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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 European Society of Cardiology Congress 2024, held in London, England. This year's meeting covered a wide array of topics, from novel treatments for heart failure to unexpected results from studies with novel anticoagulants. There were fresh perspectives on the utility of beta-blockers in patients with coronary artery disease, polypill therapy, novel uses of AI, and new treatments for amyloid.

In the following pages, you will find new data for the novel non-steroidal MRA finerenone in heart failure with preserved ejection fraction from the FINEARTS-HF trial; unexpected findings from the early termination of the OCEANIC-AF trial; and data with regard to the effects of beta-blocker therapy in coronary artery disease. There is much more than this with comprehensive coverage of over 20 presentations and 4 new guidelines.

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

Sincerely,

Prof. Marc Bonaca

Biography

Marc P. Bonaca, MD, MPH, is a Cardiologist and Vascular Medicine Specialist who serves as the Executive Director of CPC Clinical Research and CPC Community Health at the University of Colorado Anschutz Medical Campus. He is the Director of Vascular Research and an Associate Professor of Medicine at the University of Colorado School of Medicine and the inaugural holder of the William R. Hiatt Endowed Chair in Cardiovascular Research.

Dr Bonaca earned his medical degree from the University of Connecticut School of Medicine and his Masters in Public Health at Harvard University. He served as a Medical House Officer at Brigham and Women's Hospital and Harvard Medical School. After completion of his training he joined the faculty of the Cardiovascular Division and Vascular Medicine section of Brigham and Women's Hospital and Harvard Medical School and became an Investigator at the TIMI Study Group.

Dr Bonaca's research focus is on ischemic risk in patients with atherosclerotic vascular disease, risk prediction, and risk modification through the use of pharmacologic and biologic therapies. His key areas of interest include patients with peripheral artery disease, polyvascular disease and diabetes with a focus on the breadth of risk including ischemic limb outcomes, microvascular complications and major adverse cardiovascular events.

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2024 ESC Guidelines in a Nutshell

Guidelines for the management of elevated blood pressure and hypertension

The 2024 ESC Guidelines on blood pressure (BP) and hypertension include a vast scope of novelties and revisions. Among the most important are a new BP classification, new treatment targets, and pharmacological and non-pharmacological management.

The new guidelines issued 57 new and 43 revised recommendations on different aspects of hypertension management [1–3]. "We have a lot of work to do," stated Prof. John William McEvoy (National University of Ireland, Galway, Ireland), considering the still poor implementation of effective BP treatment worldwide.

For measuring BP, new recommendations do not only include the use of calibrated devices to enforce correct measurement technique (class I) but also highlight out-of-office measuring for diagnosis and patient-centred care:

- It is recommended to measure BP using a validated and calibrated device, to enforce the correct measurement technique, and to apply a consistent approach to BP measurement for each patient (class I).
- Out-of-office BP measurement is recommended for diagnostic purposes, particularly because it can detect both white-coat hypertension and masked hypertension. Where out-of-office measurements are not logistically or economically feasible, it is recommended to confirm the diagnosis with a repeat office BP measurement using the correct standardised measurement technique (class I).
- Home BP measurement for managing hypertension by using self-monitored BP is recommended to achieve better BP control (class I).
- Self-measurement, when properly performed, is recommended due to its positive effects on the acceptance of a diagnosis of hypertension, patient empowerment, and adherence to treatment (class I).

A new blood pressure classification

Instead of the former 7 categories for BP, the new Guidelines now define 3 categories. They illustrate that the cardiovascular disease (CVD) risk augmentation through BP is incremental:

- non-elevated BP (office BP <20/70 mmHg);
- elevated BP (120–139/70–89 mmHg);
- hypertension (≥140/≥90 mmHg).

For the confirmation of elevated BP and hypertension, out-of-office measurement is required. Further management is tailored according to categories. "Hypertensive individuals, regardless of age, regardless of risk, deserve a drug treatment immediately and, of course, this does not apply to the elevated BP subgroup," Prof. Rosa Maria Bruno (Hôpital Européen Georges Pompidou, France) indicated. Persons with elevated BP are subject to a stepwise risk assessment that includes the prediction of the 10-year risk of CVD, the evaluation of risk modifiers, and the consideration of further CVD testing, to determine the adequate measures indicated.

Two new class I recommendations particularly elaborate on the CVD risk assessment in elevated BP:

- It is recommended to use a risk-based approach in the treatment of elevated BP, and individuals with moderate or severe chronic kidney disease, established CVD, hypertension-mediated organ damage, diabetes mellitus, or familial hypercholesterolaemia are considered at increased risk for CVD events (class I).
- It is recommended that, irrespective of age, individuals with elevated BP and a SCORE2 or SCORE2-OP CVD risk of ≥10% are considered at increased risk for CVD for the purpose of risk-based management of their elevated BP (class I).

As there is an important focus on patient-centred care within the new guideline, a class I recommendation includes an informed discussion about CVD risk and treatment benefits tailored to the needs of a patient as part of hypertension management.

Non-pharmacological interventions

Lifestyle and non-drug measures to lower BP play an important role in the management of elevated BP. "Highlighted in our recommendations is an increase in potassium intake and there's now a lot of evidence to indicate indeed that increasing potassium intake, particularly in patients with hypertension without moderate-to-advanced kidney disease is really what should be focused upon," Prof. Rhian Touyz (McGill University, Canada) emphasised.

- In patients with hypertension without moderate-to-advanced CKD and with high daily sodium intake, an increase of potassium intake of 0.5–1.0 g/day —for example through sodium substitution with potassium-enriched salt (comprising 75% sodium chloride and 25% potassium chloride) or through diets rich in fruits and vegetables— should be considered (class IIa).
- It is recommended to restrict sugar consumption, in particular sugar-sweetened beverages, to a maximum of 10% of energy intake (class I).

Treatment targets and pharmacological management

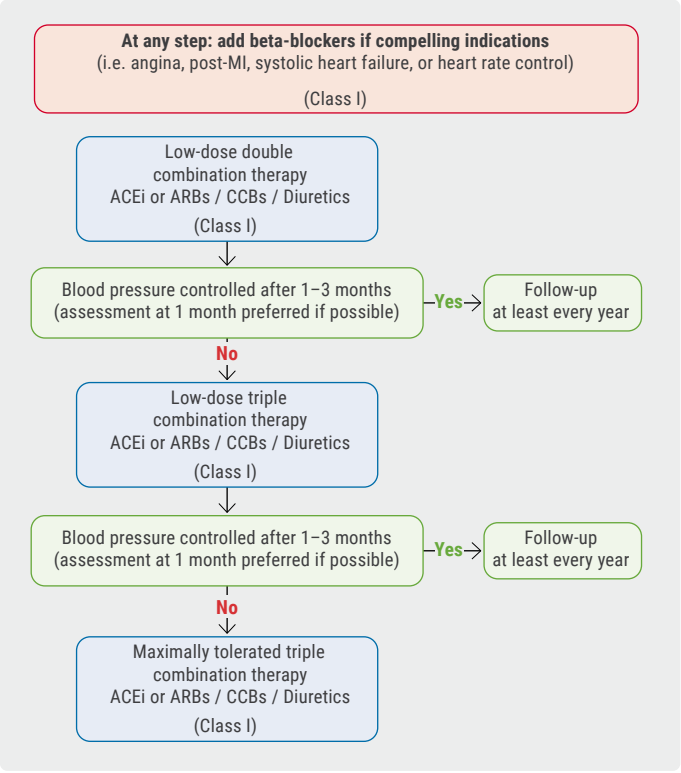
Guidance on when to start BP treatment is given in various new recommendations:

- In adults with elevated BP and low/medium CVD risk (<10% over 10 years), BP lowering with lifestyle measures is recommended and can reduce the risk of CVD (class I).
- In adults with elevated BP and sufficiently high CVD risk, after 3 months of lifestyle intervention, BP lowering with pharmacological treatment is recommended for those with confirmed BP ≥130/80 mmHg to reduce CVD risk (class I).
- It is recommended that in hypertensive patients with confirmed BP ≥140/90 mmHg, irrespective of CVD risk, lifestyle measures and pharmacological BP-lowering treatment are initiated promptly to reduce CVD risk (class I).

As for the treatment target, the committee implemented a simplified, yet intensified approach with a target of 120–129 mmHg in systolic BP. "This applies to most patients indeed, including patients with diabetes, patients with CKD, with previous stroke, and with cardiac disease," Prof. Bruno informed adding that "the lower the better." In patients with poor tolerance of this target, one should aim at going as low as possible (i.e. ALARA principle).

"We suggest that when patients have been diagnosed with hypertension, they start with a low dose of double combination therapy, and if BP has still not reached the target, low-dose triple combination therapy is suggested," said Prof. Touyz (see Figure). An initial monotherapy is, for example, recommended for elevated BP, frailty, and orthostatic hypotension. Finally, when performed in medium-to-high volume centres, renal denervation may also be considered in consenting adults with resistant hypertension on 3 drugs, or with a combination of increased CVD risk and uncontrolled BP on fewer than 3 drugs (class IIb).

Figure: Algorithm for pharmacological BP lowering. Modified from [3]



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; MI, myocardial infarction.

1. Presentations in Session '2024 ESC Guidelines Overview,' ESC Congress 2024, 30 Aug–02 Sept, London, UK.
2. Presentations in Session '2024 ESC Guidelines for the Management of Chronic Coronary Syndromes,' ESC Congress 2024, 30 Aug–02 Sept, London, UK.
3. McEvoy JW, et al. Eur Heart J. 2024; Aug 30. DOI: 10.1093/eurheartj/ehae178.

Guidelines for the management of chronic coronary syndromes

The 2024 ESC Guidelines offer a new definition and support the diagnosis and treatment of chronic coronary syndromes (CCS) for every clinician. The advice on the initial management of suspected CCS includes a stepwise approach to improve outcomes.

"Since 2019, there has been a paradigm shift in our understanding of the pathophysiology of myocardial ischaemia and CCS," stated Prof. Christiaan Vrints (University Hospital Antwerp, Belgium) [1]. This led to an updated, more comprehensive definition of the in 2019 introduced term 'CCS' that includes a range of clinical presentations or syndromes that arise due to structural or functional alterations related to chronic diseases of the coronary arteries or microcirculation [1–3]. Prof. Vrints also accentuated that the underlying pathophysiology is complex, as structural and functional abnormalities may present both at the epicardial and microvascular levels.

The new guidelines recommend a 4-step approach to the management of suspected CCS. Step 1 starts with a detailed assessment of cardiovascular risk factors, medical history, and symptom characteristics (class I), alongside a resting ECG and biochemistry. Step 2 involves further cardiac examination to rule out left ventricular (LV) dysfunction and valvular heart disease, and to evaluate the likelihood of obstructive coronary artery disease (CAD) using a new and better-calibrated likelihood model (see Figure). "The other models were essentially overestimating the probability of obstructive coronary disease," Dr Francisco Xavier Rosselló (Son Espases University Hospital, Spain) commented on the new guidance, which further details:

- It is recommended to estimate the pre-test likelihood of obstructive epicardial CAD using the risk factor-weighted clinical likelihood model (class I).
- It is recommended to use additional clinical data (e.g. examination of peripheral arteries, resting ECG, resting echocardiography, presence of vascular calcifications on previously performed imaging tests) to adjust the estimate yielded by the risk factor-weighted clinical likelihood model (class I).
- In individuals with a very low (≤5%) pre-test likelihood of obstructive CAD, deferral of further diagnostic tests should be considered (class IIa).
- In individuals with a low (>5–15%) pre-test likelihood of obstructive CAD, coronary artery calcium scoring (CACS) should be considered to reclassify subjects and to identify more individuals with very low (≤5%) CACS-weighted clinical likelihood (class IIa).

Figure: Pre-test likelihood estimation of obstructive CAD (risk factor-weighted). Modified from [3]

Symptom score

Number of risk factors	0-1 point						2 points						3 points					
	♀ Woman			♂ Man			♀ Woman			♂ Man			♀ Woman			♂ Man		
	0–1	2–3	3–4	0–1	2–3	3–4	0–1	2–3	3–4	0–1	2–3	3–4	0–1	2–3	3–4	0–1	2–3	3–4
Age 30–39	0	1	2	1	2	5	0	1	3	2	4	8	2	5	10	9	14	22
Age 40–49	1	1	3	2	4	8	1	2	5	3	6	12	4	7	12	14	20	27
Age 50–59	1	2	5	4	7	12	2	3	7	6	11	17	6	10	15	21	27	33
Age 60–69	2	4	7	8	12	17	3	6	11	12	17	25	10	14	19	32	35	39
Age 70–80	4	7	11	15	19	24	6	10	16	22	27	34	16	19	23	44	44	45

Clinical Likelihood — Very low — Low — Moderate

The third step in this approach aims at confirming the diagnosis and estimating the event risk tailored to the clinical likelihood of obstructive CAD. In individuals with low-to-moderate (>5–50%) pre-test likelihood, a coronary computed tomography angiography (CCTA) is now recommended (class I). In moderate-risk patients, functional imaging has the same class of recommendation as CCTA. "For high-risk patients, functional imaging has a class I indication, while, for patients with very high risk, invasive parameter angiography has a class I indication," Dr Rosselló informed.

Do not overlook angina or ischaemia with no obstructive CAD

"Patients with obstructive CAD only constitute the very tip of the iceberg, up to 50% of the men and 70% of the women with suspected CCS do not have obstructive CAD and they may suffer from angina with non-obstructive CAD [ANOCA] or ischaemia [INOCA]," Prof. Vrints highlighted. ANOCA and INOCA received new recommendations for diagnostics and management:

- Invasive coronary angiography with the availability of invasive functional assessments is recommended to confirm or exclude the diagnosis of obstructive CAD or ANOCA/INOCA in individuals with an uncertain diagnosis on non-invasive testing (class I).
- In symptomatic patients with ANOCA/INOCA, medical therapy based on coronary functional test results should be considered to improve symptoms and quality-of-life (class IIa).

CCS treatment

The last step in the recommended approach to the initial management of suspected CCS is all about treatment and includes lifestyle and risk modification, medication, and revascularisation. A new class I recommendation advises tailoring the selection of anti-anginal drugs to patient characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and costs.

"The guideline does not specify first- or second-line treatment but does give an order of strength of recommendation with beta-blockers, calcium channel blockers, and nitrates still holding the strongest class I or IIa," Prof. Felicita Andreotti (Gemelli University Hospital, Italy) detailed. Further new recommendations on therapy include:

- In patients with CCS and a prior MI or PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy (class I).
- In patients with CCS without prior MI or revascularisation but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong (class I).
- The GLP-1 receptor agonist semaglutide should be

considered in patients with CCS without diabetes but with overweight or obesity (BMI >27 kg/m^2), to reduce cardiovascular mortality, MI, or stroke (class IIa).
- In patients with CCS with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce MI, stroke, and need for revascularisation (class IIa).

Dr Konstantinos Koskinas (Bern University Hospital, Switzerland) encouraged his colleagues to take time to inform their patients and involve them in shared decision-making in an effort to increase long-term adherence to therapy.

Special guidance on revascularisation

For revascularisations, the guidelines recommend that physicians select the most appropriate modality based on the patient profile, coronary anatomy, procedural factors, LVEF, patient preferences, and outcome expectations (class I). Image guidance using intravascular ultrasound or optical coherence tomography for PCI is recommended for anatomically complex lesions (class I). In CCS with left main disease, important new class I recommendations on surgery have been issued:

- In patients with CCS at low surgical risk with significant left main coronary stenosis, coronary artery bypass graft surgery (CABG) is recommended:
  - over medical therapy alone to improve survival,
  - as the overall preferred revascularisation mode over PCI, given the lower risk of spontaneous MI and repeat revascularisation.
- In patients with CCS with significant left main coronary stenosis of low complexity (SYNTAX score ≤22), in whom PCI can provide equivalent completeness of revascularisation to that of CABG, PCI is recommended as an alternative to CABG, given its lower invasiveness and non-inferior survival.

1. Presentations in Session '2024 ESC Guidelines Overview,' ESC Congress 2024, 30 Aug–02 Sept, London, UK.
2. Presentations in Session '2024 ESC Guidelines for the Management of Chronic Coronary Syndromes,' ESC Congress 2024, 30 Aug–02 Sept, London, UK.
3. Vrints C, et al. Eur Heart J. 2024. DOI : 10.1093/eurheartj/ehae177.

Guidelines for the management of peripheral artery and aortic diseases

The 2024 Guidelines for the management of peripheral arterial and aortic diseases were developed by the task force of the ESC [1–3]. This groundbreaking document combines the management of peripheral arterial and aortic disease for the first time, emphasising a holistic multidisciplinary approach to vascular health.

The new guidelines recommend multidisciplinary management by an experienced team. The prevalence of peripheral arterial and aortic diseases is high: 113 million people ≥40 years are affected. Of those ages 80–84 years, nearly 15% have peripheral arterial and aortic disease [1].

PAD: Underdiagnosed and undertreated

Despite the high prevalence, particularly in women, peripheral arterial disease (PAD) is still too often overlooked. "The disease is often asymptomatic," Prof. Lucia Mazzolai (University Hospital Centre Vaudois, Switzerland) emphasised [2]. Thus, screening is necessary, as early PAD diagnosis is crucial for better outcomes. This is particularly true in women, because typical symptoms, such as intermittent claudication, are less common than in men, while atypical symptoms are more common.

The ankle-brachial index (ABI) is the recommended initial diagnostic test for PAD screening and diagnosis. An ABI ≤0.90 is chosen as a diagnostic criterion. "Duplex ultrasound is the recommended first-line imaging method to confirm PAD, especially in women," Prof. Mazzolai said. PAD is categorised according to clinical presentation and may or may not be associated with limb wounds.

The new guideline recognises the broad therapeutic aims of PAD management. As patients with PAD have a 4- to 5-time increased risk of CV events compared with patients without PAD, the goals of treatment are to reduce the risk of cardiac disease, cerebrovascular disease, and lower limb disease and to improve the quality-of-life of patients. This goal can best be achieved by an optimal multimodal medical treatment consisting of pharmacological treatment, supervised exercise training, and lifestyle behaviour.

A new recommendation is that revascularisation is not recommended in asymptomatic PAD. "Revascularisation is only recommended in symptomatic PAD patients following a period of optimal medical treatment and exercise and needs to be discussed in a multidisciplinary setting," Prof. Mazzolai said.

Another new recommendation is given for antithrombotic treatment following revascularisation. In these patients, a treatment combining rivaroxaban (2.5 mg twice daily) and aspirin (100 mg once daily) should be considered when a patient has a non-high bleeding risk (class IIa recommendation). There is also a new class I recommendation for aggressive lipid-lowering therapy with an LDL-C goal of <55 mg/dL (1.4

mmol/L). Regardless of revascularisation, supervised exercise training is recommended in patients with symptomatic PAD (class I). Walking should be recommended as the first-line training modality with a frequency and duration of 3x/week for 30 minutes.

A regular follow-up of patients with PAD is recommended, at least once a year (class I recommendation). "These patients need constant and lifelong follow-up. This is a chronic disease, we often forget this," Prof. Mazzolai concluded.

Standardisation in aortic nomenclature and measurement

"It is important for us to use the same nomenclature to be able to communicate properly," Prof. José Rodríguez Palomares (University Hospital Vall d'Hebron, Spain) pointed out [2]. Therefore, the new guidelines recommend (class I) a standardisation in aortic nomenclature and measurements. A transthoracic echocardiogram (TTE) is recommended as the first-line imaging technique in evaluating thoracic aortic diseases. A second recommendation is the evaluation of risk factors for aneurysm rupture. Aortic diameters are measured at prespecified anatomical landmarks. Aortic diameter is the most important predictor of aneurysm rupture, but not as a sole predictor. "It has to be coupled with other morphological criteria like aortic length and the aortic phenotype," explained Prof. Alessandro Della Corte (University of Campania Luigi Vanvitelli, Italy) [3]. Especially for body sizes at the lower end of the normal distribution index in aortic diameter to body surface area (BSA), nomograms, z-scores, or other indexing methods should additionally be considered for a more accurate assessment of aortic size (class IIa recommendation).

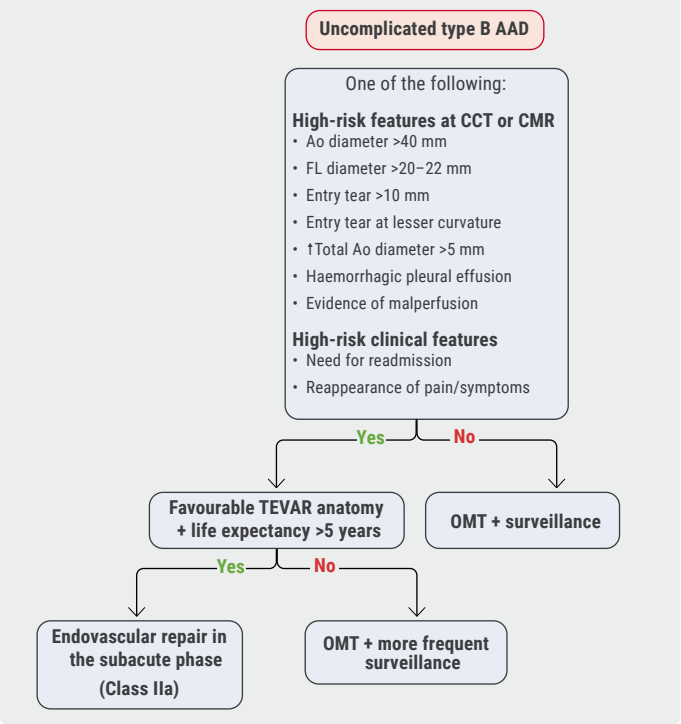
Surgery is now recommended in all patients with dilatation of the aortic root or ascending aorta with a tricuspid aortic valve and a maximum diameter of ≥55 mm. Valve-sparing aortic root replacement is recommended if the technique is feasible. In patients with low predicted risk, surgery is even advocated at smaller diameters.

The new guidelines provide an algorithm for the surveillance of patients with non-heritable thoracic aortic disease with different surgical options based on individual patients. Moreover, a new algorithm is introduced for genetic and imaging screening in patients with thoracic aortic disease. "If the patient is younger than 60 years and presents with acute aortic syndrome or aortic dilatation without CV risk factors, we should refer this patient to a specialised centre," Prof. Palomares said [2]. In case of a positive genetic test, genetic testing of at-risk biological relatives is recommended.

Another new algorithm aims to prevent delay of diagnosis in patients with acute aortic syndrome (AAS) that advocates immediate cardiovascular CT in high-risk patients. The novel algorithm for medical management of AAS is based on 3 steps. The first step consists of rate/pressure control titrated to a heart rate of 60 bpm. Second comes pain control with intravenous opiates. Step 3 follows when systolic BP remains ≥120 mmHg and entails intravenous vasodilators with the goal of the lowest possible BP that maintains adequate organ perfusion.

Finally, the guidelines contain an interventional treatment algorithm for acute aortic dissection (AAD) [1]. A new recommendation for endovascular repair is given in the subacute phase of uncomplicated type B AAD in patients with risk factors, if feasible (see Figure). The main problem in these conditions continues to be a delay in diagnoses or transferring patients to an aortic centre.

Figure: Interventional treatment algorithm for patients with uncomplicated type B acute aortic dissection (AAD). Modified from [1]



AAD, acute aortic dissection; Ao, Aorta; CCT, cardiovascular computed tomography; CMR, cardiovascular magnetic resonance FL, false lumen; OMT, optimal medical therapy, TEVAR, thoracic endovascular aortic repair.

1. Mazzolai L, et al. Eur Heart J 2024;45(36):3538-3700.
2. Presentations in Session '2024 ESC Guidelines Overview' ESC Congress 2024, 30 Aug–02 Sept, London, UK.
3. Presentations in Session '2024 ESC Guidelines for the management of peripheral arterial and aortic diseases,' ESC Congress 2024, 30 Aug–02 Sept, London, UK.

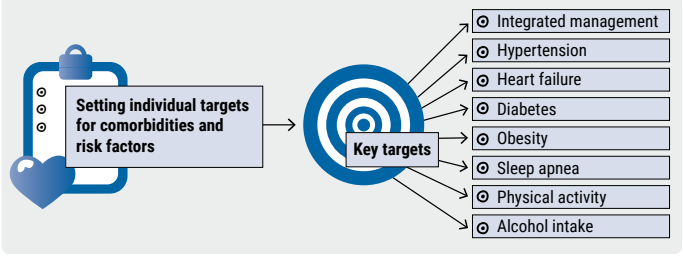
Guidelines for the management of atrial fibrillation

This 2024 update of the 2020 ESC Guidelines for the management of AF has been developed by the task force of the ESC in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) and with the special contribution of the European Heart Rhythm Association (EHRA) [1–3]. The new version places a strong focus on individualised care, early intervention, and comprehensive management of concomitant diseases.

The prevalence of AF, one of the most commonly encountered heart conditions, is expected to double in the next few decades as a consequence of the ageing population, an increasing burden of comorbidities, improved awareness, and new technologies for detection [1]. "First and very important, we recommend treating all our patients with AF according to our patient-centred integrated AF-CARE approach," explained Prof. Isabel van Gelder (University Medical Center Groningen, the Netherlands). The "C" in the AF-CARE concept stands for a focus on recognising and treating comorbidities and risk factors. The "A" stands for avoidance or prevention of stroke and thromboembolism. The "R" for reduction of symptoms by rate and rhythm control, and a new recommendation "E" for evaluation and dynamic reassessment.

"The first pillar of care is comorbidity and risk factor management. We know that a broad array of comorbidities and risk factors are associated with the recurrence and progression of AF," said Prof. Michiel Rienstra (University Medical Center Groningen, the Netherlands) [3]. There is a class I recommendation to identify and treat comorbidity and risk factors aggressively as this is crucial for the success of all other aspects of care for patients with AF. Key targets are hypertension, heart failure, obesity, obstructive sleep apnoea, alcohol intake, and diabetes mellitus (see Figure). Healthcare professionals should set individual and achievable targets for comorbidities and risk factors. These targets should be discussed with the patient in a shared decision-making process.

Figure: Management of key comorbidities, the "C" in the AF-CARE concept. Modified from [1]



To avoid stroke and thromboembolism, it is key to prevent adverse outcomes. Therefore, locally validated risk scores or the CHA_2DS_2-VA score should be used in patients with persistent AF. In this novel score, the recommendations do not differentiate between men and women. "This is an enormous simplification, and we assume that this will lead to a better adherence to our guideline recommendations," said Prof. van Gelder. In contrast, the use of bleeding risk scores is not recommended to decide on starting or withdrawing anticoagulants. There is a class I recommendation for oral anticoagulants in patients with a CHA_2DS_2-VA score of 2 or more and a class IIa for patients with a score of 1. Vitamin K antagonists are only recommended in patients with mechanical heart valves or mitral stenosis. All modifiable risk factors for bleeding should be assessed and managed. To prevent bleeding, the combination of antiplatelet agents and oral anticoagulants is not recommended.

"Thereafter, we move on to the 'R'," Prof. van Gelder said. Reducing symptoms through rate and rhythm control is essential to improve patients' quality-of-life. In the acute setting, rate-controlling drugs are recommended as initial therapy; as adjunct to rhythm control therapy or as sole treatment. Rhythm control is considered in all suitable patients, but, again, safety first.

The 'E' in the AF-CARE concept stands for regular re-evaluation of the patient, which is recommended 6 months after presentation, and then at least annually or based on clinical need.

Interventional rhythm control: always performed following shared decision-making

Many new studies have led to an upgrade in the recommendations for interventional rhythm control. "We now have a class I recommendation for catheter ablation as a first-line option for paroxysmal AF, for paroxysmal and persistent AF after failed anti-arrhythmic drugs, and, of course, for those patients where you have a high probability that tachycardia is inducing some kind of cardiomyopathy," Prof. Dipak Kotecha (University of Birmingham, UK) pointed out [2]. An endoscopic ablation or hybrid approach got a class IIa recommendation for patients with persistent AF despite anti-arrhythmic therapy. Moreover, there is a class I recommendation for surgical ablation in patients with mitral valve surgery and a class IIa recommendation for those with non-mitral valve surgery.

Prior to interventional rhythm control, a shared decision-making process is recommended (class I) for all patients to

consider procedural risks, likely benefits, and risk factors for AF recurrence. Prof. Kotecha also emphasised the importance of periodical reassessment of all patients with AF, as recommended in the novel AF-CARE approach. Equally important is to screen patients for AF after a thromboembolic event and to inform patients about the implications of AF detection.

"AF is a huge burden for patients, but it is also very variable and that can be very challenging," Prof. Kotecha said. It is often complex to recognise whether symptoms are induced by AF or one of the underlying comorbidities. There is the increased risk of stroke but also a 2-fold increase of heart failure and incremental evidence that AF might contribute to the increasing number of patients with vascular dementia. At the core of the new guideline is the management of patients in a multidisciplinary team of doctors, nurses, and other healthcare professionals.

1. Van Gelder IC, et al. Eur Heart J 2024; Aug 30. DOI: 10.1093/eurheartj/ehae176.
2. Presentations in Session '2024 ESC Guidelines Overview,' ESC Congress 2024, 30 Aug–02 Sept, London, UK.
3. Presentations in Session '2024 ESC Guidelines for the Management of Atrial Fibrillation,' ESC Congress 2024, 30 Aug–02 Sept, London, UK

Crossing Borders in Arrhythmia

EPIC-CAD: What is the best antithrombotic approach in high-risk AF plus stable CAD?

Edoxaban monotherapy was associated with lower bleeding than edoxaban plus antiplatelet therapy in patients with high-risk atrial fibrillation (AF) and stable coronary artery disease (CAD) in the large EPIC-CAD trial. Ischaemic event rates were low and the risk for bleeding was significantly reduced in the monotherapy arm.

"Choosing the optimal antithrombotic therapy for patients with CAD and AF is challenging," expressed Dr Gi-Byoung Nam (Ulsan University Hospital, South Korea) [1]. "Patients with AF need prevention of thromboembolic events with anticoagulants and patients with CAD need antiplatelet therapy to prevent ischaemic events." The combined use of these drugs comes with an increased risk of bleeding [2]. The authors of the current study hypothesised that edoxaban monotherapy would be superior to dual antithrombotic therapy in terms of a combined ischaemic and bleeding endpoint in patients with CAD and AF [1,3].

In the phase 4 EPIC-CAD trial (NCT03718559), 1,038 participants with high-risk AF and stable CAD from 18 sites in South Korea were randomised 1:1 to edoxaban monotherapy or to dual antithrombotic therapy with edoxaban plus a single anti-platelet agent. Stable CAD was defined as revascularisation for a chronic coronary syndrome at least 6 months prior, revascularisation for ACS at least 12 months prior, or anatomically confirmed coronary disease managed without revascularisation. The primary endpoint was a composite of all-cause death, stroke, systemic embolic events, myocardial infarction, unplanned urgent revascularisation, major bleeding, and clinically relevant non-major bleeding after 1 year of therapy.

Dual antithrombotic therapy led to more adverse events than edoxaban monotherapy, as revealed by the primary outcome (16.2% vs 6.8%; HR 0.44; 95% CI 0.30–0.65; P<0.001). The incidence of major ischaemic events was low in both of the 2 study arms (1.8% vs 1.6%; HR 1.23; 95% CI 0.48–3.10), whereas major or clinically relevant non-major bleeding was more common in the dual antithrombotic therapy arm than in the monotherapy arm (14.2% vs 4.7%; HR 0.34; 95% CI 0.22–0.53). Dr Nam acknowledged that the trial was underpowered for ischaemic thrombotic events as a sole endpoint.

The EPIC-CAD study suggests that edoxaban monotherapy is linked to a lower risk of bleeding compared with dual antithrombotic therapy with edoxaban and an antiplatelet agent in patients with AF and stable CAD. "The effect appeared to be driven by a decreased risk for bleeding events in the monotherapy arm," concluded Dr Nam.

1. Nam G-B, et al. Edoxaban-based long-term antithrombotic therapy for atrial fibrillation and stable coronary disease: The EPIC-CAD randomised clinical trial. HOTLINE 6, ESC Congress 2024, 30 Aug–02 Sept, London, UK.
2. Gibson CM, et al. N Engl J Med 2016;375:2423.
3. Cho MS, et al. N Engl J Med 2024; 1 Sept. DOI: 10.1056/NEJMoa2407362.

OCEANIC-AF: Asundexian inferior to apixaban for ischaemic stroke prevention in AF

The factor XIa inhibitor asundexian was inferior to apixaban in preventing stroke or systemic thromboembolism in patients with atrial fibrillation (AF) and an increased risk for stroke in the large, phase 3 OCEANIC-AF trial.

"Although direct oral anticoagulants [DOACs] are accepted as first-line therapy for patients with AF, patients treated with DOACs still face a bleeding risk of 2.7–3.5% per year," explained Dr Manesh Patel (Duke Clinical Research Institute, NC, USA) [1]. Undertreatment, underdosing, and poor treatment compliance are other challenges linked to treatment with DOACs. The phase 3 OCEANIC-AF trial (NCT05643573) compared the factor XIa inhibitor asundexian (50 mg, once daily) to the established DOAC apixaban, a factor Xa inhibitor, in a large population of patients with AF at risk for stroke or systemic embolism (n=14,830) [2]. Although the planned sample size was 18,000, the trial was terminated early due to the inferiority of the investigational agent in the primary efficacy endpoint of stroke/systemic embolism.

After a median follow-up of 155 days, the rate of stroke/systemic embolism was 1.3% in the asundexian arm versus 0.4% in the apixaban arm (HR 3.79; 95% CI 2.46–5.83) [1]. Asundexian was associated with fewer ISTH major bleeding events than apixaban (0.2% vs 0.7%; HR 0.32; 95% CI 0.18–0.55).

The OCEANIC-AF study revealed that asundexian was inferior to apixaban for the prevention of stroke and systemic embolism in a population of patients with AF and a high risk for stroke. Dr Patel argued that more research is needed to determine the optimal degree of factor XIa inhibition for stroke prevention in patients with AF. "It may be that (near) total suppression of factor XIa is needed to achieve the efficacy endpoints," he reasoned, suggesting that the dose may have been insuffient. Multiple factor XIa inhibition trials in various indications are ongoing, further informing the community about the effect of factor XIa inhibition.

1. Patel MR, et al. OCEANIC-AF: asundexian vs apixaban in patients with atrial fibrillation. HOTLINE 6, ESC Congress 2024, 30 Aug–02 Sept, London, UK.
2. Piccini JP, et al. N Engl J Med 2024; Sept 1. DOI: 10.1056/NEJMoa2407105.

MIRACLE-AF: Elegant solution to improve AF care in rural China

Through telemedicine, village doctors in rural China were able to professionalise the management of atrial fibrillation (AF) among elderly patients, improving clinical outcomes in this population with limited access to high-quality healthcare. According to the authors, the used model could serve as a blueprint for similar settings across the globe.

"Elderly patients with AF in rural China are difficult to reach due to their low educational level, limited access to information technology, long travel time to hospitals, and travel difficulties," explained Prof. Minglong Chen (First Affiliated Hospital of Nanjing Medical University, China) [1]. "The only way we can reach them is to empower village doctors to provide good quality chronic disease care."

Prof. Chen and colleagues designed a novel integrated AF care model that connects AF specialists and village doctors through telemedicine to deliver quality AF care. The cluster-randomised MIRACLE-AF trial (NCT04622514) tested the value of this care model with 1,039 participants from 30 villages. The participants were randomised to the telemedicine arm or to usual care. The first primary outcome was adherence to the ABC pathway at 12 months (i.e. **A**void stroke by appropriately using anticoagulant therapy, **B**etter symptom management with patient-centred symptom-directed rhythm or rate control, and **C**ardiovascular and comorbidity risk factor management). The second primary outcome was a composite of cardiovascular events at 36 months.

At 12 months, adherence to the ABC pathway was significantly increased in the intervention arm compared with the control arm (33.1% vs 8.7%; P<0.001). This effect was driven by the uptake of anticoagulation therapy in the telemedicine arm (85.2% vs 20.8%; P<0.001). Furthermore, participants in the intervention arm had fewer cardiovascular events at 3 years of follow-up than those in the control arm (6.2% vs 9.6% per year; HR 0.64; 95% CI 0.50–0.82; P<0.01).

Annual cardiovascular death (1.7% vs 3.4%; HR 0.50; 95% CI 0.32–0.80; P=0.004), annual stroke rate (1.5% vs 2.4%; HR 0.64; 95% CI 0.41–1.00; P=0.049), and annual hospitalisation due to heart failure or acute coronary syndrome (3.2% vs 4.7%; HR 0.69; 95% CI 0.49–0.95; P=0.025) were all significantly lower in the telemedicine arm than in the control arm.

"The MIRACLE-AF model appears to be a well-rounded solution for improving AF care delivery that could be generalised to the older population across rural China and other low- and middle-income countries with limited healthcare access," concluded Prof. Chen.

1. Chen M, et al. A novel model of integrated care of older patients with atrial fibrillation on cardiovascular outcomes in rural China. HOTLINE 9, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

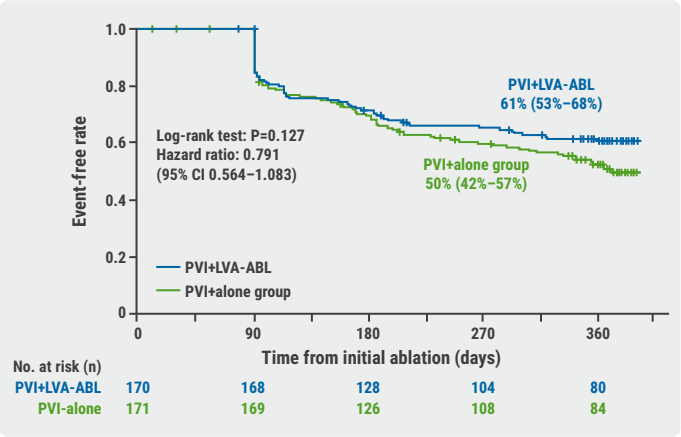
SUPPRESS-AF: What is the value of adding LVA ablation to PVI in AF?

Low-voltage-area (LVA) ablation plus pulmonary vein isolation (PVI) was not superior to PVI alone in patients with persistent atrial fibrillation (AF) with respect to recurrence of AF. However, patients with advanced left atrial remodelling did appear to benefit from adding LVA ablation to PVI.

"PVI is a standard ablation procedure for persistent AF," said Dr Masaharu Masuda (Kansai Rosai Hospital, Japan) [1,2]. However, the efficacy of this procedure is suboptimal. "And no additional ablation procedure has shown consistent benefits." In the SUPPRESS-AF trial, participants with persistent AF and left atrial LVA >5 cm^2 undergoing a first ablation (n=341) were randomised 1:1 to PVI plus LVA ablation or PVI alone. The primary endpoint was 1-year freedom from AF/atrial tachycardia (AT) recurrence after initial ablation.

At 1 year, freedom from AF/AT recurrence was reported in 61% of the participants in the additional LVA ablation group and 50% of those in the PVI-alone group, a non-significant difference (HR 0.79; 95% CI 0.56–1.08; $P_{log\text{-}rank}$=0.13; see Figure). "A subgroup analysis showed that the efficacy of LVA ablation may be more pronounced in patients with advanced atrial remodelling," mentioned Dr Masuda. Participants with a CHA_2DS_2VA score of 4 or higher, those with an NYHA class of II or higher, a left atrial diameter ≥45 mm, or an LVA size ≥20 cm^2 appeared to have a larger benefit from the additional LVA ablation procedure than participants without thesecharacteristics. Finally, there was no substantial difference between the 2 arms in terms of safety.

Figure: Freedom from AF/AT recurrence after initial ablation [2]



LVA-ABL, low-voltage-area ablation; PVI, pulmonary vein isolation.

"LVA ablation in addition to PVI is not recommended as a routine procedure for persistent AF," concluded Dr Masuda. "However, if the patient has left atrial remodelling, LVA ablation could be a therapeutic option."

1. Hindricks G, et al. Eur Heart J. 2021;42:373-498
2. Masuda M, et al. The efficacy of low-voltage-area ablation in patients with persistent atrial fibrillation: results from a SUPPRESS-AF trial. HOTLINE 10, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

Clever Ideas for Coronary Artery Disease

ABYSS: Can beta-blocker safely be interrupted post-MI?

Beta-blocker interruption after a myocardial infarction (MI) failed to meet non-inferiority criteria in the ABYSS trial. Discontinuation resulted in higher hospitalisation rates among patients with MI and a preserved left ventricular ejection fraction (LVEF) compared with continued treatment with a beta-blocker, particularly in patients with hypertension. Furthermore, no quality-of-life improvements were reported in the beta-blocker interruption arm.

The phase 3, open-label, non-inferiority ABYSS trial (NCT03498066) randomised 3,698 stabilised patients with a history of MI and a preserved LVEF (≥40%) 1:1 to beta-blocker interruption or continued treatment to assess the safety and effect on quality-of-life of the interruption strategy [1,2]. The primary endpoint was a composite of death, MI, stroke, or hospitalisation for cardiovascular reasons, with a minimal follow-up of 1 year.

After a median follow-up of 3.0 years, participants in the interruption arm had a slightly increased risk of experiencing a primary outcome event than participants in the continuation arm (23.8% vs 21.1%; HR 1.16; 95% CI 1.01–1.33; $P_{non\text{-}inferiority}$=0.44). "This effect was driven by an increase in hospitalisations for cardiovascular reasons [18.9% vs 16.6%]," explained Prof. Johanne Silvain (Pitié-Salpêtrière University Hospital, France).

Next, the authors observed no difference in quality-of-life scores between the 2 treatment arms, as measured by the EQ-5D-5L score. However, they did note that participants in the interruption arm had significantly higher systolic blood pressure (+3.7%) and diastolic blood pressure (+3.9%) at 6 months than those in the continuation arm. Similarly, the interruption strategy significantly increased the heart rate of these participants with a mean of 9.8 bpm (P<0.001) compared with baseline.

In short, the ABYSS trial showed that beta-blocker interruption was not as safe as beta-blocker continuation, leading to a higher rate of hospitalisations among patients with MI and a preserved LVEF. Prof. Silvain added that these results need to be contextualised with recent findings from the REDUCE-AMI trial and ongoing trials on the optimal use of beta-blockers after MI.

1. Silvain J, et al. N Engl J Med 2024;391:1277-1286.
2. Silvain J, et al. Assessment of Beta blocker interruption one year after an uncomplicated myocardial infarction on safety and symptomatic cardiac events requiring hospitalisation. HOTLINE 1, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

SWEDEGRAFT: Can a no-touch vein harvesting technique improve outcomes in CABG?

A no-touch vein harvesting strategy was not superior to conventional surgery in patients undergoing non-emergent coronary artery bypass grafting (CABG) in the registry-based SWEDEGRAFT trial. However, the investigational technique was associated with an increased rate of leg wound complications.

The open-label, registry-based SWEDEGRAFT trial (NCT03501303) hypothesised that no-touch vein grafts outperform conventionally harvested veins regarding graft patency and long-term clinical outcomes. To test this hypothesis, Prof. Stefan James (Uppsala University, Sweden) and colleagues randomised 900 participants from Sweden and Denmark undergoing non-emergent CABG 1:1 to the no-touch saphenous vein graft (SVG) arm or the conventional SVG arm [1]. The primary endpoint was graft failure within 2 years after CABG, defined as at least 1 SVG occluded/stenosed >50% on computed tomography angiography, PCI in a vein graft or adjacent native vessel, or death.

Although the primary endpoint was numerically in favour of the no-touch arm after a mean duration of 3.5 years following randomisation, the observed difference in primary outcome events did not reach statistical significance (19.8%, vs 24.0% in the conventional arm; difference -4.3% 95% CI -10.1 to 1.6; P=0.15). Prof. James added that the investigators did see a remarkable significant interaction effect: participants in the no-touch arm without diabetes had a lower event rate (OR 0.61; 95% CI 0.40–0.92), whereas participants in the no-touch arm with diabetes had an increased event rate (OR 2.05; 95% CI 1.08–3.88; P=0.0018), each compared with the conventional arm.

There was no significant difference between the no-touch and conventional arms with respect to major adverse cardiac events (MACE; 12.6% vs 9.9%; HR 1.30; 95% CI 0.87–1.93; P=0.20). However, leg wound complications at 3 months were significantly more common in the no-touch arm (24.7% vs 13.8%), as was the rate of participants who still had leg wound symptoms at 2 years of follow-up (49.6% vs 25.2%).

"Our trial does not support the routine use of the no-touch harvesting technique compared with the standard technique of vein handling for patients undergoing non-emergent CABG," concluded Prof. James. "It also does not support the current ESC guideline recommendation on myocardial revascularisation that says to 'consider no-touch vein harvesting when an open technique is used.'"

1. James S, et al. No-touch vein grafts in coronary artery bypass surgery: a Nordic, randomised, registry-based clinical trial on no-touch vein grafts in coronary surgery (SWEDEGRAFT). HOTLINE 4, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

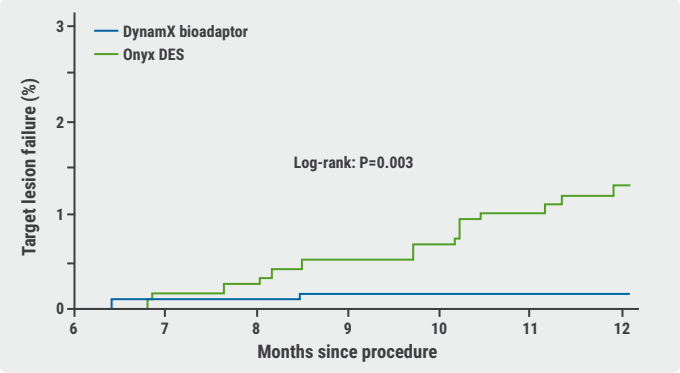
Bioadaptor meets expectations in reducing target lesion failures in coronary artery disease

A novel drug-eluting bioadaptor was associated with reduced target lesion failure (TLF) after 6 months compared with a regular drug-eluting stent (DES) in a large population of patients with coronary artery disease (CAD). According to the authors, the bioadaptor can restore the haemodynamic modulation of the target vessel, resulting in improved long-term outcomes.

"Stent-related adverse events continue to accumulate after the first year at a rate of 2–3% per year," outlined Prof. David Erlinge (Lund University, Sweden) [1]. The bioadaptor is designed to restore the haemodynamic modulation of the vessel after 6 months. The INFINITY-SWEDEHEART trial compared the conventional Onyx DES with the DynamX bioadaptor in a broad population of patients with CAD, including patients with acute coronary syndrome. The participants (n=2,400) were randomised in a 1:1 fashion, and TLF at 1 year was the primary non-inferiority endpoint.

The primary endpoint was met, with event rates of 2.35% and 2.77% for the experimental arm and control arm, respectively ($P_{non\text{-}inferiority}$<0.001). "The most interesting endpoint of this trial is, however, the pre-specified powered secondary endpoint of TLF after 6 months," according to Prof. Erlinge. Between months 6 and 12, the TLF event rate was significantly lower in the bioadaptor arm than in the conventional DES arm ($P_{log\text{-}rank}$=0.003; see Figure).

Figure: Significant reduction and plateau in TLF events after 6 months [1]



DES, drug-eluting stent; TLF, target lesion failure.

Moreover, the incidence of target-vessel myocardial infarction ($P_{log\text{-}rank}$=0.012) and target lesion revascularisation (P=0.003) was lower in the bioadaptor arm than in the control arm between months 6 and 12 of the study. Finally, target vessel failure was significantly reduced in the experimental arm after month 6 ($P_{log\text{-}rank}$=0.008).

"This large randomised-controlled trial confirmed that the unique 'unlocking' mechanism of a bioadaptor at 6 months leads to a plateauing of adverse events, resulting in better outcomes with a bioadaptor than a conventional DES in patients with CAD," concluded Prof. Erlinge.

1. Erlinge D, et al. INFINITY-SWEDEHEART: percutaneous coronary intervention with a Bioadaptor compared to a contemporary drug-eluting stent (DES) in a large broad clinical population. HOTLINE 11, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

REC-CAGEFREE I: Can we avoid permanent stenting with drug-coated balloons?

A strategy utilising a drug-coated balloon (DCB) with rescue stenting was inferior to standard drug-eluting stenting (DES) in patients with newly diagnosed coronary artery disease (CAD). Although longer follow-up is needed, findings from the REC-CAGEFREE I trial suggested that DES remains the preferred treatment strategy.

"A balloon coated with antiproliferative drugs may be used in patients with CAD to avoid the implant of a permanent scaffold," argued Dr Ling Tao (Xijing Hospital, China) [1]. To test this hypothesis, the investigator-initiated, multicentre REC-CAGEFREE I trial (NCT04561739) randomised patients with *de novo*, non-complex CAD who underwent successful pre-dilation (n=2,272) 1:1 to DCB with rescue stenting or to standard DES. The primary endpoint was a composite of cardiac death, target-vessel myocardial infarction (MI), and clinically and physiologically indicated target lesion revascularisation at 2 years.

At 2 years, the DCB arm displayed inferior outcomes to the standard-of-care arm, with primary outcome event rates of 6.4% versus 3.4% ($P_{non\text{-}inferiority}$=0.65) [1,2]. Differences between the 2 arms were seen in cardiac death (2.3% vs 1.2%; P=0.053) and revascularisation (3.1% vs 1.2%; P=0.002) rates, whereas target-vessel MI rates appeared to be similar (1.9% vs 1.6%; P=0.61). "The significant difference between the 2 arms regarding the primary endpoint was mainly present in patients with non-small vessel disease [7.5% vs 2.5%], whereas patients with small vessel disease had comparable outcomes [5.1% vs 4.4%]," added Dr Tao [1].

"DES implantation should remain the preferred treatment strategy for newly diagnosed patients with CAD, especially if they have non-small vessel disease," concluded Dr Tao. "Longer follow-up will reveal whether the higher revascularisation rates translate into higher MI or mortality rates."

1. Tao L, et al. DCB with rescue stenting versus intended stenting for de novo CAD: a multicenter, non-inferiority trial. HOTLINE 11, ESC Congress 2024, 30 Aug–02 Sept, London, UK.
2. Gao C, et al. Lancet 2024;404(10457):1040-1050.

OCCUPI: OCT-guided PCI improves outcomes in complex CAD

Patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation for complex lesions benefitted from an optical coherence tomography (OCT)-guided procedure compared with an angiography-guided procedure in terms of major adverse cardiovascular events (MACE).

"Anatomically complex coronary artery disease (CAD) still presents challenges, despite the advancements that have been made with PCI plus DES," said Prof. Byeong-Keuk Kim (Yonsei University Hospital, South Korea) [1]. The OCCUPI trial (NCT03625908) aimed to assess the possible clinical benefits of OCT for patients with complex lesions. This multicentre, open-label, randomised trial included 1,604 participants with complex coronary lesions, who were allocated to the OCT-

guided PCI arm or the angiography-guided PCI arm [1,2]. The primary endpoint was MACE at 1 year of follow-up.

The primary endpoint favoured the OCT-guided arm, with a lower event rate in this arm than in the control arm (4.6% vs 7.4%; HR 0.62; 95% CI 0.41–0.93; P=0.023) [1]. Looking at the individual components of this endpoint, Prof. Kim and co-investigators found that the occurrence of spontaneous myocardial infarction (MI; 0.9% vs 2.4%), target-vessel related MI (0.6% vs 2.1%), and target vessel revascularisation (1.5% vs 4.1%) were all significantly in favour of the OCT-guided arm. "Patients meeting all the criteria of stent optimisation in the OCT-guided arm were less likely to experience MACE than patients who did not meet all 3 criteria," added Prof. Kim (2.9% vs 8.6%; HR 0.33; 95% CI 0.17–0.65; P=0.001).

"The findings of the OCCUPI trial support the therapeutic benefit of OCT as an effective intravascular imaging modality in treating complex lesions," concluded Prof. Kim.

1. Kim B-K, et al. Optical coherence tomography-guided coronary intervention in patients with complex lesions: the OCCUPI randomised clinical trial. HOTLINE 11, ESC Congress 2024, 30 Aug–02 Sept, London, UK.
2. Hong S-J, et al. Lancet 2024;404(10457):1029-1039.

Highway to Hypertension Control

Is administering BP medication in the evening better than in the morning?

A recent meta-analysis showed that administering blood pressure (BP)-lowering drugs in the evening compared with in the morning did not decrease the risk of major adverse cardiovascular events (MACE). Thus, the authors argue that daily BP-lowering medication can be taken at a time that is most convenient for the patient.

"BP follows a circadian rhythm, with a peak after awakening and the lowest values during sleep," explained Dr Ricky Turgeon (University of British Columbia, Canada) [1]. "The lack of BP decline at night has been associated with an increased risk for MACE. It might, therefore, be that evening administration of BP-lowering medication yields better outcomes with respect to MACE."

Dr Turgeon and co-investigators performed a meta-analysis to analyse the risk of MACE as an effect of the time of day that antihypertensive agents are taken. The analysis included 5 trials (i.e. MAPEC, Hygia, TIME, BedMed, and BedMed-Frail) with data from 46,606 participants. Most trials had a follow-up duration of approximately 5 years.

No significant effect was seen of evening administration compared with morning administration on MACE (HR 0.71; 95% CI 0.43–1.16). "If we excluded the 2 trials with a high risk of bias, the effect of evening administration appeared to be even closer to 1," added Dr Turgeon (HR 0.94; 95% CI 0.86–1.03).

"Thus, evening administration was not associated with a reduced risk of MACE," concluded Dr Turgeon. "The evidence does not support the concept of chronotherapy in hypertension management."

1. Turgeon R, et al. Meta-analysis of trials of antihypertensive medication bedtime dosing including individual-patient data from BedMed and BedMed-Frail. HOTLINE 2, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

Low-dose 3-drug pill GMRx2 shows promise in lowering BP

The new anti-hypertensive low-dose, triple combination pill called GMRx2 was superior to dual therapies or placebo in reducing blood pressure (BP) in two phase 3, international trials, with no substantial difference in safety outcomes.

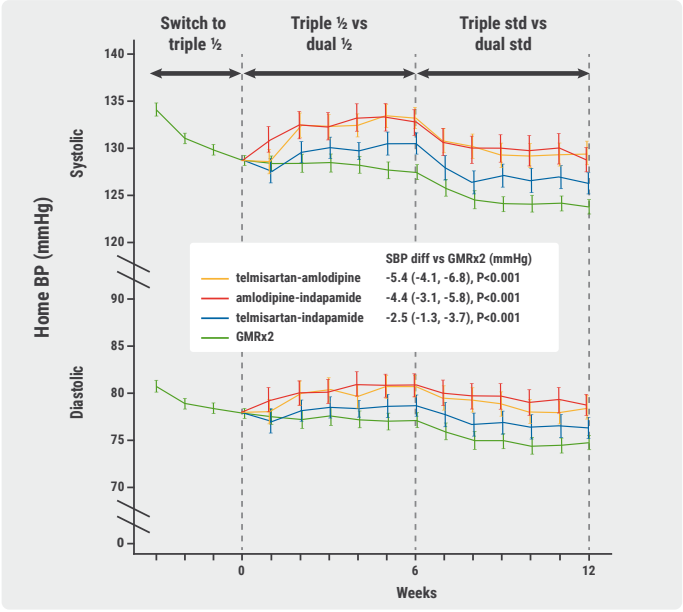
GMRx2 has a standard dose of 40 mg telmisartan, 5 mg amlodipine, and 2.5 mg indapamide and the planned indication is hypertension, including initial treatment. Prof. Anthony Rodgers (George Institute, Australia) discussed the results of two recent trials assessing the efficacy and safety of GMRx2 compared with placebo and 3 dual treatments [1].

In a placebo-controlled trial study (NCT04518306), 295 participants with home systolic BP between 130 and 154 mmHg were randomised 2:2:1 to 1/4 of the GMRx2 standard dose, 1/2 of the GMRx2 standard dose, or a placebo. After 4 weeks of therapy, the active arms were significantly more efficacious than placebo, with mean in-clinic reductions of systolic BP of

-8 and diastolic BP of -4 for the lowest dose, and -10 and -5 for the higher dose. In total, none of the participants withdrew due to adverse events (AEs) in the lowest dose group, compared with 5% and 2% of the participants in the higher dose group and placebo group, respectively. According to Prof. Rodgers, the active agent was safe and tolerable, with hypotension (4–5%) and mild-to-moderate abnormal laboratory findings (8–10%) as the most common side effects.

An active-controlled trial (NCT04518293) started with a 4-week run-in period on 1/2 of the GMRx2 standard dose. Subsequently, 1,385 participants with a systolic BP between 110–154 mmHg were randomised 2:1:1:1 to 1/2 of the GMRx2 standard dose or 1 of 3 dual therapy regimens. After 6 weeks, all participants received the standard dose of the respective therapies. The primary endpoint was systolic BP at week 12. At week 12, GMRx2 outperformed all dual therapies with respect to systolic BP, with mean differences ranging between 2.5 and 5.4 mmHg (P<0.001 for all; see Figure). The rate of treatment withdrawals due to AEs was 2% in the GMRx2 arm and 1% in the other arms. "There were no apparent differences between the study arms with respect to safety," commented Prof. Rodgers.

Figure: Home blood pressure over time by treatment group [1]



BP, blood pressure; SBP, systolic blood pressure.

The novel GMRx2 single 3-drug pill was superior to dual therapies and placebo in terms of lowering BP, without increasing toxicity.

1. Rodgers A, et al. GMRx2: single pill combination of telmisartan, amlodipine and indapamide to treat hypertension, including initial treatment: Two pivotal trials of novel low dose triple combination. HOTLINE 2, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

VERONICA: Improving BP control in Africa with a simple strategy

A single 3-drug pill (GMRx2) protocol to reduce blood pressure (BP) among Nigerian patients with hypertension yielded excellent efficacy results and a good safety profile, demonstrating that a simple treatment protocol can strongly improve the current standard-of-care for this population.

"There is a need for simple, low-cost, scalable treatment strategies for patients with hypertension in Africa," according to Dr Dike Ojji (Abuja University, Nigeria) [1]. "Most patients still receive only 1 anti-hypertensive agent, while guidelines recommend that patients should receive at least 2 agents."

The investigator-initiated VERONICA-Nigeria trial randomised 300 self-identified Black African adults with uncontrolled hypertension from Nigeria 1:1 to a single 3-drug pill-based treatment protocol with a low-dose combination of telmisartan, amlodipine, and indapamide, or to the standard-of-care Nigerian hypertension treatment protocol, which starts with 1 agent (i.e. amlodipine) and may be changed to 2 agents if the result is insufficient. Prof. Ojji and colleagues looked at the change in home-measured systolic BP at 6 months.

After 6 months of treatment, participants in the 3-drug pill/GMRx2 group had an average 5.8 mmHg lower systolic BP than those in the standard-of-care group. For diastolic BP, the corresponding difference was -3.6 mmHg. Furthermore, 62% of the participants in the experimental arm versus 28% of those in the control arm had achieved a BP <130/80 mmHg (P<0.001).

"No patients in either study arm had discontinued treatment due to adverse events," continued Dr Ojji. "The only safety issue we noticed was a slight increase in hypo-potassium (<3.5 mmol/L) in the GMRx2 arm (34% vs 18%)." When the researchers looked at participants with a potassium level <3.0 mmol/L, they noticed that the proportion had dropped from 34% to 9% in the experimental arm.

In conclusion, the single 3-drug pill protocol was more effective than the standard-of-care BP protocol in lowering BP in Black African patients. The BP control rate at 1 month was 80%, which was maintained throughout the study.

1. Ojji D, et al. VERONICA-Nigeria - deliVERy of Optimal blood pressure coNtrol in afrICA. HOTLINE 2, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

Dr Abdullahi Mohamed
Herlev-Gentofte Hospital, Denmark

Meet the Expert:
Dr Abdullahi Mohamed on Iron Deficiency in Patients with HF

Dr Abdullahi Mohamed discusses his research on iron deficiency in patients with heart failure (HF), particularly focusing on the varying prevalence of iron deficiency and its impact on patient outcomes based on different diagnostic criteria. His study, which analysed data from over 9,000 patients with new-onset HF in the Danish Heart Failure Registry, found that iron deficiency defined by transferrin saturation (TSAT) <20% or serum iron ≤13 µmol/L is strongly associated with increased mortality and first hospitalisation in patients with chronic heart failure, regardless of anaemia status [1]. In contrast, the current European Society of Cardiology (ESC) Guidelines for iron deficiency were found to be less predictive of adverse outcomes, highlighting the need to reassess these criteria in clinical practice. Dr Mohamed's research aims to redefine iron deficiency to improve the management and prognosis of HF.

"For the last year and a half, I have been researching iron deficiency in patients with HF. At the time, iron deficiency in HF was a relatively new and hyped topic, seen as a possible new treatment on top of the already established, evidence-based medical therapies for HF. We started by looking at the definition of iron deficiency and found it somewhat arbitrary. The definition was primarily based on criteria used for patients with chronic kidney disease, who were thought to be a similar patient group due to shared characteristics, like systemic inflammation. This definition was then used in several trials, even though it hadn't been validated in the way you would typically expect—for instance, through bone marrow staining to confirm iron deficiency. Instead, they used surrogate biomarkers in the blood to infer low iron levels in the bone marrow."

And biomarkers in the blood are not a reliable surrogate?

"Exactly, it's not a good surrogate. The gold standard would be to check bone marrow for every patient, but that's not feasible, so we use biomarkers. But before spending so much money on these trials, you'd expect that they would have ensured the definition was accurate. That's why we examined it further."

Why are patients with HF at increased risk for iron deficiency?

"There are several reasons. One of them is that these patients are often on blood thinners, which can cause small, unnoticed bleeding in the gut. Over time, this can lead to iron deficiency. Another major reason found in the literature is low-grade inflammation, which increases levels of a protein called hepcidin. Hepcidin rises with inflammation and traps iron in enterocytes and hepatocytes, making it unavailable for the body to use."

Why is it important to treat comorbidities like iron deficiency in comprehensive HF therapy?

"HF patients usually present with a bundle of comorbidities, and iron deficiency is just one of many. We know that patients with iron deficiency who receive treatment often have a better quality of life—they can do more, walk longer distances, and generally have more energy. Treating iron deficiency also reduces hospitalisations for HF. It's primarily about improving quality of life."

What are the proposed new definitions for iron deficiency?

"We looked at 4 different definitions, including the ESC Guidelines. One study tried to validate these definitions using bone marrow staining, which is the gold standard. They found that patients with transferrin saturation under 20% or serum iron levels of 13 micromoles per litre or less were more likely to have low iron in the bone marrow. These patients also had a higher risk of all-cause mortality, whereas the ESC Guidelines didn't show this association. However, the ESC Guidelines haven't changed, possibly because the study I mentioned had [...]

Curious?
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High-end Trials in Heart Failure

FINEARTS-HF: Finerenone improves outcomes in heart failure with preserved ejection fraction

The results of the FINEARTS-HF trial show that the non-steroidal mineralocorticoid receptor agonist (MRA) finerenone significantly reduced the risk of cardiovascular death and heart failure (HF) events in patients with HF and mildly reduced or preserved ejection fraction (LVEF ≥40%). These results complement previous efficacy data in patients with reduced LVEF and patients with chronic kidney disease.

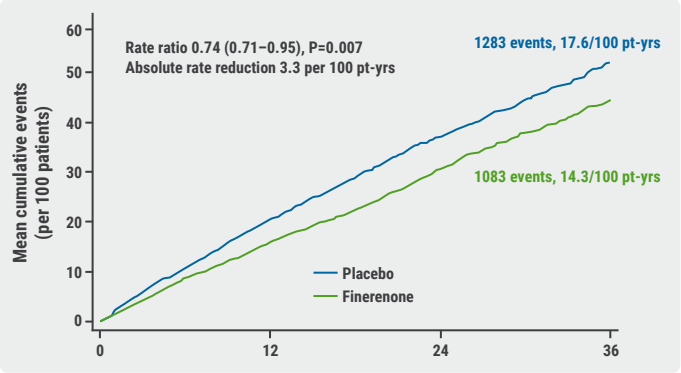
The cardiovascular and kidney-related benefits of finerenone in patients with reduced LVEF were recently demonstrated in 2 large clinical trials: FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) [1,2]. The FIGARO-DKD trial focused on cardiovascular outcomes, while the FIDELIO-DKD trial emphasised renal outcomes. Both trials showed that finerenone significantly reduced the risk of kidney failure, decreased the progression of albuminuria, and lowered the incidence of cardiovascular events.

Prof. Scott Solomon (Brigham and Women's Hospital, MA, USA) presented the results of the FINEARTS-HF trial (NCT04435626), which were simultaneously published in the *New England Journal of Medicine* [3,4]. This multicentre, randomised, double-blind, phase 3 trial involving 6,001 participants demonstrated that finerenone reduced the composite outcome of cardiovascular death and total HF events compared with placebo by 16% (rate ratio 0.84; 95% CI 0.74–0.95; P=0.007; see Figure). The trial also met secondary outcomes, including reduced total worsening HF events and improved patient-reported health status as measured by the Kansas City Cardiomyopathy Questionnaire.

The findings mark a significant advancement in the treatment of patients with HF with LVEF ≥40%, a group for whom effective, guideline-directed therapies have been limited. While finerenone was generally well tolerated, increased levels of hyperkalaemia were noted, though these rarely led to hospitalisation. Rates of hypokalemia were significantly lower with finerenone.

Prof. Solomon concluded by positioning finerenone "as a promising option for managing HF in patients with mildly reduced or preserved ejection fraction, addressing a critical need in cardiovascular care." Further regulatory discussions and approvals are anticipated following these findings.

Figure: FINEARTS-HF primary endpoint – CV death and total HF events [4]



CV, cardiovascular; HF, heart failure; pt-yrs, patient-years.

1. Bakris GL, et al. N Engl J Med 2020;383(23):2219-2229.
2. Pitt B, et al. N Engl J Med 2021;385(24):2252-2263.
3. Solomon S, et al. N Engl J Med 2024;391:1475-1485.
4. Solomon S, et al. FINEARTS-HF – Finerenone in heart failure with mildly reduced and preserved ejection fraction. HOTLINE 7, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

MRAs show varied efficacy in heart failure across ejection fractions

A meta-analysis of almost 14,000 patients with heart failure (HF) assessed the differential impact of mineralocorticoid receptor antagonists (MRAs) on patients with HF across the spectrum of ejection fractions. The conclusion was that although the evidence was somewhat stronger for patients with reduced ejection fractions, the non-steroidal MRA finerenone also showed efficacy in patients with higher ejection fractions.

While MRAs are well-established in reducing hospitalisations and mortality in HF with reduced ejection fraction (HFrEF), their benefits in HF with mildly reduced (HFmrEF) or preserved ejection fraction (HFpEF) have been less clear. Prof. Pardeep Jhund (University of Glasgow, Scotland) presented a meta-analysis on this topic, which was simultaneously published in *The Lancet*. The analysis pooled data from 4 major trials: RALES and EMPHASIS-HF, which focused on HFrEF, and TOPCAT and FINEARTS-HF, which focused on HFmrEF and HFpEF [1–6].

The meta-analysis included 13,846 patients and revealed that MRAs significantly reduced the risk of cardiovascular death or HF hospitalisation versus placebo, with a hazard ratio (HR) of 0.77 (95% CI 0.72–0.83; P<0.001). However, the efficacy varied significantly between the HF subtypes. In patients with HFrEF, MRAs showed greater benefit, reducing the risk by 34% (HR 0.66; 95% CI 0.59–0.73; P<0.001). In contrast, the reduction was more modest in patients with HFmrEF or HFpEF, with a 13% risk reduction (HR 0.87; 95% CI 0.79–0.95; P=0.004).

The analysis also found that MRAs significantly decreased HF hospitalisations as an individual component in both HFrEF (HR 0.63; 95% CI 0.55–0.72; P<0.001) and HFmrEF/HFpEF (HR 0.82; 95% CI 0.74–0.91; P<0.001) populations. Cardiovascular death was reduced in patients with HFrEF (HR 0.72; 95% CI 0.63–0.82; P<0.001) but not in those with HFmrEF or HFpEF (HR 0.92; 95% CI 0.80–1.05; P=0.20). Similarly, all-cause mortality was reduced in HFrEF (HR 0.73; 95% CI 0.65–0.83; P<0.001) but not in patients with HFmrEF or HFpEF (HR 0.94; 95% CI 0.85–1.03; P=0.19).

In terms of safety, the use of MRAs was associated with a doubled risk of hyperkalaemia compared with placebo (OR 2.27; 95% CI 2.02–2.56; P<0.001), though the incidence of severe hyperkalaemia (serum potassium >6.0 mmol/L) remained low at 2.9% versus 1.4%, and there were no deaths due to hyperkalaemia. In line with this, MRAs reduced the risk of hypokalaemia by half (OR 0.51; 95% CI 0.45–0.57; P<0.001).

These findings suggest that MRAs reduce cardiovascular death and hospitalisations accross the spectrum of EF. It remains to be investigated whether differences between newer generations of non-steroidal MRAs that have differential effects in cardiac and kidney tissue and different tolerability than traditional steroidal MRAs explain positive findings in FINEARTS-HF relative to other trials. This new meta-analysis reinforces the need for tailored treatment approaches depending on the type of HF and ejection fraction at the individual level.

1. Jhund P, et al. MRAs in heart failure – An individual patient data meta-analysis of randomised trials. HOTLINE 7, ESC Congress 2024, 30 Aug–02 Sept, London, UK.
2. Jhund P, et al. Lancet 2024;404(10458):1119-1131.
3. Pitt B, et al. N Engl J Med 1999;341(10):709-17.
4. Zannad F, et al. N Engl J Med 2011;364(1):11-21.
5. Pitt B, et al. N Engl J Med 2014;370(15):1383-92.
6. Solomon S, et al. N Engl J Med 2024;391:1475-1485.

RESHAPE-HF2: Not a “tie-breaker” for TEER in heart failure

The much-anticipated RESHAPE-HF2 trial aimed to clarify the role of transcatheter edge-to-edge repair (TEER) with the MitraClip device in patients with heart failure (HF) with functional mitral regurgitation (FMR). Despite significantly reducing the risk of hospitalisation and cardiovascular death and improving health status within the first year, the trial results did not definitively settle the ongoing debate initiated by the conflicting COAPT and MITRA-FR trials.

The COAPT trial and the MITRA-FR trial were landmark studies that evaluated the use of TEER with the MitraClip device in patients with HF and FMR. The COAPT trial demonstrated that MitraClip when added to optimal medical therapy (OMT) significantly reduced HF hospitalisations and all-cause mortality, indicating a substantial benefit for patients [1]. Conversely, the MITRA-FR trial did not show a significant difference in outcomes between the MitraClip plus OMT and OMT alone, leading to ongoing debates about the appropriate patient population and clinical settings for using this device [2].

The conflicting results from these trials underscore the complexity of treating FMR and the necessity for further research to better define which patients benefit most from TEER. With this unresolved question as the backdrop, Prof. Stefan Anker (Charité Universitätsmedizin, Germany) presented the key findings from RESHAPE-HF2 (NCT02444338), with 3 simultaneous publications of editorials calling for an in-depth analysis of the results from this study to settle this 6-year-old debate [3]. RESHAPE-HF2 was an investigator-initiated, prospective, randomised, parallel-controlled, multicentre trial; the results were published simultaneously in the *New England Journal of Medicine* [4]. A meta-analysis of all 3 trials was also simultaneously published in the *Journal of the American College of Cardiology* [5].

The participants (n=505) were randomly assigned to either receive transcatheter mitral-valve repair alongside guideline-recommended medical therapy (device group) or medical therapy alone (control group). The primary endpoints were the rates of first or recurrent hospitalisation for HF or cardiovascular death over 24 months, the rate of first or recurrent hospitalisation for HF alone, and the change in health status as measured by the Kansas City Cardiomyopathy Questionnaire-Overall Summary score (KCCQ-OS) at 12 months.

At 24 months, the device group showed a significant reduction in the rate of first or recurrent hospitalisation for HF or cardiovascular death, with 37.0 events per 100 patient-years compared with 58.9 events per 100 patient-years in the control group (rate ratio 0.64; 95% CI 0.48–0.85; P=0.002). The rate of first or recurrent HF hospitalisation alone was also lower in the device group (26.9 events per 100 patient-years vs 46.6 in the control group; rate ratio 0.59; 95% CI 0.42–0.82; P=0.002). However, there was no significant difference in all-cause mortality between the 2 groups.

Additionally, participants in the device group experienced a more substantial improvement in their KCCQ-OS scores, indicating better health status, with an average increase of 21.6 points compared with an 8.0-point increase in the control group (mean difference 10.9 points; 95% CI 6.8–15.0; P<0.001). Device-specific safety events were minimal, occurring in only 1.6% of the participants.

The trial's conclusions have been met with both support and scepticism, published in a series of editorials concurrent with the articles. Some experts, including COAPT's Prof. Gregg Stone, view the results as reinforcing the superiority of MitraClip over OMT [6]. Conversely, MITRA-FR's Prof. Jean-François Obadia and others question the trial's design, including its multiple endpoints, protocol amendments, and patient selection criteria, arguing that RESHAPE-HF2 does not conclusively resolve the debate [7,8].

In conclusion, while RESHAPE-HF2 contributes valuable data, it does not provide the clear guidance many had hoped for. The trial supports the use of MitraClip in specific patient populations but leaves open questions about its broader applicability, especially in terms of mortality benefits. Further studies are needed to determine the optimal use of TEER in HF management.

1. Stone GW, N Engl J Med 2018;379(24):2307-2318.
2. Obadia JF, et al. N Engl J Med 2018;379(24):2297-2306.
3. Anker S, et al. RESHAPE-HF2 – Percutaneous repair of moderate-to-severe or severe functional mitral regurgitation in patients with symptomatic heart failure. HOTLINE 3, ESC Congress 2024, 30 Aug–02 Sept, London, UK.
4. Anker S, et al. N Engl J Med 2024; Aug 31. DOI: 10.1056/NEJMoa2314328.
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6. Stone GW, Penta B. J Am Coll Cardiol. 2024. DOI: 10.1016/j.jacc.2024.08.037.
7. Ponikowski P, et al. J Am Coll Cardiol. 2024. DOI: 10.1016/j.jacc.2024.08.027.
8. Obadia J-S, et al. J Am Coll Cardiol. 2024. DOI: 10.1016/j.jacc.2024.08.026.

MATTERHORN: Transcatheter repair matches surgery for HF with secondary mitral regurgitation

In the MATTERHORN trial, transcatheter edge-to-edge repair (TEER) was found to be as effective as surgery for treating patients with secondary mitral regurgitation. TEER had a better safety profile than surgical intervention.

Prof. Volker Rudolph (Heart and Diabetes Center NRW, Bad Oeynhausen, Germany) presented the results of the single-centre, non-inferiority MATTERHORN trial (NCT02371512), which were simultaneously published in the *New England Journal of Medicine* [1,2]. This trial aimed to offer critical insights for clinicians managing patients with heart failure (HF) and secondary mitral regurgitation. It compared the effectiveness and safety of TEER with traditional surgical mitral-valve repair or replacement in patients who remained symptomatic despite receiving guideline-directed medical therapy.

The trial randomly assigned participants (n=210; average age of 70.5 years; 39.9% women) to undergo TEER or mitral-valve surgery in a 1:1 ratio. The primary efficacy endpoint was a composite of death, HF hospitalisation, mitral-valve reintervention, assist device implantation, or stroke within 1 year. The primary safety endpoint evaluated major adverse events within 30 days post-procedure.

After 1 year, the composite efficacy endpoint was reached by 16.7% of participants in the TEER group compared with 22.5% in the surgery group (mean difference -6 percentage points; 95% CI -17 to 6; $P_{non\text{-}inferiority}$<0.001). In terms of safety, the TEER group experienced significantly fewer major adverse events within 30 days, with only 14.9% affected versus 54.8% in the surgery group (mean difference -40 percentage points; 95% CI -51 to -27; P<0.001).

One peculiarity of this trial is the lack of a medical treatment arm. By not having a medical therapy arm, the investigators assume that any intervention is superior to none. Nevertheless, the study concluded that TEER is non-inferior to mitral-valve surgery for patients with HF and secondary mitral regurgitation, offering a less invasive alternative with a significantly better safety profile. These findings may influence future treatment guidelines, providing an evidence-based option for patients who are unsuitable or at high risk for surgery.

1. Rudolph V, et al. MATTERHORN – Transcatheter versus surgical mitral valve repair in patients with heart failure and secondary mitral regurgitation. HOTLINE 3, ESC Congress 2024, 30 Aug–02 Sept, London, UK.
2. Baldus S, et al. N Engl J Med 2024; 31 Aug. DOI: 10.1056/NEJMoa240873.

Practical Gains in Screening and Diagnostics

SCOFF: To fast or not to fast, that's the question

No fasting led to better health outcomes and patient satisfaction than fasting in a population of patients who were undergoing cardiac catheterisation procedures, inciting the debate on whether fasting should be maintained before elective procedures requiring general/regional anaesthesia or procedural sedation and analgesia.

The pragmatic SCOFF trial randomised 716 participants scheduled for cardiac catheterisation procedures 1:1 to fasting or no fasting before their procedure. The participants were stratified for procedure site and procedure type (i.e. coronary or device intervention). In the fasting arm, participants fasted solid foods for 6 hours and clear liquids for 2 hours. The primary endpoint was a composite of aspiration pneumonia, hypotension, hyperglycaemia, and hypoglycaemia. Dr David Ferreira (John Hunter Hospital, Australia) presented the results [1].

With primary endpoint event rates of 19.1% in the fasting arm and 12.0% in the no-fasting arm, non-inferiority of no fasting to fasting was met. "No fasting was even superior to fasting," added Dr Ferreira. The effect appeared to be spread across the various components of the primary outcome, except for aspiration pneumonia, of which no cases were reported in either arm (see Table). Patient Satisfaction Scores were also in favour of the no fasting arm (mean 11 vs 15; Bayes factor >100). "However, performance bias is likely to have influenced the outcomes of this measure," commented Dr Ferreira.

Table: Primary composite outcome breakdown [1]

Outcomes	Fasting (n=358)	No fasting (n=358)
Primary outcome		
Composite of procedure-related aspiration pneumonia, hypotension, hyperglycaemia, hypoglyceamia no./total no. (%)	68/356 (19.1)	43/356 (12.0)
Components of the primary outcome		
Hypotension no./total no. (%)	32/358 (8.9)	22/358 (6.1)
Hyperglycaemia no./total no. (%)	30/356 (8.4)	23/356 (6.5)
Hypoglycaemia no./total no. (%)	7/356 (2.0)	2/356 (0.6)
Aspiration pneumonia no./total no. (%)	0/358 (0)	0/358 (0)

"No fasting was non-inferior and superior to fasting prior to coronary catheterisation and cardiac implantable device-related procedures for the primary composite outcome of aspiration pneumonia, hypotension, hyperglycaemia, and hypoglycaemia," concluded Dr Ferreira.

1. Ferreira D, et al. Safety and care of no fasting prior to catheterisation laboratory procedures: a non-inferiority randomised control trial (SCOFF trial): fasting versus no fasting prior to cardiac catheterisation procedures. HOTLINE 8, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

STEEER-AF: Shockingly low adherence to ESC atrial fibrillation guidelines

Guideline adherence is remarkably poor among patients with atrial fibrillation (AF) across 6 European countries, an objective assessment of the STEEER-AF trial determined. Fortunately, a short online intervention for healthcare professionals was able to increase their patients' adherence to rhythm control recommendations.

"Although we know that adherence to guidelines and patient education improve outcomes in patients with AF, we do not have solid evidence regarding the actual adherence to ESC Guidelines," outlined Prof. Dipak Kotecha (University of Birmingham, UK) [1]. The STEEER-AF trial (NCT04396418), conducted by the ESC, assessed guideline adherence and tested an educational intervention to improve guideline adherence.

The investigators measured the adherence to class I and class III recommendations for stroke prevention and rhythm control among 1,732 patients with AF from France, Germany, Italy, Poland, Spain, and the UK. Additionally, 70 treatment centres were randomised 1:1 to an intervention group or a usual-care group. In the intervention group, the responsible healthcare professionals followed an online educational programme on improving patient adherence in the AF population.

Baseline adherence to all relevant class I and III ESC guideline recommendations were low for stroke prevention (61.0%) and abysmal for rhythm control (21.0%). On the bright side, the intervention was associated with a 51% increase in adherence to rhythm control guideline recommendations (21.4% to 33.9%), significantly outperforming the control arm (20.5% to 22.9%; adjusted risk ratio 1.51; 95% CI 1.04–2.18; P=0.03). For

stroke prevention, the corresponding results in the intervention arm were 63.4% at baseline to 67.5% at follow-up; in the usual-care arm, the adherence rate went from 58.6% to 60.9% (adjusted risk ratio 1.10; 95% CI 0.97–1.24; P=0.13).

"The outcomes of this trial should be an eye-opener for the community," argued Prof. Kotecha. "We have all these excellent trials with novel options to improve the outcomes for our patients. However, it is now demonstrated that the implementation is lacking. Without adherence, patients do not achieve their optimal outcomes," emphasised Prof. Kotecha.

1. Kotecha D, et al. STEEER-AF: Stroke prevention and rhythm control therapy: evaluation of an educational programme of the ESC in a cluster-randomised trial in patients with atrial fibrillation. HOTLINE 6, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

WESTCOR-POC: Point-of-care hs-troponin testing increases emergency department efficiency

Point-of-care high-sensitivity troponin I (hs-cTnI) testing reduced the length of stay in the emergency department, with comparable safety as centralised hs-cTnI testing in the WESTCOR-POC trial. This improved efficiency of the emergency department is particularly relevant for patients with myocardial infarction (MI).

"Overcrowding is a common problem in emergency departments," stated Dr Viola Thulin (Haukeland University Hospital, Norway) [1]. "This leads to longer waiting times, which is detrimental for patients who come in with MI." The current randomised-controlled WESTCOR-POC trial (NCT05354804) compared point-of-care hs-cTnI testing at 0 and 1 hours to central laboratory hs-cTnI testing at 0 and 1 hours among 1,614 participants with symptoms suggestive of acute coronary syndrome. The primary endpoint was the length of stay at the emergency department.

A small but significant drop was seen in the duration of emergency department stay in the point-of-care testing group versus the control group (174 vs 180 min; P=0.024). "Given that this is a large proportion of the patients visiting the emergency department, this is still a relevant difference," commented Dr Thulin. For patients who were seen by a physician within 60 minutes, the difference in duration of stay was more pronounced (147 vs 162 min; P<0.001) as was the difference in patients who had an acute MI (137 vs 180 min; P=0.005). "There were no differences with respect to the safety of the two procedures," said Dr Thulin (see Table).

Table: No differences in safety outcomes [1]

	Point-of-care n (%)	Standard n (%)	Odds ratio (95% CI)	P-value
Composite 30-day death and AMI	51 (7.0)	39 (5.1)	1.4 (0.9–2.2)	0.123
Composite 30-day AMI, acute revascularisation, death	83 (11.4)	72 (9.4)	1.2 (0.9–1.7)	0.208
- AMI	47 (6.5)	37 (4.8)	1.4 (0.9–2.1)	0.176
- Acute revascularisation	61 (8.4)	63 (8.2)	1.0 (0.7–1.5)	0.920
- Death	4 (0.5)	4 (0.5)	1.1 (0.3–4.2)	0.942

AMI, acute myocardial infarction; CI, confidence interval.

"Our study showed that point-of-care hs-cTnI testing can reduce the length of stay in an emergency department," concluded Dr Thulin. "However, the benefits from point-of-care hs-cTnI testing are dependent on local logistics and workflow."

1. Thulin IVL, et al. Efficiency and safety of point-of-care high-sensitivity troponin in the emergency department. HOTLINE 12, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

PROTEUS: Can AI improve decision-making around stress echocardiography?

AI augmentation of stress echocardiography did not meet the pre-specified non-inferiority endpoint for appropriate referral to angiography compared with standard decision-making in the PROTEUS trial. However, this effect appeared to be driven by a lower-than-expected angiography referral rate in the study and the investigators observed some positive signs for the AI intervention.

The multicentre, randomised-controlled PROTEUS trial (NCT05028179) tested whether AI-augmented interpretation of stress echocardiography improved the accuracy of clinician selection to refer patients for angiography. "The AI device we used captured left ventricular motion between rest and stress as an additional assessment," explained Dr Ross Upton (Ultromics, UK) [1].

Patients who were referred for stress echocardiography for the investigation of ischaemic heart disease were randomised to standard-of-care or AI-augmented stress echocardiography. The primary endpoint was evidence of severe coronary artery disease within 6 months after stress echocardiography in patients who were referred for angiography. "Non-inferiority was accepted when the lower bound of the 95% confidence interval of the AUROC difference between intervention and control did not surpass -0.05," explained Dr Upton.

The primary endpoint was not met, with an AUROC of 0.55 for the control group and 0.63 for the intervention group (difference 0.09; 95% CI -0.22 to 0.39). "The referral rate was only 8% in the current trial, whereas the data was powered on data from the EVAREST trial [NCT03674255], in which 15% of the population were referred for angiography," said Dr Upton. According to the authors, this low angiography referral rate was most likely responsible for the trial not meeting its primary endpoint. Finally, a subgroup analysis suggested that sites that performed fewer stress echocardiographies may benefit from AI-augmented stress echocardiography (AUROC 0.33 vs 0.58; difference 0.25; 95% CI -0.02 to 0.62).

"Despite the low number of angiography referrals, the results indicate that AI augmentation may have utility in low volume stress echocardiography centres," concluded Dr Upton.

1. Upton R, et al. PROTEUS: a prospective randomised controlled trial evaluating the use of artificial intelligence in stress echocardiography. HOTLINE 12, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

RAPIDxAI: Can AI-augmented chest pain assessment improve cardiovascular outcomes?

An AI tool that distinguished between type 1 myocardial infarction (MI) and non-type 1 MI in the setting of assessing cardiac chest pain at the emergency department did not reduce major cardiovascular adverse events compared with usual care in a hospital setting. However, exploratory analyses suggest there may be value in this tool with some finetuning in diagnosing and managing patients with elevated high-sensitivity cardiac troponin (hs-cTn).

Dr Derek Chew (Monash University, Australia) and colleagues designed an AI tool to guide cardiac chest pain assessment in the emergency department [1]. The clinical decision support tool mostly aimed to differentiate type 1 MI from other forms of myocardial injury. The investigators compared the use of this AI tool to usual care in a multicentre, cluster-randomised trial.

The participants (n=3,029) from 12 Australian hospitals were randomised 1:1 to the intervention arm, in which patients stratified by phenotype by the AI tool received treatment recommendations that fitted this phenotype, or to the control arm, in which patients were not stratified by this tool. The primary endpoint was a composite of cardiovascular death, MI, and cardiac readmission at 6 months.

No effect was observed on the primary endpoint (HR 0.99; 95% CI 0.86–1.14; $P_{cluster}$=0.87). In the type 1 MI cohort of participants (n=578), the authors noted an increase in statin use, $P2Y_{12}$ inhibitors, and mineralocorticoid receptor antagonists in the intervention arm, but not in invasive management or revascularisation. In the non-type 1 MI cohort (n=2,441), the authors saw a slight decrease in angiography, beta-blocker use, and revascularisation in the intervention arm compared with the control arm. An exploratory analysis, excluding 165 participants with ST-elevation MI, a population in which the use of an algorithm may be less useful, did suggest that the AI tool helps to reduce the rate of cardiovascular death or MI (HR 0.81; 95% CI 0.66–0.99; $P_{cluster}$=0.048).

Although the new AI tool did not improve cardiovascular outcomes in this study, the trial produced some hypothesis-generating data that may help to assess the value of the tool in a more specific group of patients.

1. Lambrakis K, et al. RAPIDxAI: Re-engineering the clinical approach to suspected cardiac chest pain assessment in the emergency department using artificial intelligence. HOTLINE 12, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

Miscellaneous Achievements in Cardiology

HELIOS-B: Vutrisiran candidate for SoC in ATTR cardiomyopathy

Vutrisiran reduced all-cause mortality and recurrent cardiovascular events in patients with transthyretin amyloidosis (ATTR) with cardiomyopathy versus placebo, despite a substantial proportion of the phase 3 HELIOS-B study population being on tafamidis background therapy.

"ATTR cardiomyopathy leads to heart failure, arrhythmias, hospitalisations, and reduced survival," said Prof. Marianna Fontana (University College London, UK) [1]. "We are, however, seeing a trend towards earlier diagnosis, improved management for heart failure, and better treatment options for ATTR cardiomyopathy, such as tafamidis and SGLT2 inhibitors." Prof. Fontana and colleagues investigated the RNA interference therapeutic vutrisiran in patients with ATTR cardiomyopathy in the double-blind, randomised-controlled, phase 3 HELIOS-B trial (NCT04153149).

The participants (n=655) were randomised 1:1 to vutrisiran or placebo every 12 weeks for up to 36 months. The primary endpoint was a composite of all-cause mortality and recurrent cardiovascular events at 36 months. "Approximately 40% of the participants were on tafamidis at baseline, raising the bar for vutrisiran to demonstrate its efficacy," emphasised Prof. Fontana.

The primary endpoint was met, with a hazard ratio of 0.72, and a P-value of 0.012 (95% CI 0.55–0.93) [1,2]. "This effect was driven by both components of the primary endpoint," added Prof. Fontana [1]. Important secondary endpoints were also in favour of the vutrisiran arm, including change in the 6-minute walk test at 30 months (LS mean difference 26.46; P=0.00008) and Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Score change at 30 months (LS mean difference 5.80; P=0.0008).

The safety profiles of vutrisiran and placebo were similar, with 67.1% and 61.7% of the participants experiencing serious adverse events (AEs) in the placebo and vutrisiran arm, respectively. In addition, there were no AEs that were typical for vutrisiran.

"Vutrisiran has the potential to become a standard-of-care for previously untreated patients with ATTR cardiomyopathy and for those who progress on stabilising therapies," concluded Prof. Fontana.

1. Fontana M, et al. HELIOS-B: Primary results from phase 3 study of vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. HOTLINE 1, ESC Congress 2024, 30 Aug–02 Sept, London, UK.
2. Fontana M, et al. N Engl J Med 2024; Aug 30. DOI: 10.1056/NEJMoa2409134.

Does RAS inhibitor discontinuation affect outcomes after non-cardiac surgery?

No difference was seen between a strategy of renin-angiotensin system (RAS) inhibitor continuation or discontinuation in terms of postoperative complications among patients who underwent major non-cardiac surgery in the STOP-or-NOT trial.

"It is unclear what the impact of RAS inhibitor continuation versus discontinuation is on postoperative outcomes among patients on RAS inhibitor therapy who undergo major non-cardiac surgery," expressed Prof. Matthieu Legrand (University of California San Francisco, CA, USA) [1]. The multicentre STOP-or-NOT trial (NCT03374449) randomised 2,222 participants scheduled for major non-cardiac surgery 1:1 to RAS inhibitor discontinuation or RAS inhibitor continuation.

The participants in the discontinuation arm discontinued their RAS inhibitor 48 hours prior to the day of surgery, whereas participants in the continuation arm were treated with RAS inhibitors until the day of surgery. The primary outcome was the major postoperative complication and mortality rate 28 days after surgery.

In both arms, 22% of the participants had a primary outcome event, displaying no difference between the 2 arms (RR 1.02; 95% CI 0.83–1.25). "There was no difference with respect to individual event types or time-to-event either," added Prof. Legrand. Finally, the 2 arms showed similar outcomes regarding length of hospitalisation and length of stay at an intensive care unit.

"Both RAS inhibitor continuation and RAS inhibitor discontinuation appear acceptable strategies to use for patients on

RAS inhibitors who undergo major non-cardiac surgery, with comparable post-operative complication rates," concluded Prof. Legrand.

1. Legrand M, et al. Renin-angiotensin system inhibitors continuation versus discontinuation before major non-cardiac surgery: the STOP-or-NOT randomised controlled trial. HOTLINE 1, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

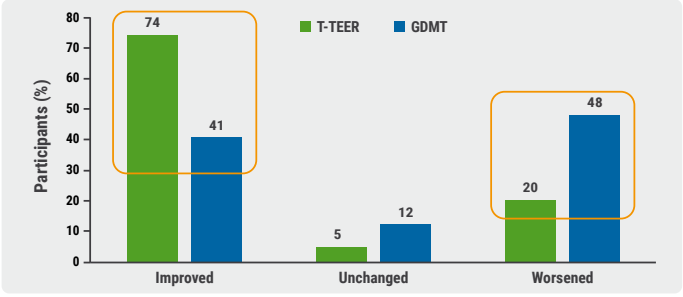
Novel approach to managing severe tricuspid regurgitation proves its value

The tricuspid transcatheter edge-to-edge repair (T-TEER) technique was associated with improved clinical outcomes compared with guideline-directed medical treatment (GDMT) in a population of patients with severe tricuspid regurgitation (TR).

"Right-sided heart failure [HF] and TR are associated with poor quality-of-life, and increased risks for hospitalisation and death," said Prof. Erwan Donal (Rennes University Hospital, France) [1]. According to Prof. Donal, it remained unclear which patients may benefit from tricuspid valve interventions and the ideal timing for these procedures. "In the first academic randomised trial about transcatheter correction of TR, we randomised 300 patients with severe TR and signs and symptoms of HF in the previous 12 months to T-TEER, a percutaneous repair procedure using the TriClipTM device, plus GDMT, or to GDMT alone." The primary endpoint of the TRI.Fr trial was a clinical composite score of major cardiovascular events, changes in NYHA class, or patient global assessment.

After 1 year of follow-up, the primary outcome measure showed that 74.1% of the participants in the T-TEER group improved, compared with 40.6% of those in the control group (HR 0.67; 95% CI 0.61–0.72; P<0.0001; see Figure). "We observed improvements across all elements of the clinical composite endpoint," added Prof. Donal. In total, 93.2% of the participants in the experimental arm achieved a TR grade of less than 4+ compared with 46.5% of participants in the control arm (P<0.001).

Figure: Primary endpoint in the intention-to-treat population [1]



GDMT, guideline-directed medical treatment; T-TEER, tricuspid transcatheter edge-to-edge repair.

The investigators also reported a mean difference of 14.5 points in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Score between the study arms at 12 months in favour of the T-TEER group, reflecting a clinically meaningful improvement in quality-of-life for patients undergoing T-TEER plus GDMT (P<0.0001).

"T-TEER plus GDMT proved superior to GDMT alone with a significant reduction in TR severity," concluded Prof. Donal.

1. Donal E, et al. Multicentric randomised evaluation of a tricuspid valve percutaneous repair system (T-TEER) in the treatment of severe tricuspid regurgitation: TRI.Fr. HOTLINE 3, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

NOTION-3: TAVI plus PCI improves outcomes in CAD plus severe aortic stenosis

In patients with stable coronary artery disease (CAD) and severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI), the addition of percutaneous coronary intervention (PCI) to the treatment strategy was associated with a reduction in major adverse cardiovascular events (MACE) compared with TAVI plus conservative treatment. Since these 2 conditions often co-exist, these NOTION-3 findings may help to improve the clinical outcomes for a large group of patients.

"TAVI and PCI are performed simultaneously in about 15% of patients undergoing TAVI for severe aortic stenosis," according to Dr Jacob Lønborg (Copenhagen University Hospital, Denmark) [1]. "There is, however, no evidence from clinical trials to support this strategy." Thus, the aim of the NOTION-3 study (NCT03058627) was to test the hypothesis that routine revascularisation with PCI in addition to TAVI will improve clinical outcomes in patients with stable CAD and severe aortic stenosis compared with TAVI plus conservative management. The 455 participants were randomised 1:1 to TAVI plus conservative management or TAVI plus PCI. The primary endpoint was MACE at 1–5 years of follow-up.

After a median of 2 years of follow-up, TAVI plus PCI reduced MACE relative to TAVI alone, with event rates of 26% and 36%, respectively (HR 0.71; 95% CI 0.51–0.99; P=0.04). Looking at individual components of MACE, the authors observed no statistically significant difference between the 2 study arms regarding all-cause mortality (23% vs 27%; HR 0.85; 95% CI 0.59–1.23) but did report improved outcomes in the PCI arm for myocardial infarction (7% vs 14%; HR 0.54; 95% CI 0.30–0.97), and urgent revascularisation (2% vs 11%; HR 0.20; 95% CI 0.08–0.51). "We did notice an increased risk for bleeding

in the PCI arm," said Dr Lønborg (28% vs 20%; HR 1.51; 95% CI 1.03–2.22). "On the other hand, acute kidney failure was more common in the conservative treatment arm" (5% vs 11%; HR 0.45; 95% CI 0.23–0.89).

"Based on the results of our study, adding PCI to TAVI appears to be a solid strategy to treat patients with severe aortic stenosis and stable CAD," concluded Dr Lønborg.

1. Lønborg J, et al. NOTION-3: PCI in patients undergoing transcatheter aortic valve implantation. HOTLINE 5, ESC Congress 2024, 30 Aug–02 Sept, London, UK.

RHEIA: TAVI outperformed surgery in women with aortic stenosis

Transcatheter aortic valve implantation (TAVI) outperformed surgical valve replacement in terms of a composite outcome of death, stroke, or rehospitalisation in women with severe aortic stenosis. The less invasive TAVI treatment was also more beneficial concerning the use of healthcare resources, according to the RHEIA trial.

"Evidence suggests that TAVI may be preferred over surgery in patients with severe aortic stenosis due to a lower mortality rate with the first approach," stated Prof. Hélène Eltchaninoff (University Hospital of Rouen, France). "However, women have been under-represented in studies comparing TAVI and surgery in low-risk patients."

The RHEIA trial (NCT04160130) included women with severe aortic stenosis to compare TAVI with surgery and confirm the benefit of TAVI over surgery in women. The 443 participants were randomised 1:1 to TAVI or surgery and were evaluated for a primary composite endpoint of all-cause mortality, stroke, and rehospitalisation after 1 year of follow-up.

The primary endpoint event rate was significantly higher in the surgery arm than in the TAVI arm (15.6% vs 8.9%; HR 0.55; 95% CI 0.34–0.88; $P_{log\text{-}rank}$=0.03) [1]. "The effect was driven by a reduction in rehospitalisations in the TAVI arm," explained Prof. Eltchaninoff (4.8% vs 11.4%; P=0.02). "We also saw that the incidence of new-onset atrial fibrillation was 7 times higher in the surgery arm than in the TAVI arm" (28.8% vs 3.3%; P<0.001). On the other hand, new permanent pacemakers were more common in the TAVI arm (8.8% vs 2.9%; P=0.01). Finally, participants in the TAVI arm had a shorter length of index hospital stay than participants in the surgery arm (median 4 vs 9 days).

"In women with severe aortic stenosis, TAVI was superior to surgery for the primary composite endpoint of death, stroke, or rehospitalisation," concluded Prof. Eltchaninoff.

1. Eltchaninoff H, et al. RHEIA: randomised research in women all comers with aortic stenosis: transcatheter versus surgical aortic valve replacement in women. HOTLINE 5, ESC Congress 2024, 30 Aug–02 Sept, London, UK.