. Session 410-14, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.
2. Hoeper MM, et al. New J Engl Med 2023; March 6. DOI: 10.1056/NEJMoa2213558.

Fixed-dose macitentan plus tadalafil superior to either agent alone in PAH

Fixed-dose combination therapy with macitentan 10 mg daily + tadalafil 40 mg daily was superior to either agent as monotherapy in reducing pulmonary vascular resistance (PVR) at 6 weeks in patients with pulmonary arterial hypertension (PAH). This was the main finding of the phase 3 A DUE trial.

Macitentan 10 mg daily + tadalafil 40 mg is already recommended by most guidelines as a combination therapy in patients with newly diagnosed PAH and most patients at follow-up [1,2]. A fixed-dose combination as a single tablet could improve adherence and simplify treatment. The prospective, randomised, adaptive A DUE trial (NCT03904693) sought to confirm the safety and efficacy of macitentan 10 mg/tadalafil 40 mg daily as a fixed-dose combination by comparing it with macitentan and tadalafil monotherapies [3].

First author Prof. Kelly Chin (UT Southwestern Medical Center, TX, USA) explained that 187 treatment-naïve adult patients with PAH in WHO functional class II or III were enrolled. They had to be on a stable dose of an endothelin receptor antagonist (ERA) or a phosphodiesterase 5 inhibitor (PDE5i) for ≥3 months. The mean age was 51 years, 78% were

women, and 50% had idiopathic pulmonary hypertension. The participants were randomised depending on their baseline therapy:

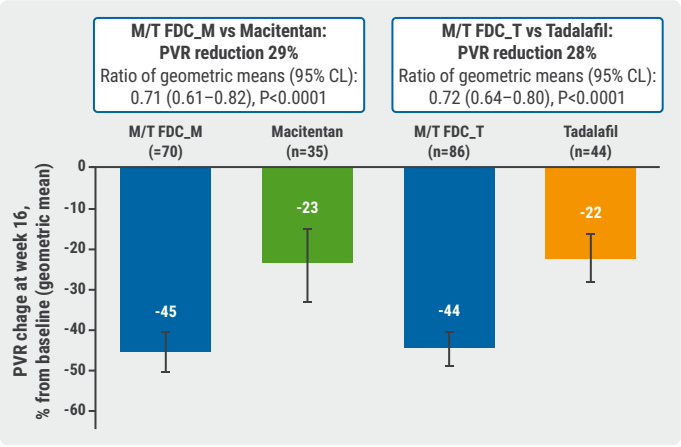
- Treatment-naïve participants were randomised 1:2:1 to macitentan 10 mg daily monotherapy, fixed-dose combination, or tadalafil 40 mg daily.
- Participants who were on an ERA (prior-ERA) were randomised 1:2 to macitentan 10 mg daily monotherapy or fixed-dose combination.
- Participants using a PDE5i (prior-PDS5i) were randomised to tadalafil 40 mg daily monotherapy or fixed-dose combination.

All in all, 35 patients received macitentan, 44 tadalafil, and 108 fixed-dose macitentan + tadalafil.

After a follow-up of 16 weeks, fixed-dose macitentan + tadalafil had led to a highly significant improvement in PVR compared with macitentan and tadalafil monotherapies, said Prof. Chin (see Figure).

A trend was observed in favour of fixed-dose macitentan + tadalafil for clinically relevant improvement in 6-minute walking distance (6MWD) after 16 weeks, which was the secondary endpoint. The change in 6MWD versus macitentan monotherapy was 16.04 metres (95% CI 17.00 to 49.08; P=0.380); the change versus tadalafil monotherapy was 25.37 metres (95% CI -0.93 to 51.59; P=0.059). The nature and rate of adverse events (AEs) were as expected

Figure: Change in PVR from baseline at week 16 [3]



M/T FDC_M, fixed-dose macitentan + tadalafil (n=70; prior-ERA users n=21, treatment-naïve n=49); M/T FDC_T, fixed-dose macitentan + tadalafil (n=86; treatment-naïve n=49, prior-PDE5i n=36).

based on previous studies. Prof. Chin noted that there was a greater number of total and serious AEs in the fixed-dose macitentan + tadalafil groups, which was also in line with previous studies.

"A DUE supports fixed-dose macitentan + tadalafil as a single tablet for initial dual combination therapy and rapid escalation in PAH," Prof. Chin concluded.

1. Humbert M, et al. Eur Heart J. 2022;43(38):3618–731.
2. Humbert M, et al. Eur Respir J. 2023;61(1):2200879.
3. Chin K, et al. Efficacy and safety of macitentan tadalafil fixed dose combination in pulmonary arterial hypertension: Results from the randomized controlled phase III A DUE study. Session 409-14, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Coronary Revascularisation

Immediate complete revascularisation non-inferior to staged complete revascularisation

In patients with acute coronary syndrome (ACS) and multivessel coronary disease, an immediate complete revascularisation strategy was non-inferior to staged complete revascularisation for the composite primary outcome in the BIOVASC trial. Furthermore, it was associated with lower rates of myocardial infarction (MI) and unplanned ischaemia-driven revascularisation at 1-year follow-up.

This was the overall conclusion from the results of the randomised BIOVASC trial (NCT03621501), which were presented by Dr Roberto Diletti (Erasmus MC, the Netherlands) [1,2]. He explained that multiple studies have established the clinical benefit of complete revascularisation by percutaneous coronary intervention (PCI) compared with a culprit lesion-only PCI. The BIOVASC study aimed to establish the optimal timing for non-culprit lesion revascularisation. Enrolled were 1,525 patients from 4 European countries, who were randomised to immediate revascularisation

(n=764) or staged complete revascularisation (n=761). Of the participants, 40% had ST-segment elevation myocardial infarction (STEMI), 52% had non-STEMI, and 8% had unstable angina. The primary outcome was a composite of all-cause mortality, MI, any unplanned ischaemia-driven revascularisation, or cerebrovascular events in the first year following the procedure.

In the immediate treatment group, 7.6% had a primary endpoint event at 1 year versus 9.4% in the staged group, meeting the non-inferiority criteria (HR 0.78; $P_{non\text{-}inferiority}$ =0.0011). However, in the prespecified analysis of clinical events at 30 days, immediate complete revascularisation was superior (2.2% vs 5.8%; HR 0.38; $P_{superiority}$ =0.0007).

After 1 year, no difference was seen in all-cause death between the 2 groups (1.9% vs 1.2%; HR 1.56; P=0.30), but a second MI was less frequent in the immediate treatment group (1.9% vs 4.5%; HR 0.41; P=0.0045), as were unplanned ischaemia-driven revascularisations (4.2% vs 6.7%; HR 0.61; P=0.030).

Dr Diletti offered 2 possible explanations for the high rate of MIs in the staged group (4.5%). The operator may have misjudged the culprit lesion, or there are more unstable plaques so treating only the culprit lesion "does not do the job."

1. Diletti R, et al. Complete revascularization strategies in patients presenting with acute coronary syndromes and multivessel coronary disease. Session 405-16, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.
2. Diletti R, et al. The Lancet. 2023; March 5. DOI: 10.1016/S0140-6736(23)00351–3.

RENOVATE-COMPLEX-PCI results support intravascular-guided PCI for complex lesions

The randomised RENOVATE-COMPLEX-PCI trial showed that percutaneous coronary intervention (PCI) guided by intravascular imaging for complex coronary artery lesions was associated with a lower risk of death than angiography-guided PCI.

RENOVATE-COMPLEX-PCI (NCT03381872) was an investigator-initiated, prospective, randomised, open-label trial at 20 sites in South Korea [1]. The participants had coronary artery disease requiring PCI and had a complex coronary artery lesion. They were randomised 2:1 to undergo either intravascular imaging–guided PCI or angiography-guided PCI. For patients in the intravascular imaging group, the choice between intravascular ultrasonography (IVUS) and optical coherence tomography (OCT) was made at the operators' discretion. Intravascular imaging could be used at any time during the PCI procedure but was mandatory after stent implantation. The primary endpoint was a composite of death from cardiac causes, target vessel-related myocardial infarction (MI), or clinically-driven target vessel revascularisation (TVR).

The results after a median follow-up of 2.1 years were presented by Prof. Joo-Yong Hahn (Sungkyunkwan University School of Medicine, South Korea). Of the 5,586 assessed patients, 1,639 were randomised to intravascular imaging-guided PCI (n=1,092) or angiography-guided PCI (n=547). The median age was 66 years, and 21% of the participants were women. The primary endpoint was met by 7.7% of patients in the intravascular imaging group and by 12.3% in the angiography group (HR 0.64; 95% C 0.45–0.89; P=0.008): a statistically significant difference. Target vessel failure excluding procedural MI was seen in 8.7% and 5.1% of patients, respectively (HR 0.59; 95% CI 0.39–0.90; P=0.008).

Cardiac death occurred in 1.7% and 3.8% of participants in the intravascular imaging group and angiography group (HR 0.47; 95% CI 0.24–0.93), and target vessel-related MI in 3.7% and 5.6% (HR 0.74; 95% CI 0.45–1.22), respectively. The incidence of TVR was not significantly different: 3.4% and 5.5%, respectively (HR 0.69; 95% CI 0.40–1.18). Prof. Hahn added that in a prespecified subanalysis, between-group differences were consistent across various subgroups, including the type of imaging device, initial presentation, and diabetes. No differences were observed in the safety of both procedures.

Prof. Hahn concluded that "the results support the use of intravascular imaging-guided PCI in patients with complex coronary lesions."

1. Hahn J-Y, et al. Intravascular imaging-guided versus angiography-guided procedural optimization in complex percutaneous coronary intervention. Session 405-10, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Heart Failure and Cardiomyopathy

No need to restrict vigorous exercise in selected HCM patients?

Patients with hypertrophic cardiomyopathy (HCM) who engaged in vigorous exercise did not experience an increased risk of death, cardiac arrest, appropriate ICD shocks, or arrhythmic syncope compared with patients who engaged in low-to-moderate exercise. Overall event rates in the LIVE-HCM trial were low, with <5% experiencing the composite endpoint over 3 years.

Vigorous exercise for people with HCM is often restricted because of the perceived risk of ventricular arrhythmia and sudden death. However, no prospective, comparative data has been published on the consequences of vigorous exercise for HCM patients. Therefore, a consortium of 42 medical centres in the US, UK, Canada, Australia, and New Zealand (i.e. the LIVE consortium) set up the LIVE-HCM study [1]. Prof. Rachel Lampert (Yale School of Medicine, CT, USA) explained that they wanted to know whether vigorous exercise, including competitive sports, is associated with an increased risk for life-threatening ventricular arrhythmia or mortality in HCM patients.

Inclusion criteria were a diagnosis of HCM or genotype+ (i.e. phenotype-negative patients with a genetic variant for HCM but without left ventricular hypertrophy). Exclusion criteria were conditions precluding exercise (including NYHA Class III or IV); syndromic, infiltrative disease; and the inability to complete questionnaires. The study enrolled 1,534 patients with HCM between 8 and 60 years old in 5 countries; 20% were younger than 25 years and 40% were women. The participants were followed prospectively for 3 years. Their exercise habits and symptoms were surveyed every 6 months and classified as vigorous (42% of participants), moderate (43%), or sedentary (16%). The primary endpoint was a composite of death, resuscitated cardiac arrest, syncope (i.e. definitely or likely arrhythmic or undetermined), and appropriate shock from an implantable cardioverter defibrillator.

In the primary analysis, the composite endpoint was met by 77 participants: 33 in the vigorous exercise group versus 44 in the non-vigorous exercise groups (HR 1.01; 90% CI 0.68–1.48; P=0.98). The corresponding rate per 1,000 person-years was 15.3 (95% CI 11.4–20.5) in the vigorous group versus 15.9 (95% CI 11.3–22.4) in the non-vigorous groups. Event rates were similar for between-group comparisons of individual endpoints, but these events did not occur frequently enough to allow for meaningful comparison.

Secondary/post-hoc analyses compared the incidence of the composite endpoint in vigorous versus sedentary participants (HR 0.77; 90% CI 0.45–1.30; P=0.41); moderate versus sedentary participants (HR 0.69; 95% CI 0.40–1.16; P=0.24); and vigorous versus moderate participants (HR 1.12; 95% CI 0.73–1.71; P=0.66). All events occurred in participants with overt HCM and none in carriers of the genetic variant. Participating in high-intensity competitive sports did also not increase the risk.

Prof. Lampert concluded that the study results of the LIVE-HCM trial do not support a universal restriction of vigorous exercise in patients with HCM.

1. Lampert RJ. Vigorous exercise in individuals with hypertrophic cardiomyopathy (HCM): Primary results of the prospective, multinational Lifestyle And Exercise In HCM (LIVE-HCM) Study. Session 410-08, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

No difference in CV outcomes between PET or CMR and SPECT

The AIMI-HF trial found no significant advantage of advanced imaging modalities with PET or CMR compared with SPECT on a cardiovascular (CV) composite in patients with heart failure (HF) due to ischaemic heart disease. However, in a subgroup of patients evaluated for ischaemia, an advanced imaging strategy may be associated with a reduction in CV death.

Prof. Lisa Mielniczuk (University of Ottawa, Canada), who presented the results, said that the role of revascularisation in patients with HF due to underlying ischaemic heart disease remains subject to debate [1]. The overall objective of the pragmatic AIMY-HF (NCT01288560) was to determine the impact of advanced imaging modalities with PET or CMR compared with SPECT on a CV composite of cardiac death, myocardial infarction (MI), resuscitated cardiac arrest, and cardiac hospitalisation.

Enrolled participants had HF with reduced ejection fraction (HFrEF) and suspected or known coronary artery disease. Participants were first evaluated for either the burden of their ischaemia or existing evidence of myocardial viability. Then 271 participants from 15 sites were randomised to advanced (CMR or PET) or standard (SPECT) imaging modalities, depending on availability at their site. An additional registry arm was created (n=1,110) to enhance the study's power and to allow patients to be included who could not be randomised, either due to contraindication or clinician preference. The primary outcome was time to CV composite. Of the 1,381 participants, 672 had ischaemia as the primary clinical question and 709 myocardial viability. The advanced imaging group had 1,069 patients, and the SPECT group included 312. The median follow-up was 24.1 months.

In the total study population, the cumulative incidence of the primary composite outcome occurred in 31% and 35% of patients undergoing CMR or PET and SPECT, respectively. The difference was not statistically significant (HR 0.95; 95% CI 0.71–1.25; P=0.696). In the ischaemia cohort, the difference did not reach statistical significance either (HR 0.86; 95% CI 0.61–1.21; P=0.388). Prof. Mielniczuk added that there was a marginally significant reduction in cardiac death in the PET arm of the ischaemia cohort versus the SPECT arm (HR 0.61; 95% CI 0.38–1.00; P=0.05).

Turning to the randomised patients, no difference was observed in the primary composite outcome either, occurring in 28% in the CMT or PET group versus 30% in the SPECT group (HR 0.88; 95% CI 0.55–1.43; P=0.662). There was also no significant difference in cardiac death.

In the total population, patients in the advanced imaging group were more likely to undergo revascularisation (P<0.0001), with 61% undergoing revascularisation via CABG. Although not reaching statistical significance, a trend was observed toward benefit for patients who underwent revascularisation after CMT or PET imaging.

Prof. Mielniczuk concluded that the imaging strategy was not associated with a difference in CV outcomes in patients with HF. Whether an advanced imaging modality is associated with a reduction in CV death compared with SPECT would need to be evaluated in future studies.

1. Mielniczuk L. Ischemia and viability imaging in heart failure: The alternative imaging modalities in ischemic heart failure trial. Session 403-12, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Interventional and Structural Cardiology

Benefits of MitraClip sustained to 5 years in COAPT trial

After 5 years, results of the COAPT study showed that transcatheter edge-to-edge repair (TEER) procedures using a transcatheter clip device to reduce mitral regurgitation (MR) was safe and led to a lower rate of hospitalisation for heart failure (HF) and lower all-cause mortality than medical therapy alone in patients with severe HF.

COAPT (NCT01626079) randomised 614 patients with HF with a very specific background: they had moderate-to-severe (3+) or severe (4+) secondary MR and remained symptomatic despite maximally-tolerated guideline-directed medical therapy (GDMT). The participants were randomised 1:1 to MR correction with the MitraClipTM device (n=302) or to GDMT alone (n=312). "At 2 years, the MitraClip led to a substantial reduction in HF hospitalisations and improved survival and quality of life compared with maximally-tolerated GDMT alone," said lead author Prof. Gregg Stone (Icahn School of Medicine at Mount Sinai, NY, USA) [1,2]. As per protocol, subjects randomised to GDMT were allowed to cross over to the MitraClip only after 2 years.

At 5 years of follow-up, the positive effect on the primary endpoint of all HF hospitalisations was sustained in the device group [1]. There had been 314 HF hospitalisations among 151 patients in the device group versus 447 among 208 patients in the control group, yielding an annualised hospitalisation rate of 33.1% and 57.2%, respectively (HR 0.53; 95% CI 0.41–0.68; P<0.001).

The secondary composite endpoint of death or HF hospitalisation was reached by 73.6% in the device group versus 91.5% in the control group (HR 0.53; 95% CI 0.44–0.64; P<0.001). This result was consistent in all prespecified subgroups. All-cause mortality was 57.3% in the device group and 67.2% in the control group (HR 0.72; 95% CI 0.58–0.89; P<0.001). Symptomatic status (NYHA class) in the device group was also improved throughout the 5-year follow-up, and MitraClip treatment provided durable repair of mitral regurgitation.

Prof. Stone said the difference in mortality originated from the first 2 years. "We believe the lack of divergence in the last 3 years is largely explained by the effect of cross over from the control to the device group." Of 138 surviving patients in the control group, 62 (45.9%) elected to cross over to undergo TEER. The prognosis of this cross-over group was substantially improved, similar to that of patients originally assigned to device treatment. "However, nearly half of the control group had died before becoming eligible for cross over at 2 years," noted Prof. Stone. "HF patients appropriate for TEER with the MitraClip should therefore be identified and considered for treatment as early as possible."

1. Stone GW, et al. Transcatheter Edge-to-edge Repair Of Functional Mitral Regurgitation In Heart Failure: Final Five-year Results From The COAPT Trial. Session 405-12, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.
2. Stone GW, et al. N Engl J Med 2018;379:2307–2318.

Transcatheter repair for patients with tricuspid regurgitation

Tricuspid transcatheter edge-to-edge repair (TEER) reduced the severity of tricuspid regurgitation (TR) at 1 year and was associated with an improved quality of life in patients with severe tricuspid regurgitation. These were the main findings of the prospective, randomised TRILUMINATE trial.

TRILUMINATE (NCT03904147) was designed to evaluate the safety and effectiveness of medical therapy alone or percutaneous TEER the TriClipTM G4 Delivery System for severe TR usage [1]. First author Dr Paul Sorajja (Minneapolis Heart Institute, MI, USA) said over 450 participants had thus far been enrolled at 65 centres in the USA, Canada, and Europe; he went on to present the main results of the first 350 patients [2]. Key inclusion and exclusion criteria are shown in the Table.

Table: Enrolment criteria of the TRILUMINATE trial. Derived from [2]

Key inclusion criteria	Key exclusion criteria
• Severe symptomatic TR	• Indication for other valve disease intervention
• Stable GDMT and/or device therapy for heart failure for ≥30 days	• Severe pulmonary HTN
• ≥ Intermediate risk of mortality/ morbidity with tricuspid valve surgery	• Left ventricular ejection fraction ≤20%
	• Anatomy not suitable for TriClip therapy

GDMT, guideline-directed medical therapy; HTN, hypertension.

The participants were randomly assigned to TEER (n=175) or medical therapy (n=175). The mean age was 78 years, and 54.9% were women. The primary endpoint was a composite assessed hierarchically of all-cause death or the number of participants with tricuspid valve surgery, hospitalisation for HF, and quality of life improvement assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 1 year. The secondary endpoints were: 1) freedom from major adverse events (MAE) after procedure attempt at 30 days (in the experimental group only); 2) change in quality of life as measured with the KCCQ; 3) TR reduction to moderate or less at 30 days; 4) change in 6-minute walking distance (6MWD) at 1 year.

The results for the primary endpoint favoured the TEER group (win ratio 1.48; 95% CI 1.06–2.13; P=0.02). Dr Sorajja noted that this result was driven mainly by the improvement in quality of life. The incidence of death or tricuspid-valve surgery and hospitalisation for heart failure in both groups were similar. The KCCQ score improved by a mean (±SD) of 12.3±1.8 points, as compared with 0.6±1.8 points in the control group (P<0.001). TR was reduced by TEER to moderate or less in 87% of patients compared with only 4.8% in the control group; this reduction was sustained for 1 year of follow-up. The degree of TR reduction was related to the degree of improvement in quality of life. The 30-day MAE rate was only 1.7%; death and pacemaker implant both occurred in 0.6%. Survival without valve surgery was high at 1 year in both groups: around 90%.

"These results are very meaningful for a highly symptomatic population whose quality of life is impacted by TR," said Dr Sorajja. "With the excellent benefit-to-risk ratio of the TriClip system, a historically untreated population will have a treatment option to improve their quality of life."

1. Sorajja P, et al. N Engl J Med 2023; Mar 4. DOI: 10.1056/NEJMoa2300525.
2. Sorajja P, et al. Triluminate pivotal: A landmark randomized clinical trial of transcatheter tricuspid valve edge-to-edge repair for tricuspid regurgitation. Session 402-08, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Durable benefits of TAVR versus surgical aortic valve replacement in aortic stenosis patients

The 3-year results of the Evolut Low Risk trial demonstrated durable benefits of transcatheter aortic valve replacement (TAVR) compared with surgery among low-risk patients with aortic stenosis. The absolute difference remained consistent after 3 years, with a 30% relative reduction in the risk of death or disabling stroke.

TAVR has been FDA-approved for patients with aortic stenosis of all surgical risk levels since 2019 and has now surpassed surgical AVR (SAVR) in procedural volumes in the USA, said Prof. John Forrest (Yale Medicine, CT, USA) [1]. The 2-year outcomes of the randomised, multicentre Evolut Low Risk trial (NCT02701283) showed that TAVR for the treatment of severe symptomatic aortic stenosis in low-risk patients was non-inferior to surgery for the primary endpoint of all-cause death or disabling stroke [2]. Prof. Forrest presented the 3-year clinical and echocardiographic outcomes from the Evolut Low Risk trial.

The participants of the Evolut Low Risk trial had severe aortic stenosis with a low risk of death from surgery (>3%). Patients with bicuspid aortic valves were excluded. Between 2016 and 2019, 1,414 patients were randomised to TAVR with a self-expanding, supra-annular valve (n=730) or surgery (n=684). The participants had a mean age of 74 years and 35% were women.

At 3 years, the primary endpoint of all-cause mortality or disabling stroke had occurred in 7.4% of the TAVR group and 10.4% of the surgery group. At 30 days, the difference between treatment arms was already -1.8%, and this remained broadly consistent over time (see Figure). All-cause mortality was 6.3% for TAVR and 8.3% for surgery ($P_{log\text{-}rank}$=0.16). The respective percentages for disabling stroke were 2.3 and 3.4 ($P_{log\text{-}rank}$=0.19).

Mild paravalvular regurgitation (20.3% TAVR vs 2.5% surgery) and pacemaker placement (23.2% TAVR vs 9.1% surgery; P<0.001) were less frequent in the surgery group compared with TAVR. Rates of moderate or greater paravalvular regurgitation for both groups were <1%. The TAVR group showed significantly improved valve haemodynamics, with a mean gradient of 9.1 mmHg compared with 12.1 mmHg in the surgery group (P<0.001).

Prof. Forrest concluded that "the excellent valve performance and durable outcomes up to 3 years affirm the role of TAVR with the Evolut valve in this low-risk population."

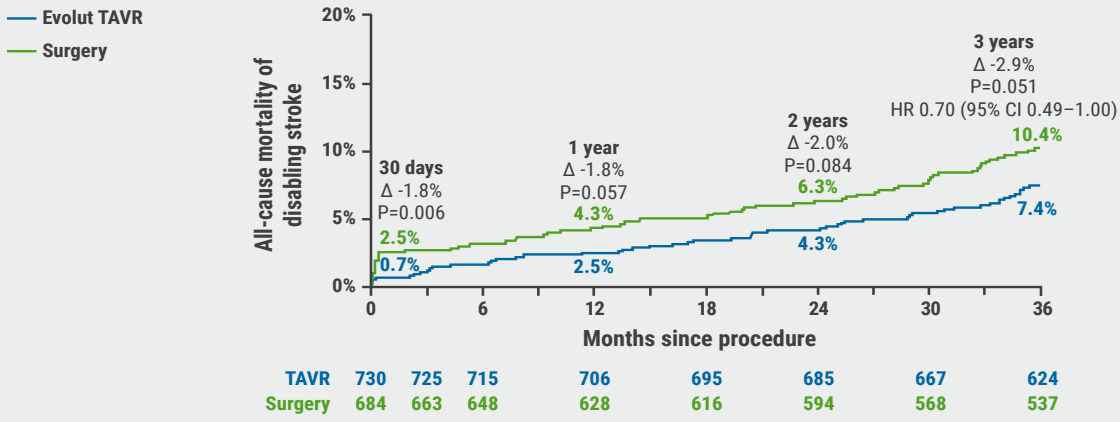
1. Forrest J, et al. Transcatheter versus surgical aortic valve replacement in aortic stenosis patients at low surgical risk: 3-year outcomes from the Evolut Low Risk trial. Session 405-14, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.
2. Forrest JK, et al. J Am Coll Cardiol. 2022;79(9):882–896.

Minimally invasive versus conventional sternotomy for mitral valve repair

The best surgical approach for mitral valve repair is subject to wide debate. Findings from the randomised UK Mini Mitral trial showed similar improvement in patients undergoing minimally invasive or conventional surgical techniques for mitral valve repair in physical activity, surgical outcomes, and quality of life.

Dr Enoch Akowuah (James Cook University Hospital, UK) presented the results of the first multicentre, randomised controlled trial comparing 2 surgical approaches to mitral valve repair [1]. The UK Mini Mitral trial (ISRCTN13930454) screened 1,167 patients and enrolled 330 patients with severe degenerative mitral regurgitation from 10 centres in the UK. The mean age was 67 years, 29% were women, and 40% had atrial fibrillation. They were randomised 1:1 to mitral valve repair by sternotomy or mini-thoracotomy.

Figure: Primary endpoint of all-cause mortality or disabling stroke [1]



Surgeons had to have completed at least 50 procedures, and expertise-based randomisation was performed to account for the learning curve. The primary endpoint was a change in physical functioning and post-surgery return to daily activities, measured by the change in score on the 36-item short form (SF-36v2) physical functioning scale, from baseline to 12 weeks post-procedure.

At 12 weeks, no significant difference was seen between groups for the primary outcome of SF-36v2: mini-mitral valve repair 43.12 ±10.13 versus sternotomy 41.75 ±10.68; mean score difference 0.675 (95% CI -1.89 to 3.26; P=0.61). However, after 6 weeks, physical function had improved in the mini-thoracotomy group but not yet in the sternotomy group. The repair rate was high: 96% in both groups.

Dr Akowuah called the echocardiographic outcomes at 1 year excellent (93% mild MR or less). The length of hospital stay was shorter in the mini-thoracotomy group than in the sternotomy group, with a median of 5 versus 6 days. Early discharge was more than twice as likely in the mini-thoracotomy group. In this group, days alive and out of hospital were also more numerous at 30 days (difference 1.05; P=0.03) as well as at 90 days (1.03; P=0.03). Quality-of-life outcomes favoured the mini-thoracotomy at all time points. Rates of death, hospitalisation for heart failure, and reintervention on the mitral valve at 1 year were similar and low.

1. Akowuah E, et al. Minimally invasive versus conventional sternotomy for mitral valve repair surgery: an expertise based multicentre randomised controlled trial (UK Mini Mitral). Session 405-08, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

PCI not better than GDMT in severe ischaemic cardiomyopathy

Coronary revascularisation with multivessel percutaneous coronary intervention (PCI) failed to show additional survival benefit beyond guideline-directed medical therapy (GDMT) alone in patients with severely impaired left ventricular function and extensive coronary artery disease (CAD), according to results from the REVIVED-BCIS2 trial.

The secondary study of the REVIVED-BCIS2 trial (NCT01920048) set out to test 4 hypotheses, namely (1) that viability characterisation predicts event-free survival; (2) that this characterisation predicts left ventricular (LV) recovery; (3) that it can predict response to PCI or medical therapy; and (4) that LV recovery predicts event-free survival.

Prof. Divaka Perera (King's College London, UK) explained that viability was assessed in 2 directions: as potential for recovery (n=610), and as presence of scar tissue (n=478) [1].

The 700 participants had a left ventricular ejection fraction (LVEF) of ≤35% and extensive coronary disease (British Cardiovascular Intervention Society Jeopardy Score ≥6) and viability in ≥4 dysfunctional myocardial segments. They were randomised to multivessel PCI (n=347) or GDMT (n=353). The mean age was 70 years, 13% were women, and 39% had diabetes. The duration of follow-up was 3.4 years.

Looking at all-viable myocardium, including all the normal segments, patients with a higher LVEF had a lower risk of all-cause mortality or heart failure hospitalisation (adjusted HR per 10% increase in viable myocardial volume: 0.93; 95% CI 0.87–1.00; P=0.048). In patients with a dysfunctional-yet-viable myocardium at baseline, this interaction was not present (adjusted HR per 10% increase in volume 0.98; 95% CI 0.93–1.04; P=0.56).

In patients with scar burden, the adjusted HR per 10% increase in scar volume was 1.18 (95% CI 1.04–1.33; P=0.009), a "highly significant" result. Furthermore, no impact was seen of viability assessment (i.e. abundance of dysfunctional-yet-viable segments or scar burden) on the effect of PCI versus GDMT (all P values were non-significant). Lastly, reverse LV remodelling (≥4.7%) lowered the incidence of all-cause death or heart failure hospitalisation versus no remodelling (HR 0.62; 95% CI 0.41–0.95; P=0.029).

Prof. Perera concluded that assessing viability characteristics at baseline does not allow for the selection of patients with ischaemic cardiomyopathy who will benefit more from PCI than from GDMT alone. "We also found that the abundance of dysfunctional-yet-viable segments was not associated with prognosis or likelihood of LV recovery. This result is perhaps surprising as it challenges the idea of hibernation." However, characterising the myocardium in terms of scar burden is highly predictive of LV recovery, independent of baseline LVEF or the extent of CAD. "In fact, if you were to correct LVEF for scar burden, it is no longer associated with outcome or early recovery." Finally, this trial confirmed that an improved LVEF improves prognosis.

1. Perera D, et al. Effect Of Myocardial Viability, Percutaneous Coronary Intervention And Functional Recovery On Clinical Outcomes In The REVIVED-BCIS2 Randomized Trial. Session 403-10, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Prevention

Statins associated with reduced heart dysfunction from anthracyclines

The STOP-CA trial results suggest that statins may be cardioprotective in patients receiving chemotherapy with anthracyclines for lymphoma. The participants in this phase 2, multicentre, randomised trial were significantly less likely to experience heart dysfunction after taking atorvastatin for 1 year.

Each year, over 1 million cancer patients worldwide are treated with anthracyclines such as doxorubicin, epirubicin, and idarubicin. Prof. Tomas Neilan (Massachusetts General Hospital, MA, US) pointed out that these agents have been known to be cardiotoxic [1]. Patients treated with anthracyclines have a 10 to 15-fold increased risk of heart failure. Prof. Neilan explained the choice to include lymphoma patients in STOP-CA (NCT02943590) by the high survival rate, which renders the impact of late toxicities of added importance.

The study enrolled 300 patients with lymphoma scheduled to receive treatment with an anthracycline at a median dose of 300 mg/m^2. The median age was 52 years, and 47% were women. The participants were randomised to atorvastatin 40 mg daily or a matching placebo, starting before their first dose of anthracyclines and continuing for 1 year. The study's primary endpoint was the proportion of participants with a decline in left ventricular ejection fraction (LVEF) of ≥10% to a final value of <55% after 1 year.

The study was completed by 286 patients (95%). Adherence to atorvastatin was documented in >90%. At baseline, the LVEF was 63% across the cohort; after 1 year it was 58%. The LVEF decreased by 4.1% in the atorvastatin group and by 5.4% in the placebo group. The primary endpoint occurred in 9% of the atorvastatin group and 22% of the placebo group (P=0.002). The odds of a ≥10% decline in LVEF to <55% after anthracyclines was almost 3 times higher in the placebo group: OR 2.9 (95% CI 1.4–6.4). A decline in LVEF of ≥5% to <55% was observed in 13% of the atorvastatin group and 29% of the placebo group (P=0.001).

Atorvastatin 40 mg was safe with no effect on heart rate, blood pressure, or blood parameters (other than lipids), and no serious study-related side effects. There were 11 cases of heart failure, with no difference between groups (P=0.77). Prof. Neilan noted that it is unclear whether the 12-month beneficial effect of atorvastatin would have been noted had the LVEF been checked at a later time point. Future confirmatory and mechanistic studies may help to clarify the role of statins in this population.

1. Neilan T, et al. Statins to prevent the cardiotoxicity from anthracyclines: The STOP-CA trial. Session 402-10, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Multifaceted strategy improves prescription of therapies for diabetes and ASCVD

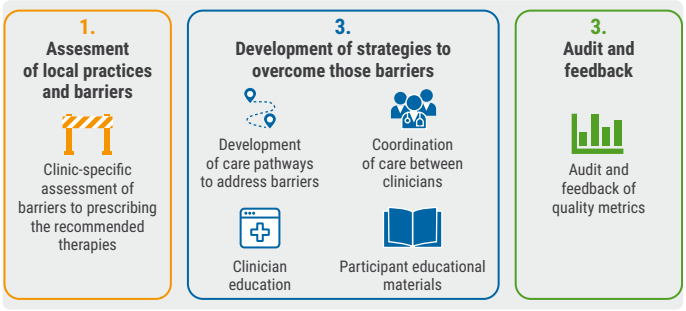
A coordinated, multifaceted intervention proved effective in increasing the prescription of 3 classes of guideline-recommended therapies in adults with type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD). This was found in the cluster randomised clinical trial COORDINATE-Diabetes, carried out in cardiology clinics across the USA.

High-intensity statins, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ACEi/ARBs), and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been shown to improve outcomes for patients with T2D and ASCVD. Yet, "these therapies are highly underused in clinical practice: 37.4% use none and only 2.7% take all 3," said study presenter Prof. Neha Pagidipati (Duke University Hospital, NC, USA) [1].

The COORDINATE-Diabetes study (NCT03936660) evaluated the effect of a clinic-level intervention that incorporated assessment, education, and feedback on the prescription of high-intensity statins, ACEi or ARBs, and SGLT2i and/or glucagon-like peptide 1 receptor agonists (GLP1RAs). Clinics in the intervention group collaborated to develop a multifaceted intervention (see Figure on the next page).

The study enrolled 1,049 patients, 459 of whom were treated in clinics in the intervention group and 590 received usual care. The mean age was 70 years, and 32% were women. The primary outcome was the proportion of patients prescribed all 3 groups of therapies at 6 to 12 months after enrolment.

Figure: The multifaceted intervention of COORDINATE–Diabetes [1]



The primary endpoint was reached by 173 out of 457 (37.9%) in the intervention group and 85 out of 588 (14.5%) in the control group; an absolute difference of 23.4% (adjusted OR 4.38; 95% CI 2.49– 7.71; P<0.001). Dr Pagidipati said this difference was primarily driven by a large increase in prescriptions for SGLT2i and GLP1RAs.

She added that the composite secondary outcome of all-cause death or hospitalisation for myocardial infarction, stroke, decompensated heart failure, or urgent revascularisation was reached by 5% in the intervention group and 6.8% in the control group (adjusted HR 0.79; 95% CI 0.46–1.33). "This difference is not statistically significant, but it is in line with what we would expect based on previously published data," said Prof. Pagidipati. "The next step is to scale this intervention across cardiology practices to deliver high-quality care more broadly."

1. Pagidipati N, et al. Coordinating Cardiology Clinics Randomized Trial Of Interventions To Improve Outcomes (COORDINATE) - Diabetes: Primary Results. Session 409-16, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Dyslipidaemia

Bempedoic acid benefits statin-intolerant patients at high cardiovascular risk

Among statin-intolerant patients, treatment with first-in-class bempedoic acid lowered low-density lipoprotein cholesterol (LDL-C) and effectively reduced the risk of major adverse cardiovascular events (MACE). This was demonstrated in the phase 3, double-blind, randomised, placebo-controlled CLEAR Outcomes trial.

Bempedoic acid is a first-in-class, orally-administered ATP citrate lyase (ACL) inhibitor that reduces LDL-C. As a prodrug, it is activated in the hepatocyte; thus, avoiding potential muscle adverse effects associated with statins. The effects of bempedoic acid on cardiovascular morbidity and mortality had not yet been assessed. Therefore, the CLEAR Outcomes trial (NCT02993406) was set up and its results were presented by Prof. Steven Nissen (Cleveland Clinic, OH, USA) [1,2].

The CLEAR Outcomes was a double-blind, randomised, placebo-controlled trial in patients with statin intolerance who had, or were at high risk for, cardiovascular disease. The 13,970 participants from 32 countries were randomised 1:1 to bempedoic acid 180 mg/day or a matching placebo. The primary endpoint was a 4-component composite of MACE, defined as non-fatal myocardial infarction (MI), non-fatal stroke, coronary revascularisation, or cardiovascular death. The median follow-up was 40.6 months, and 48.1% were women. The mean LDL-C level at baseline was 139.0 mg/dL in both groups.

After 6 months, LDL-C reduction was greater with bempedoic acid than with placebo by 29.2 mg/dL, with an observed difference of 21.1% (-21.7% vs -0.6%). Addition of other therapies (including PCSK9 inhibitors) narrowed the LDL-C differences to 15.5% (-26.1% vs -10.6%) after 60 months. The incidence of a primary endpoint event was significantly lower with bempedoic acid compared with placebo. The primary endpoint was met by 819 (11.7%) and 927 (13.3%) patients in the bempedoic acid and placebo group, respectively (HR 0.87; 95% CI 0.79–0.96; P=0.004). Notably, the HR in women was the same in both groups: 0.86. The overall absolute risk reduction was 1.6% (number needed to treat 63).

The following key secondary endpoints also showed a significant difference:

1. non-fatal stroke, non-fatal MI, or cardiovascular death (MACE-3; HR 0.85; 95% CI 0.76–0.96; P=0.006);
2. fatal or non-fatal MI (HR 0.77; 95% CI 0.66–0.91; P=0.002); and
3. coronary revascularisation (HR 0.81; 95% CI 0.72–0.92; P=0.001).

Bempedoic acid was very well tolerated and did not increase the risk of diabetes. However, the incidences of gout and cholelithiasis were higher with bempedoic acid than with placebo (3.1% vs 2.1% and 2.2% vs 1.2%, respectively).

"Management of patients unable or unwilling to take statins represents a challenging and frustrating clinical issue," Dr Nissen concluded. "Regardless of whether this problem represents the nocebo effect or actual intolerance, these high-risk patients need effective alternative therapies. The CLEAR Outcomes trial provides a sound rationale for the use of bempedoic acid to reduce major adverse cardiovascular outcomes in patients who are intolerant to statins."

1. Nissen S, et al. Bempedoic acid and cardiovascular outcomes in statin intolerant patients at high cardiovascular risk. Session 402-06, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.
2. Nissen S, et al. N Engl J Med 2023; Mar 4. DOI:10.1056/NEJMoa2215024.

Evolocumab improves coronary plaque morphology in stable CAD

More intensive lipid lowering with the addition of evolocumab for 26 weeks was associated with a significant and substantial benefit on coronary plaque characteristics in patients with coronary artery disease (CAD) receiving maximally tolerated statins. The results of the YELLOW III further support more aggressive lipid lowering in this population.

Despite high-intensity statin therapy, CAD patients still have a considerable residual risk of cardiovascular events. PCSK9 inhibitors have been shown to reduce this residual risk, said Prof. Annapoorna Kini (Icahn School of Medicine at Mount Sinai, NY, USA), who presented the phase 4 YELLOW III (NCT04710368) results [1]. Previous studies from her group have shown reduced maximum lipid core burden index in any 4-mm segment along the coronary artery ($maxLCBI_{4mm}$; YELLOW I) and increased fibrous cap thickness (FCT) (YELLOW II) in obstructive lesions of CAD patients after rosuvastatin 40 mg therapy for 6–12 weeks [2,3].

The YELLOW III study aimed to assess the effect of 26 weeks of evolocumab (140 mg every 2 weeks) on coronary plaque morphology using optical coherence tomography (OCT) and near-infrared spectroscopy intravascular ultrasound (NIRS/IVUS), as well as peripheral blood mononuclear cell (PBMC) gene expression analysis [1]. The participants had stable CAD and were on maximally tolerated statin therapy. The 2 primary endpoints were the change in FCT assessed by OCT and change in $maxLCBI_{4mm}$ by NIRS.

Of 329 screened patients, 137 were enrolled and 110 completed the 26-week follow-up. The results showed a significant FCT increase measured by OCT from 70.9 to 97.7 (absolute change 26.8; P<0.001). Furthermore, NIRS showed a reduction in $maxLCBI_{4mm}$ from 306.8 to 213.1 (absolute change -93.7; P<0.001). A reduction was also seen in atheroma volume by IVUS in angiographically non-obstructive lesions. The prevalence of thin-cap fibroatheroma (TCFA) lesions was reduced from 48% to 13%. At 6 months follow-up, 20% of patients did not demonstrate FCT thickening, and 24% did not experience LCBI reduction.

"The first multimodality imaging report in stable patients with non-obstructive lesions and lower levels of LDL-C at baseline, compared to previous trials, further supports aggressive lipid lowering in the patient population," concluded Prof. Kini. "PBMC transcriptomic data will allow predictive models for detecting subjects who demonstrate the greatest response regarding plaque morphology to PCSK9 inhibition therapy."

1. Kini AS, et al. Effect of evolocumab on coronary plaque characteristics in stable coronary artery disease: A multimodality imaging study (the YELLOW III study). Session 403-14, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.
2. Kini AS, et al. J Am Coll Cardiol. 2013;62(1):21–29.
3. Kini AS, et al. J Am Coll Cardiol. 2017;69(6):628–640.

Inflammation stronger predictor of MACE than cholesterol levels

A collaborative analysis of the PROMINENT, REDUCE-IT, and STRENGTH trials (n=31,245) showed that residual inflammatory risk is a better predictor of future major adverse cardiovascular events (MACE), cardiovascular (CV) death, and all-cause mortality than residual cholesterol risk in statin-treated patients. Thus, targeting low-density lipoprotein cholesterol (LDL-C) alone is unlikely to completely reduce atherosclerotic risk.

Prof. Paul Ridker (Brigham and Women's Hospital, MA, USA) explained that the study aimed to determine the relative importance of high-sensitivity C-reactive protein (hsCRP) and LDL-C as determinants of risk for MACE, CV death, and all-cause death among patients receiving statins who were eligible for inclusion in these selected trials [1]. This could then resolve the clinically highly relevant question of whether to add a second LDL-lowering agent or rather an agent that inhibits inflammation to a statin.

Prof. Ridker and colleagues performed a collaborative analysis of patients with (a high risk of) atherosclerotic disease receiving contemporary statins who participated in the PROMINENT

(NCT03071692), REDUCE-IT (NCT01492361), or STRENGTH (NCT02104817) trials. Included were 9,988, 8,179, and 13,078 participants from these respective studies, totalling 31,245 participants. Assessed were quartiles of increasing baseline hsCRP and LDL-C.

Comparing the highest (4th) quartile to the first (referent) quartile, residual inflammatory risk measured by hsCRP was significantly associated with:

1. incident MACE (HR 1.31; 95% CI 1.20–1.43; P<0.0001);
2. CV mortality (HR 2.68 95%; CI 2.22–3.23; P<0.0001); and
3. all-cause mortality (HR 2.42 95%; CI 2.12–2.77; P<0.0001).

Residual cholesterol risk was not associated with MACE (HR 1.07; 95% CI 0.98–1.17; P=0.11). It was associated with CV death and all-cause death, but HRs were much lower: 1.27 (95% CI 1.07–1.50; P=0.0086) and 1.16 (95% CI 1.03–1.32; P=0.025), respectively.

In all 3 trials, patients with elevated hsCRP were at high CV risk irrespective of their LDL-C levels, Prof. Ridker concluded. So, which options are available to prescribe in addition to a statin? Prof. Ridker mentioned colchicine (0.5 mg) for patients with stable atherosclerosis and normal eGFR; bempedoic acid, which reduces both LDL-C and hsCRP; or SGLT2i and GLP1RAs, both of which have concomitant anti-inflammatory effects. "We believe the combined use of aggressive LDL-lowering and inflammation-inhibiting therapies will become standard of care for almost all atherosclerotic patients."

1. Ridker P, et al. Residual inflammatory risk in contemporary statin treated patients: A collaborative analyses of 31,197 participants in the PROMINENT, REDUCE-IT, and STRENGTH trials. Session 411-10, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Oral PCSK9 inhibitor significantly lowers LDL-C

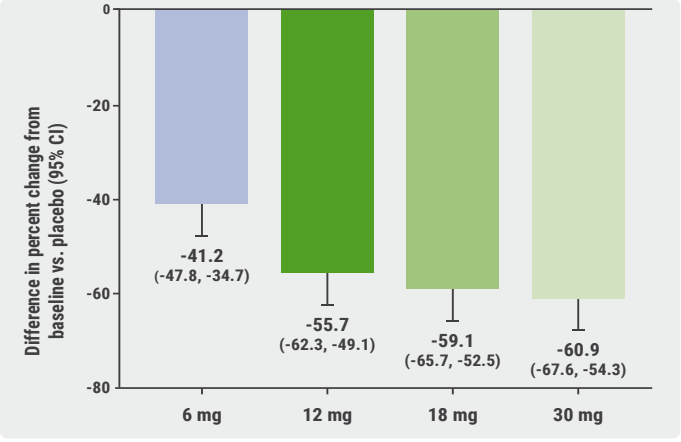
The experimental oral PCSK9 inhibitor MK-0616 demonstrated statistically significant and robust, dose-dependent reductions in LDL-cholesterol (LDL-C) in patients with hypercholesterolemia and was well tolerated in a phase 2b, randomised, international trial. All doses were statistically superior to placebo, and the results were consistent across subgroups.

Prof. Christie Ballantyne (Baylor College of Medicine, TX, USA) explained that injectable treatments targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) have been shown to provide "excellent" reductions in LDL-C and the risk of atherosclerotic cardiovascular disease, but they have been poorly adopted due to access barriers and the need for multiple injections [1]. "An oral PCSK9 inhibitor may widen access and improve the attainment of guideline-recommended treatment goals."

An oral PCSK9 inhibitor with the provisional name of MK-0616 was subjected to a phase 2b randomised controlled trial (NCT05261126) [1]. The straightforward primary objective was per cent change from baseline in LDL-C at week 8 in participants with hypercholesterolemia. A total of 381 adults were enrolled; 49% were women, and the median age was 62 years. They had a mean LDL-C of 119.5 mg/dL and 38.6% had clinical atherosclerotic cardiovascular disease; about 60% were taking a statin at study entry. Participants were randomised to placebo or one of the 4 doses of MK-0616 for 8 weeks, after which treatment was withdrawn to assess adverse events in the following 8 weeks.

All doses of MK-0616 demonstrated statistically superior and dose-dependent reductions in LDL-C versus placebo (P<0.001). Efficacy was nearly complete after 2 weeks, and a persistent effect over the 8-week treatment period was observed, as measured by the least squares mean percentage change in LDL-C. The Figure shows the primary endpoint results for the efficacy population.

Figure: L DL-C significant percent change from baseline versus placebo at week 8 for the efficacy population [1]



Apolipoprotein-B (ApoB) was also significantly lowered at week 8, with a mean difference versus placebo of 32.8% (6 mg group) to 51.8% (30 mg group). The reduction versus placebo in non-HDL-C was between 35.9% and 55.8%, in these dosage groups. The proportion of patients who attained LDL-C goals ranged from 80.5% to 90.8%, versus 9.3% in the placebo group.

MK-0616 was well tolerated; the proportion of participants with ≥1 adverse event was between 39.5% and 43.4% in the treatment arms and 44.0% in the placebo arm.

1. Ballantyne CM. Efficacy and safety of the oral PCSK9 inhibitor MK-0616: a phase 2b randomized controlled trial. Session 410-16, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Miscellaneous

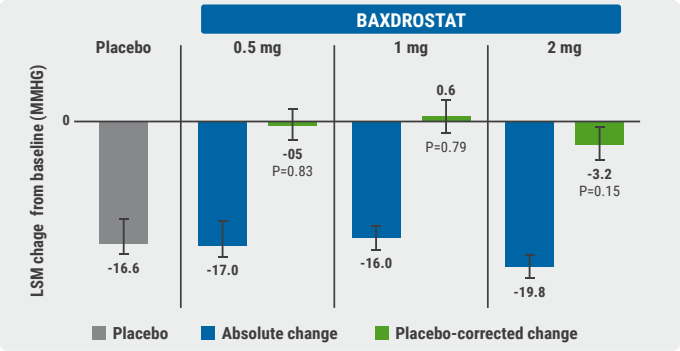
Baxdrostat in patients with uncontrolled hypertension

In the placebo-controlled phase 2 HALO trial, baxdrostat did not achieve a statistically significant change from baseline in mean seated systolic blood pressure (SBP) in patients with uncontrolled hypertension. The placebo effect in this study was substantial. In a post-hoc analysis, SBP was significantly lowered in patients adherent to the highest dose of 2 mg.

The results of the phase 2 HALO study (NCT05137002) were highly anticipated since there have not been any new agents to treat uncontrolled hypertension in well over a decade, said Dr Deepak Bhatt (Icahn School of Medicine at Mount Sinai, NY, USA) [1]. Baxdrostat is a highly selective aldosterone synthase inhibitor. Its efficacy and safety were evaluated in the randomised, double-blind, placebo-controlled, multicentre, phase 2 HALO trial. The participants had to be on a stable regimen of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), an ACEi/ARB plus a thiazide diuretic, or an ACEi/ARB plus a calcium channel blocker, and have a mean seated SBP ≥140 mmHg. The primary endpoint was change from baseline in mean seated SBP after 8 weeks of treatment. A total of 249 patients were randomised 1:1:1:1 to baxdrostat 0.5 mg, 1 mg, 2 mg, or placebo; 227 completed the trial.

The primary endpoint was not met with any baxdrostat dose. SBP change was -17.0, -16.0, and -19.8 mmHg in the 0.5 mg, 1 mg, and 2 mg groups, respectively, but there was also a large decrease (-16.6 mmHg) in the placebo group (see Figure).

Figure: Placebo-corrected change from baseline in mean seated SBP at 8 weeks [1]



Similarly, none of the baxdrostat doses were associated with a significant difference in placebo-corrected diastolic blood pressure (DBP), which was a secondary endpoint. Change in DBP at 8 weeks did not significantly differ either; nor did the percentage of patients achieving a seated SBP response <130 mmHg at 8 weeks. Baxdrostat significantly reduced serum aldosterone levels at all doses. The treatment was well tolerated.

Dr Bhatt explained that a post-hoc analysis was done in patients who were adherent to the highest baxdrostat dose of 2 mg. The reason was that 20 of 54 (36%) patients in the 2 mg arm who completed 8 weeks of treatment had baxdrostat levels <0.2 ng/dL, indicating non-adherence (despite dosing records by pill count showing >95% adherence in all groups). This subgroup analysis suggested a placebo-corrected SBP reduction of 7.9 mmHg in patients adherent to baxdrostat 2 mg.

1. Bhatt DL, et al. Results from a phase 2, double-blind, placebo-controlled trial evaluating the efficacy and safety of baxdrostat in patients with uncontrolled hypertension. Session 403-08, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Hormone therapy for gender dysphoria associated with increased CV risk

People with gender dysphoria on hormone replacement therapy (HRT) as part of gender affirmation therapy have substantially increased odds of serious cardiac events and other problems, including ischaemic stroke, pulmonary embolism, ST-elevation myocardial infarction (STEMI), non-STEMI, drug abuse, and hypothyroidism.

Between 1 million to 1.6 million Americans identify as trans-gender, according to the study's first author Dr Ibrahim Ahmed (Mercy Catholic Medical Center, PA, USA) [1]. Among them, HRT use is rising rapidly, especially among teens and young adults. The aim of this retrospective study was 2-fold: to characterise the demographics of gender dysphoria patients using HRT and to study the impact of this therapy on cardiovascular(CV) outcomes in the setting of gender dysphoria, of which little is known. The researchers accessed the 2019 Nationwide Inpatient Sample database to identify admissions of adults diagnosed with gender dysphoria and the use of HRT. The primary outcome was CV events in HRT users versus non-users.

Of 21,335 identified gender dysphoria patients, 1,675 had used HRT. Compared with non-users, patients in the HRT cohort were slightly older (31 vs 34 years) and were less often women (47% vs 55%); race distribution was similar in the 2 groups.

HRT was significantly associated with:
1. ischaemic stroke: OR 7.15 (95% CI 2.74–18.67; P<0.001);
2. pulmonary embolism: OR 4.92 (95% CI 2.08–11.62; P<0.001);
3. STEMI: OR 5.90 (95% CI 1.07–32.42; P<0.05);
4. non-STEMI: OR 3.30 (95% CI 1.20–9.04; P<0.05).

HRT was not significantly associated with atrial fibrillation, diabetes mellitus, hypertension, haemorrhagic stroke, and systolic heart failure, Dr Ahmed added. The all-cause mortality rate in HRT users was similar: 0.60% versus 0.48% (P=0.774). The mean length of hospital stay was also similar (5.71 vs 6.09 days; P=0.321), as was the mean total hospitalisation charge ($61,012 vs $49,930; P=0.598).

"It's all about risks and benefits," said Dr Ahmed. "Starting transitioning is a big part of a person's life and helping them feel more themselves, but HRT also has numerous side effects. It's not free of risk." He added that "a careful risk-benefit discussion" should precede HRT in patients with gender dysphoria.

1. Ahmed I, et al. Cardiovascular outcomes in gender dysphoric patients undergoing hormone replacement therapy. Session 1068-05, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Pulsed-field ablation appears safe and effective for atrial fibrillation

Pulsed-field ablation (PFA) was found to be a successful and safe procedure for atrial fibrillation (AF) in the prospective, multicentre PULSED AF trial. At 12 months, both the paroxysmal and persistent AF cohorts met the predetermined effectiveness goals.

The risk of collateral tissue damage limits the use of thermal modes of ablation. PFA creates lesions non-thermally and within milliseconds through the mechanism of irreversible electroporation (IRE), explained study presenter Prof. Atul Verma (McGill University Health Centre, Canada) [1]. This involves exposing the tissue to high electric field gradients, inducing cell death through cell membrane hyper-permeabilisation.

The PULSED AF trial (NCT04198701) investigated PFA in patients with AF [2]. PULSED AF was designed as a prospective, global, non-randomised, paired single-arm trial in 41 centres in 9 countries. The 300 patients in the primary cohort had paroxysmal (n=150) or persistent (n=150) symptomatic AF resistant to class I and III antiarrhythmic drugs. They were all treated with PFA using the Medtronic PulseSelect PFA system.

The primary effectiveness endpoint was freedom from a composite of acute procedural failure, arrhythmia recurrence, or antiarrhythmic escalation over 12 months, apart from the first 3 months post-procedure to allow for recovery.

Prof. Verma presented the acute and long-term outcomes of the trial [1]. Of the participants, 96% reached the 12-month follow-up. By that time, 66.2% (95% CI 57.9–73.2) of patients with paroxysmal AF and 55.1% (95% CI 46.7–62.7) of patients with persistent AF met the primary endpoint. In both groups, the pre-specified benchmark goal (50% and 40%, respectively) was beaten by a statistically significant margin. Prof. Verma put this result in perspective by saying: "This is at least as good as the results we would get from thermal ablation." A more typical endpoint is the freedom from AF recurrence at 12 months, which was reached by 69.5% and 62.3% in the paroxysmal and persistent group, respectively. Freedom from symptomatic recurrence was achieved in about 80% of both groups.

The primary safety endpoint, freedom from a composite of serious procedure-related and device-related adverse events, occurred in 1 patient from each cohort (0.7%; 95% CI 0.1–4.6; P=0.002). "This is one of the lowest complication rates ever reported in a catheter-ablation trial anywhere," according to Prof. Verma. PFA resulted in clinically meaningful improvements in quality of life. "The procedure time was very short," added Prof. Verma, "despite this being a new procedure."

The study was limited by the lack of a control group. Larger studies will have to demonstrate more definitive evidence of PFA's safety.

1. Verma A, et al. Pulsed field ablation treatment in paroxysmal and persistent atrial fibrillation patients: Acute and long-term outcomes from the PULSED AF Pivotal Trial. Session 409-08, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.
2. Verma A, et al. Circulation. 2023 Mar 6. Doi: 10.1161/CIRCULATIONAHA.123.063988.

Half-dose tenecteplase safe and effective for STEMI without timely PCI

Pharmaco-invasive therapy with half-dose tenecteplase may provide a safe and effective reperfusion alternative in elderly patients with ST-segment elevation myocardial infarction (STEMI) who could not undergo primary PCI within 1 hour. The rate of intracranial haemorrhage (ICH) in the tenecteplase group was higher than anticipated.

A significant amount of patients with STEMI do not receive primary PCI within 120 minutes after the first medical contact, which elevates their risk of death. In these cases, a pharmaco-invasive strategy is recommended. However, full-dose anteplase or tenecteplase are associated with increased rates

of ICH and major non-intracranial bleeding from the age of about 60 years onwards, as was shown by the ASSENT-4 PCI (NCT00168792) and the STREAM-1 (NCT00623623) trials [1,2].

The STREAM-2 trial (NCT02777580) was an investigator-initiated, prospective, randomised open-label trial conducted in 49 centres in 10 countries. The trial set out to compare the safety and efficacy of reperfusion with half-dose tenecteplase with primary PCI among STEMI patients ≥60 years who could not have primary PCI within 1 hour. The 604 participants had a STEMI <3 hours from symptom onset with ≥2 mm ST segment elevation in ≥2 contiguous leads.

The participants were randomised 2:1 to half-dose tenecteplase followed by PCI within 6–24 hours (n=401) or primary PCI (n=203). The mean patient age was 71 years; 32% were women. The duration of follow-up was 30 days. The mean systolic blood pressure was 134 mmHg, and the mean heart rate was 76 bpm. There was a difference of 80 minutes in the time to treatment; the time delay was 110 minutes in the half-dose tenecteplase group versus 190 minutes in the primary PCI group (P<0.001).

The primary clinical efficacy outcome was a composite of death, heart failure, recurrent MI (reMI), and/or shock at 30 days. The clinical efficacy outcomes are shown in the Table.

Table: The primary clinical efficacy outcomes of STREAM-2. Derived from [3]

	Half-dose TNK	Primary PCI	Relative risk (95% CI)
Death, HF, shock, reMI	12.8	13.3	0.96 (0.62–1.48)
Death from any cause	9.3	8.9	1.04 (0.61–1.79)
Cardiogenic shock	4.5	5.4	0.83 (0.40–1.72)
HF	3.5	4.4	0.79 (0.35–1.79)
ReMI	2.5	2.5	1.02 (0.35–2.93)
Death from cardiac causes	7.3	8.4	0.87 (0.49–1.54)

CI, confidence interval; reMI, recurrent myocardial infarction; HF, heart failure; TNK, tenecteplase; PCI, percutaneous coronary intervention.

The clinical safety at 30 days in the half-dose tenecteplase compared as follows to the direct PCI group:

1. total stroke: 2.3% versus 0.5% (RR 4.57; 95% CI 0.58–35.80; P>0.05);
2. ICH: 1.5% versus 0% (RR 6.61; 95 CI 0.81–53.89; P=ns); and
3. major non-ICH: 1.3% versus 1.0% (RR 1.27; 95% CI 0.25–6.48; P>0.05).

In the half-dose tenecteplase group, 3 of the 6 cases of ICH were attributed to protocol violations; non-intracranial bleeding was low overall.

1. Van der Werf F, et al. Lancet. 2006;367(9510):569–78.
2. Armstrong PW, et al. N Engl J Med 2013;368:1379–87.
3. Van de Werf F, et al. Pharmaco-invasive Reperfusion Strategy With Half-dose Tenecteplase In Older St-elevation Myocardial Infarction Patients. Session 407-12, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

Key correlates of incident dementia identified in the MESA study

The Multi-Ethnic Study of Atherosclerosis (MESA) deeply phenotyped dementia in a multi-ethnic cardiovascular cohort and identified key correlates of incident dementia. Among these were risk factors for cardiovascular diseases (CVD) and atherosclerosis, subclinical myocyte damage, vascular function, inflammation, physical activity, hepatic steatosis, and a history of cancer.

MESA was set up to study the correlates, predictors, and progression of subclinical CVD in a diverse population of 6,814 Americans between the ages of 45 and 84 years who had no evidence of clinical CVD at baseline. As the specific vascular contributions to dementia remain insufficiently understood, MESA set up a study to identify the correlates of incident dementia in a cardiovascular cohort. The results were presented as a poster at the ACC 2023 meeting by Dr Mohammad Ostovaneh (Johns Hopkins Hospital, MD, USA) [1].

The study included 6,806 MESA participants who had sufficient follow-up data for incident dementia. At the baseline exam, MESA collected data on almost 200 variables including demographic risk factors, past medical history, anthropometric measurements, laboratory markers, electrocardiogram, cardiac and aortic MRI, coronary artery calcium, and liver fat. From this data, correlates of incident dementia were identified using Random Survival Forest analysis, a non-parametric machine learning strategy to build a risk prediction model of survival.

Dr Ostovaneh and colleagues identified 326 cases of dementia over the course of 14 years. Beyond age, the major independent correlates of dementia included:

- coronary artery calcification;
- high-sensitivity troponin;
- common carotid artery intima-media thickness;
- N-terminal prohormone of brain natriuretic peptide (NT-proBNP);
- physical activity;
- pulse pressure;
- tumour necrosis factor-α;
- a history of cancer; and
- liver-to-spleen attenuation ratio.

Participants over 62 years at baseline had similar dementia correlates to the cohort as a whole but, in this subgroup, IL-2 soluble receptor, apolipoprotein E, and descending aortic strain were also associated with dementia.

1. Ostovaneh M, et al. Deep phenotyping of dementia in a multi-ethnic cardiovascular cohort: The multi-ethnic study of atherosclerosis (MESA). Session 906-09, ACC Scientific Session 2023, 4–6 March, New Orleans, USA.

1. NAME OF THE MEDICINAL PRODUCT Eliquis 2.5 mg film-coated tablets, Eliquis 5 mg film-coated tablets. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** Each film-coated tablet contains 2.5 mg or 5 mg apixaban. Excipient(s) with known effect Each 2.5 mg film-coated tablet contains 51.4 mg lactose. Each 5 mg film-coated tablet contains 102.9 mg lactose. For the full list of excipients, see section 6.1 of the SmPC. **3. PHARMACEUTICAL FORM** Film-coated tablet (tablet). 2,5 mg: Yellow, round tablets (diameter of 5.95 mm) debossed with 893 on one side and 2½ on the other side. 5 mg: Pink, oval tablets (9.73 mm x 5.16 mm) debossed with 894 on one side and 5 on the other side. **4. CLINICAL PARTICULARS 4.1 Therapeutic indications** Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients). **4.2 Posology and method of administration** Posology *Prevention of VTE (VTEp): elective hip or knee replacement surgery* The recommended dose of apixaban is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery. Physicians may consider the potential benefits of earlier anticoagulation for VTE prophylaxis as well as the risks of post-surgical bleeding in deciding on the time of administration within this time window. *In patients undergoing hip replacement surgery* The recommended duration of treatment is 32 to 38 days. *In patients undergoing knee replacement surgery* The recommended duration of treatment is 10 to 14 days. *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)* The recommended dose of apixaban is 5 mg taken orally twice daily. Dose reduction The recommended dose of apixaban is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L). Therapy should be continued long-term. *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)* The recommended dose of apixaban for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g., recent surgery, trauma, immobilisation). The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant, as indicated below: Treatment of DVT or PE: 10 mg twice daily for the first 7 days (Maximum daily dose: 20 mg), followed by 5 mg twice daily (Maximum daily dose: 10 mg). Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE: 2.5 mg twice daily (Maximum daily dose: 5 mg). The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. *Missed dose* If a dose is missed, the patient should take Eliquis immediately and then continue with twice daily intake as before. *Switching* Switching treatment from parenteral anticoagulants to Eliquis (and *vice versa*) can be done at the next scheduled dose. These medicinal products should not be administered simultaneously. *Switching from vitamin K antagonist (VKA) therapy to Eliquis* When converting patients from vitamin K antagonist (VKA) therapy to Eliquis, warfarin or other VKA therapy should be discontinued and Eliquis started when the international normalised ratio (INR) is < 2. *Switching from Eliquis to VKA therapy* When converting patients from Eliquis to VKA therapy, administration of Eliquis should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of Eliquis with VKA therapy, an INR should be obtained prior to the next scheduled dose of Eliquis. Coadministration of Eliquis and VKA therapy should be continued until the INR is ≥ 2. *Renal impairment* In patients with mild or moderate renal impairment, the following recommendations apply:- for the prevention of VTE in elective hip or knee replacement surgery (VTEp), for the treatment of VT, treatment of PE and prevention of recurrent DVT and PE (VTEt), no dose adjustment is necessary.- for the prevention of stroke and systemic embolism in patients with NVAF and serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg, a dose reduction is necessary and described above. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary. In patients with severe renal impairment (creatinine clearance 15-29 mL/min) the following recommendations apply:- for the prevention of VTE in elective hip or knee replacement surgery (VTEp), for the treatment of VT, treatment of PE and prevention of recurrent DVT and PE (VTEt), apixaban is to be used with caution;- for the prevention of stroke and systemic embolism in patients with NVAF, patients should receive the lower dose of apixaban 2.5 mg twice daily. In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended. *Hepatic impairment* Eliquis is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. It is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment. Patients with elevated liver enzymes alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 x ULN or total bilirubin ≥ 1.5 x ULN were excluded in clinical studies. Therefore Eliquis should be used with caution in this population. Prior to initiating Eliquis, liver function testing should be performed. *Body weight* VTEp and VTEt - No dose adjustment required. NVAF - No dose adjustment required, unless criteria for dose reduction are met (see Dose reduction at the beginning of section 4.2). *Gender* No dose adjustment required. *Patients undergoing catheter ablation (NVAF)* Patients can continue apixaban use while undergoing catheter ablation (see sections 4.3). *Patients undergoing cardioversion* Apixaban can be initiated or continued in NVAF patients who may require cardioversion. For patients not previously treated with anticoagulants, exclusion of left atrial thrombus using an image guided approach (e.g. transesophageal echocardiography (TEE) or computed tomographic scan (CT)) prior to cardioversion should be considered, in accordance with established medical guidelines. For patients initiating treatment with apixaban, 5 mg should be given twice daily for at least 2.5 days (5 single doses) before cardioversion to ensure adequate anticoagulation. The dosing regimen should be reduced to 2.5 mg apixaban given twice daily for at least 2.5 days (5 single doses) if the patient meets the criteria for dose reduction (see above sections *Dose reduction and Renal impairment*). If cardioversion is required before 5 doses of apixaban can be administered, a 10 mg loading dose should be given, followed by 5 mg twice daily. The dosing regimen should be reduced to a 5 mg loading dose followed by 2.5 mg twice daily if the patient meets the criteria for dose reduction (see above sections *Dose reduction* and *Renal impairment*). The administration of the loading dose should be given at least 2 hours before cardioversion. For all patients undergoing cardioversion, confirmation should be sought prior to cardioversion that the patient has taken apixaban as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account. *Patients with NVAF and acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI)* There is limited experience of treatment with apixaban at the recommended dose for NVAF patients when used in combination with antiplatelet agents in patients with ACS and/or undergoing PCI after haemostasis is achieved. *Paediatric population* The safety and efficacy of Eliquis in children and adolescents below age 18 have not been established. No data are available. Method of administration Oral use. Eliquis should be swallowed with water, with or without food. For patients who are unable to swallow whole tablets, Eliquis tablets may be crushed and suspended in water, or 5% glucose in water (G5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, Eliquis tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube. Crushed Eliquis tablets are stable in water, G5W, apple juice, and apple puree for up to 4 hours. **4.3 Contraindications** • Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC. • Active clinically significant bleeding. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. • Lesion or condition if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. • Concomitant treatment with any other anticoagulant agent e.g., unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under specific circumstances of switching anticoagulant therapy, when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. **4.8 Undesirable effects** Summary of the safety profile The safety of apixaban has been investigated in 7 Phase III clinical studies including more than 21,000 patients: more than 5,000 patients in VTEp studies, more than 11,000 patients in NVAF studies and more than 4,000 patients in the VTE treatment (VTEt) studies, for an average total exposure of 20 days, 1.7 years and 221 days respectively. Common adverse reactions were haemorrhage, contusion, epistaxis, and haematoma (see the list below for adverse reaction profile and frequencies by indication). In the VTEp studies, in total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. The overall incidence of adverse reactions related to bleeding with apixaban was 10% in the apixaban vs enoxaparin studies. In the NVAF studies, the overall incidence of adverse reactions related to bleeding with apixaban was 24.3% in the apixaban vs warfarin study and 9.6% in the apixaban vs acetylsalicylic acid study. In the apixaban vs warfarin study the incidence of ISTH major gastrointestinal bleeds (including upper GI, lower GI, and rectal bleeding) with apixaban was 0.76%/year. The incidence of ISTH major intraocular bleeding with apixaban was 0.18%/year. In the VTEt studies, the overall incidence of adverse reactions related to bleeding with apixaban was 15.6% in the apixaban vs enoxaparin/warfarin study and 13.3% in the apixaban vs placebo study. List of adverse reactions The list below shows the adverse reactions ranked under headings of system organ class and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data) for VTEp, NVAF, and VTEt respectively. *Blood and lymphatic system disorders* Anaemia – VTEp Common – NVAF Common – VTEt Common. Thrombocytopenia – VTEp Uncommon – NVAF Uncommon – VTEt Common. *Immune system disorders* Hypersensitivity, allergic oedema and Anaphylaxis – VTEp Rare – NVAF Uncommon – VTEt Uncommon. Pruritus – VTEp Uncommon –NVAF Uncommon – VTEt Uncommon*. Angioedema – VTEt not known – NVAF not known – VTEt not known. *Nervous system disorders* Brain haemorrhage† – VTEp Not known – NVAF Uncommon – VTEt Rare. *Eye disorders* Eye haemorrhage (including conjunctival haemorrhage) – VTEp Rare – NVAF Common – VTEt Uncommon. *Vascular disorders* Haemorrhage, haematoma – VTEp Common – NVAF Common – VTEt Common. Hypotension (including procedural hypotension) – VTEp Uncommon – NVAF Common – VTEt Uncommon. Intra-abdominal haemorrhage – VTEp Not known – NVAF Uncommon – VTEt Not known. *Respiratory, thoracic and mediastinal disorders* Epistaxis – VTEp Uncommon – NVAF Common – VTEt Common. Haemoptysis – VTEp Rare – NVAF Uncommon – VTEt Uncommon. Respiratory tract haemorrhage – VTEp Not known – NVAF rare – VTEt Rare. *Gastrointestinal disorders* Nausea – VTEp Common – NVAF Common – VTEt Common. Gastrointestinal haemorrhage – VTEp Uncommon – NVAF Common – VTEt Common. Haemorrhoidal haemorrhage – VTEp Not known – NVAF Uncommon – VTEt Uncommon. Mouth haemorrhage - VTEp Not known – NVAF Uncommon – VTEt Common. Haematochezia – VTEp Uncommon – NVAF Uncommon – VTEt Uncommon. Rectal haemorrhage, gingival bleeding – VTEp Rare – NVAF Common – VTEt Common. Retroperitoneal haemorrhage – VTEp Not known – NVAF Rare – VTEt Not known. *Hepatobiliary disorders* Liver function test abnormal, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased – VTEp Uncommon – NVAF Uncommon – VTEt Uncommon. Gamma-glutamyltransferase increased - VTEp Uncommon – NVAF Common – VTEt Common. Alanine aminotransferase increased - VTEp Uncommon – NVAF Uncommon – VTEt Common *Skin and subcutaneous tissue disorders* Skin rash – VTEp Not known – NVAF Uncommon – VTEt Common. Alopecia – VTEp Rare – NVAF Uncommon – VTEt Uncommon. Erythema multiforme – VTEp Not known – NVAF Very rare – VTEt Not known. Cutaneous vasculitis -VTEp Not known – NVAF Not known – VTEt Not known. *Musculoskeletal and connective tissue disorders* Muscle haemorrhage – VTEp Rare – NVAF Rare – VTEt Uncommon. *Renal and urinary disorders* Haematuria – VTEp Uncommon – NVAF Common – VTEt Common. *Reproductive system and breast disorders* Abnormal vaginal haemorrhage, urogenital haemorrhage – VTEp Uncommon – NVAF Uncommon – VTEt Common. *General disorders and administration site conditions* Application site bleeding – VTEp Not known – NVAF Uncommon – VTEt Uncommon. *Investigations* Occult blood positive – VTEp Not known – NVAF Uncommon – VTEt Uncommon. *Injury, poisoning and procedural complications* Contusion – VTEp Common – NVAF Common – VTEt Common. Post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage – VTEp Uncommon – NVAF Uncommon – VTEt Uncommon. Traumatic haemorrhage – VTEp Not known – NVAF Uncommon – VTEt Uncommon. * There were no occurrences of generalized pruritus in CV185057 (long term prevention of VTE). † The term “Brain haemorrhage” encompasses all intracranial or intraspinal haemorrhages (ie., haemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural haemorrhages). The use of Eliquis may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. *VTEp: Prevention of VTE in patients undergoing hip or knee replacement surgery. NVAF: Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors. VTEt: Treatment of DVT and PE, and prevention of recurrent DVT and PE.* Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V. **7. MARKETING AUTHORISATION HOLDER** Bristol-Myers Squibb/Pfizer EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland. **8. MARKETING AUTHORISATION NUMBER(S)** EU/1/11/691/001-015. **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** Date of first authorisation: 18 May 2011 Date of latest renewal: 11 January 2021. **10. DATE OF REVISION OF THE TEXT** August 2022. **11. AVAILABILITY** By prescription only. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Eliquis® apixaban

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There is a risk minimisation plan (RMP) for this product. Please consult/download the material on the FAMHP website:
https://www.afmps.be/ fr/humain/medicaments/medicaments/bon_usage/programme_de_gestion_de_risques/rma
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***** Based on the results of the phase 3 (ITT analysis) pivotal studies of the different DOACs available in Belgium and Luxembourg [1,4-6]

† ELIQUIS® is indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

1. Granger CB et al. N Engl J Med 2011; 365, 981-992. **2.** IQVIA data Belgium March 2023. **3.** IQVIA MIDAS, DoT Q3 2022.
4. Giugliano RP et al. N Engl J Med 2013; 369: 2093-2104. **5.** Patel MR et al. N Engl J Med 2011; 365: 883-91. **6.** Connolly SJ et al. N Engl J Med 2009; 361: 1139-51.

DOAC: direct-acting oral anticoagulant VKA: vitamin K antagonist CVA: cerebrovascular accident

230415 - May 2023

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