STEP-HFpEF: practice-changing results for semaglutide
In patients with HFpEF and obesity, treatment with semaglutide resulted in greater weight loss and improved HF-related symptoms compared with placebo, without disturbing toxicity.

Inorganic nitrate reduces CIN
Dietary inorganic nitrate significantly reduced contrast-induced nephropathy in patients at risk for renal injury undergoing coronary angiography for acute coronary syndrome.

Acoramidis improves survival in ATTR-CM
Acoramidis demonstrated clinical and functional benefits over placebo and was well tolerated in patients with transthyretin amyloid cardiomyopathy in the ATTRibute-CM trial.
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Dear colleagues,

Thank you for your interest in this edition of Medicom's Conference Report covering the European Society of Cardiology Congress occurring in Amsterdam, the Netherlands, in August of 2023. As one of the largest and most comprehensive cardiovascular meetings, ESC always promises a congress filled with late-breaking clinical trials, innovative science, and new developments in structural cardiology. This year's congress certainly did not disappoint!

In the following pages, you can read about outcomes from the latest clinical trials, including a breakthrough in treatment approaches for the obesity phenotype of heart failure with preserved ejection fraction, the STEP HFpEF trial, natriuresis-guided diuresis in heart failure, use of inorganic nitrates for contrast-induced nephropathy, and studies providing new data on the use of antithrombotic therapies. With dedicated sections on guideline updates, trials in heart failure, updates in prevention, and studies in acute coronary syndrome and PCI, we hope there is a broad representation of the rich science that was presented.

As always, our summaries are written independently and are peer-reviewed for balance. We hope you find this edition informative, engaging, and balanced and thank you again for your readership.

Sincerely,

Marc Bonaca
Guidelines for the management of endocarditis

The 2023 ESC Guidelines for the management of endocarditis are an update of the previous version published in 2015. In the guidelines, antibiotic prophylaxis is recommended for high-risk patients before certain procedures.

Infective endocarditis is a rare condition but a major public health challenge; in 2019, the estimated incidence was 13.8 cases per 100,000 subjects per year, and it accounted for 66,300 deaths worldwide. The publication of important new data since the 2015 ESC Guidelines for the management of infective endocarditis, mandated an update of the recommendations [1–3]. There are 3 important factors in the pathophysiology of endocarditis:

- predisposing conditions of the patient;
- the pathogen in the blood stream; and
- the immune response of the host.

Prevention based on risk assessment and encouragement of hygiene

"Prevention is about defining patients with a predisposition for this disease," explained Dr Stefano Caselli (HerzGefässZentrum im Park, Switzerland) [3].

Antibiotic prophylaxis is only recommended for high-risk patients; the highest risk is seen in patients who experienced previous infective endocarditis. In addition, patients with prosthetic valves, mitral and aortic bioprostheses, patients with congenital heart disease, and those with ventricular assist devices are at high risk. In the intermediate-risk category are patients with rheumatic heart disease, non-rheumatic valve disease, congenital valve defects, cardiovascular implanted electronic devices, and hypertrophic cardiomyopathy.

For patients at very high risk, antibiotic prophylaxis is indicated under certain circumstances, such as orodental procedures (class I). In contrast, only general preventive measures in terms of increased hygiene are recommended for medium-risk patients and should "ideally be extended to low-risk individuals." These measures include good oral hygiene (twice-daily tooth cleaning and at least twice-yearly professional cleaning for high-risk patients, and yearly for others), strict cutaneous hygiene, and discouragement of piercings and tattoos.

Procedures at risk are not exclusively dental procedures, but also procedures such as dialysis, bone marrow puncture, lower and upper gastrointestinal endoscopy, and bronchoscopy. This led to a new recommendation for systemic antibiotic prophylaxis that may be considered for high-risk patients undergoing an invasive diagnostic or therapeutic procedure of the respiratory, gastrointestinal, or genitourinary tract, the skin, or the musculoskeletal system.

Moreover, there is a new recommendation for antibiotic prophylaxis before transcatheter aortic valve implantation (TAVI) and other transcatheter valvular procedures, covering common skin flora including Enterococcus spp. and S. aureus. "It is very important that we educate patients on the significance of hygiene," Dr Caselli emphasised.

Diagnosis includes both transoesophageal and transthoracic ultrasound

"The diagnosis of infective endocarditis is based on clinical suspicion, consistent microbiological findings, and the detection of matching lesions on cardiac imaging," said Prof. Nina Ajmone Marsan (Leiden University Medical Center, the Netherlands). Diagnosis begins with clinical classification, a blood culture, and transoesophageal and transthoracic ultrasound. It is emphasised that both methods should always be used (class I).

There are recommendations for other imaging methods, in particular for cardiac computed tomography angiography (CTA), which is recommended for patients with possible native valve endocarditis (NVE) to detect valvular lesions, or in NVE and prosthetic valve endocarditis (PVE) to diagnose paravalvular or periprosthetic complications, if echocardiography is inconclusive.

Echocardiography is the first imaging technique to diagnose infective endocarditis, although the use of other imaging techniques, either for the diagnosis of cardiac involvement or distant lesions, is highly encouraged.
The guideline also includes a specific diagnostic algorithm to support decision-making, especially for NVE, PVE, and infective endocarditis associated with cardiovascular-implanted electronic devices.

The diagnosis of endocarditis is made using a set of major and minor criteria. A definitive diagnosis can be made when 2 major criteria (e.g., blood cultures of typical micro-organisms consistent with infective endocarditis or imaging positive for infective endocarditis) or 1 major and 3 minor criteria (e.g., temperature >38 °C), or 5 minor criteria are met. Possible endocarditis is present if 1 major and 1 or 2 minor criteria or 3–4 minor criteria are fulfilled.

**Therapy: preferably in a multidisciplinary team**

Dr Emil Fosbøl (Rigshospitalet, Denmark) emphasised that the management of endocarditis can be demanding and should therefore be performed in a multidisciplinary endocarditis team [3]. Prophylactic, empirical, and targeted antibiotic therapy suggestions are similar to the 2015 ESC Guidelines.

Therapy is always started with intravenous administration of antibiotics. New in this guideline is an outpatient paradigm for antibiotic therapy (see Figure). As Dr Fosbøl explained, the new recommendation was given as a consequence of the POET study (NCT01375257), one of the few existing randomised-controlled trials in endocarditis [4]. This study has shown that this strategy is not only associated with a shorter hospital stay but also with better clinical outcomes.

![Figure: Antibiotic treatment of infective endocarditis with a focus on outpatient care after stabilisation. Modified from [1]](image)

Oral treatment can be started by many patients after 10 days of intravenous therapy. Exceptions are infections with pathogens that are difficult to treat and patients with severe comorbidities, such as liver cirrhosis or a particularly problematic clinic. The guideline lists several criteria for stability (e.g., no fever over 2 days, an acceptable concentration of C-reactive protein). Stabilisation is key for the switch to oral therapy: there is a recommendation to perform transoesophageal ultrasound in every patient before switching to oral therapy (class I).

“We are not forced to keep patients in hospital for 6 weeks; indeed, it seems to harm them,” Dr Fosbøl said. But he also emphasised to only discharge patients early if they can be assumed to have excellent adherence. In addition, close monitoring is always indicated.

Surgical treatment is indicated in difficult cases (e.g. locally uncontrolled infections (abscess, fistula) or infections with fungi or multi-resistant germs). Specific indications are listed in the more than 50 new recommendations.

The 2023 ESC Guidelines emphasise the need to screen all diabetic patients for CVD and chronic kidney disease (CKD), and it is advised to tailor further management according to individual risk assessment (see Figure) [1–3].

![Figure: Central treatment strategies according to concomitant diagnoses in T2DM. Modified from [3]](image)

**Cardiovascular disease and diabetes: new guidelines**

A multitude of topics was discussed in the new 2023 ESC Guidelines on the management of cardiovascular disease (CVD) and diabetes. Besides CVD risk reduction, kidney disease and heart failure played an important role in the more than 50 new recommendations.

The 2023 ESC Guidelines emphasise the need to screen all diabetic patients for CVD and chronic kidney disease (CKD), and it is advised to tailor further management according to individual risk assessment (see Figure) [1–3].
risk of fatal and non-fatal CVD events for the individual patient. Besides including known conventional and specific risk factors, it also incorporates a calibration for different risk regions in Europe. As of now, assessment with SCORE2-Diabetes is recommended for patients with type 2 diabetes (T2DM) without symptomatic atherosclerotic CVD (ASCVD) or severe target-organ damage (class I).

When T2DM and ASCVD are present

"The new guidelines introduce a novel concept, with special attention to the proven CV benefit or proven safety of glucose-lowering medication," Prof. Nikolaus Marx (RWTH University Hospital Aachen, Germany) stressed. He also underlined that GLP-1 receptor agonists and SGLT2 inhibitors are recommended for CV risk reduction independent of the HbA1c result and concomitant glucose-lowering medication (class I). The new recommendations further include that:

• it is recommended to prioritise the use of glucose-lowering agents with proven CV benefit, followed by agents with proven CV safety, over agents without proven CV benefit or proven CV safety (class I);
• it is recommended to switch glucose-lowering treatment from agents without proven CV benefit or proven safety to agents with proven CV benefit (class I);
• if additional glucose control is needed, metformin should be considered for patients with T2DM and ASCVD (class IIa); and
• if additional glucose control is needed, pioglitazone may be considered for patients with T2DM and ASCVD without heart failure (HF) (class IIb).

Heart failure and diabetes

"It is of the utmost importance to identify patients with both HF and T2DM," Dr Katharina Schuett (RWTH University Hospital Aachen, Germany) stated. In the 2023 Guidelines, a systematic survey for HF symptoms and/or signs of HF is recommended at each clinical encounter for all patients with diabetes (class I). Diagnostics in case of suspected HF comprise a recommendation for a 12-lead ECG, transthoracic echocardiography, a chest X-ray, and routine blood tests for comorbidities including blood count, urea, creatinine, electrolytes, thyroid function, lipids, and iron status (all class I). Importantly, in case of suspected HF, BNP/NT-pro BNP testing is also recommended (class I).

As for new therapeutic strategies, the following advice is given:

• SGLT2 inhibitors (i.e. dapagliflozin, empagliflozin, or sotagliflozin) are recommended for all patients with HF with reduced ejection fraction (HFrEF) and T2DM, to reduce the risk of HF hospitalisation and CV death (class I);
• an intensive strategy of early initiation of evidence-based treatment (SGLT2 inhibitors, ARNI/ACE inhibitors, beta-blockers, and MRAs) with rapid up-titration to trial-defined target doses starting before discharge and with frequent follow-up visits in the first 6 weeks following HF hospitalisation, is recommended to reduce re-admissions or mortality (class I); and
• empagliflozin or dapagliflozin are recommended for patients with T2DM and left-ventricular EF >40% (HFmEF and HFpEF), to reduce the risk of HF hospitalisation or CV death (class I).

Comorbid CKD in T2DM needs attention

Prof. Dirk Müller-Wieland (RWTH University Hospital Aachen, Germany) stressed that the aim of treatment for patients with CKD and T2DM is to reduce both the CV risk and the kidney failure risk. As a first step to identifying these patients, it is recommended that patients with diabetes are routinely screened for kidney disease by assessing estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) (class I). Amid the presented new class I recommendations were:

• SGLT2 inhibitors (canagliflozin, empagliflozin, or dapagliflozin) are recommended for patients with T2DM and CKD with an eGFR ≥20 mL/min/1.73 m², to reduce the risk of CVD and kidney failure;
• finerenone is recommended in addition to an ACE inhibitor or ARB for patients with T2DM and eGFR >60 mL/min/1.73 m² with a UACR ≥30 mg/mmol (≥300 mg/g), or eGFR 25–60 mL/min/1.73 m² and UACR ≥3 mg/mmol (≥30 mg/g) to reduce CV events and kidney failure;
• intensive LDL-C lowering with statins or a statin/ezetimibe combination is recommended; and
• low-dose acetylsalicylic acid (75–100 mg once daily) is recommended for patients with CKD and ASCVD.

"Start treatment early, don’t wait for the nephrologist," was a key message conveyed by Prof. Müller-Wieland. A kidney specialist’s advice may be considered for managing raised serum phosphate, other evidence of CKD–Mineral and Bone Disorder, and renal anaemia (class IIb).

Antithrombotic treatments

Prof. Bianca Rocca (Catholic University School of Medicine, Italy) emphasised that antithrombotic therapy is central in the management of CVD associated with diabetes. New and
revised recommendations are especially concerned with acute (ACS) and chronic coronary syndromes (CCS), and the prevention of gastrointestinal bleeding:

- clopidogrel 75 mg once daily following appropriate loading (e.g. 600 mg or at least 5 days already on maintenance therapy) is recommended in addition to acetylsalicylic acid for 6 months, following coronary stenting for patients with CCS, irrespective of stent type, unless a shorter duration is indicated due to the risk or occurrence of life-threatening bleeding (class I);
- for patients with diabetes and ACS treated with dual antiplatelet therapy who are undergoing CABG and do not require long-term oral anticoagulant (OAC) therapy, resuming a P2Y12-receptor inhibitor as soon as deemed safe after surgery and continuing it up to 12 months is recommended (class I);
- adding very low-dose rivaroxaban (2.5 mg twice daily) to low-dose acetylsalicylic acid for long-term prevention of serious vascular events should be considered for patients with diabetes and CCS or symptomatic peripheral arterial disease without high bleeding risk (class IIa);
- for patients with ACS or CCS and diabetes undergoing coronary stent implantation and having an indication for anticoagulation, prolonging triple therapy with low-dose acetylsalicylic acid, clopidogrel, and an OAC should be considered up to 1 month (class IIa). A treatment period of up to 3 months may be considered (class IIb) if the thrombotic risk outweighs the bleeding risk in the individual patient;
- when antithrombotic drugs are used in combination, proton pump inhibitors are recommended to prevent gastrointestinal bleeding (class I); and
- when a single antiplatelet or anticoagulant drug is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding, considering the bleeding risk of the individual patient (class IIa).

As another important overall aspect, Prof. Massimo Federici (University of Rome Tor Vergata, Italy) mentioned that the new guidelines endorse a person-centred approach in order to facilitate shared decision-making.


Guidelines for the management of cardiomyopathies

The increasing role of genetics, both as a predisposition for certain cardiomyopathies and as a risk factor for sudden cardiac death, is considered in the newly developed 2023 ESC Guidelines for the management of cardiomyopathies.

Prof. Elena Arbelo (University of Barcelona, Spain) pointed out that this is a new guideline, not an update of an existing guideline, which covers all subtypes of cardiomyopathies (CMs) [1]. The only exception is the section on hypertrophic cardiomyopathy (HCM), which was a focused update of the 2014 ESC Guidelines on the diagnosis and management of HCM [2]. The novel guideline contains 158 recommendations, almost half of which are class I. Unfortunately, the evidence for this guideline is based on retrospective data in 65% of cases, due to the rarity of the disease.

In general, CM is defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to cause the observed myocardial abnormality.

Phenotypic approach to cardiomyopathies

A key aspect of the novel guideline is the phenotypic approach and the systematic characterisation of these CMs. "We have to look for morphological and functional traits," Prof. Arbelo explained. Particularly, it is important to identify non-ischaemic ventricular scars and other myocardial tissue characterisation features on cardiac magnetic resonance (CMR). "With that, we will be able to establish 5 different CM phenotypes:"

- hypertrophic cardiomyopathy (HCM);
- dilated cardiomyopathy (DCM);
- non-dilated left ventricular cardiomyopathy (NDLVC);
- arrhythmogenic right ventricular cardiomyopathy (ARVC); and
- restrictive cardiomyopathy (RCM).

There are specific conditions that were formerly considered to be external causes of CM and were recently proved to have genetic contributors. Examples are:

- titin gene truncating variants (TTNtv) represent a prevalent genetic predisposition for alcoholic CM;
- TTNtv also appear to be associated with an increased risk of cancer therapy-induced CM; and
- rare truncating variants in 8 genes are found in 15% of women with peripartum CM.

As another important overall aspect, Prof. Massimo Federici (University of Rome Tor Vergata, Italy) mentioned that the new guidelines endorse a person-centred approach in order to facilitate shared decision-making.
In the new guideline, the multidisciplinary care of patients with CM is emphasised. A shared and coordinated approach between CM specialists and general adult and paediatric cardiology centres is strongly recommended (class I recommendation, level C).

There are also recommendations regarding the diagnostic workflow of CM. All patients with suspected or established CM should undergo systematic evaluation using a multiparametric approach that includes clinical evaluation, pedigree analysis, ECG, Holter monitoring, laboratory tests, and multimodality imaging. Moreover, all patients with suspected CM should undergo evaluation for family history and a 3–4-generation family tree should be created to aid in diagnosis, provide clues to underlying aetiology, determine inheritance patterns, and identify at-risk relatives.

**Contrast-enhanced cardiac magnetic resonance in every patient**

"I want to emphasise the importance of CMR, not only for the diagnosis of CM, but also to allow monitoring of disease progression and risk stratification and management," said Prof. Arbelo. Therefore, contrast-enhanced CMR is recommended in every patient with signs of CM at the initial evaluation. Certain examples of CMR imaging tissue characterisation can raise the suspicion of specific aetiologies, as shown for HCM (see Table). Moreover, in families with CM in which a disease-causing variant has been identified, contrast-enhanced CMR should be considered in genotype-positive/phenotype-negative family members, to aid diagnosis and detection of early disease.

<table>
<thead>
<tr>
<th>Cardiomyopathy phenotype</th>
<th>Finding</th>
<th>Specific diseases to be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>Posterolateral LGE and concentric LVH Low native T1</td>
<td>Anderson-Fabry disease</td>
</tr>
<tr>
<td></td>
<td>Diffuse subendocardial LGE High native T1</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Patchy mid-wall in hypertrophied areas</td>
<td>Sarcomeric HCM</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy.

The genetic section is an important new addition to the guideline. Genetic testing should be offered to all patients fulfilling diagnostic criteria for CM. If a confident genetic diagnosis has been established in an individual with CM in the family, cascade genetic testing with pre- and post-test counselling is recommended for adult at-risk relatives (class I) and paediatric at-risk relatives (class IIa). In addition, clinical psychological support should be offered to all patients who have undergone implantable cardioverter-defibrillator (ICD) implantation or who have a family history of sudden cardiac death (SCD).

**From the description of phenotype to an aetiology-driven management**

Dr Juan Pablo Kaski (University College London, UK) pointed out that a key element of the guideline is the concept of the diagnostic workflow, which starts with a detailed description of the phenotype but leads towards an aetiology-driven management.

Most recommendations regarding HCM, being the most frequent CM with a prevalence of 0.2% in adults, did not change. However, there is a new treatment recommendation regarding the management of left ventricular outflow tract obstruction (LVOTO): the cardiac myosin ATPase inhibitor mavacamten, a first-in-class drug, is recommended as second-line treatment (class IIa) for patients who are still symptomatic after therapy with beta-blockers, verapamil, or diltiazem.

"Sudden death risk prevention in CMs, in particular in primary prevention, is a major aspect of the management of CM," Dr Kaski said. Therefore, there are additional recommendations for the prevention of SCD in patients with HCM. For example, a broader indication for prophylactic ICD implantation is given for patients who are in the low-risk category (<4% estimated 5-year risk of SCD). Shared decision-making with the patient is advised in these cases.

**Genotype: of key importance for prediction of sudden cardiac death**

According to a new recommendation, the patient’s genotype should be considered in the estimation of SCD risk in DCM. A new table depicts high-risk genotypes and associated predictors of SCD. Many subtypes are inherited in an autosomal dominant way. When such a mutation is found, testing of relatives can be considered.

Finally, there are recommendations favouring regular low- or moderate-intensity exercise in all able individuals with CM. An individualised risk assessment should be performed so that an exercise prescription can be provided, bearing in mind the prevention of life-threatening arrhythmias during exercise.

Guidelines for acute coronary syndrome

For the first time, the ESC has issued a guideline that encompasses ST-elevation myocardial infarction (STEMI), non-STEMI, and unstable angina under the umbrella of acute coronary syndrome (ACS). The scope of the new recommendations ranges from invasive treatment and antithrombotic therapy to special situations.

“The main novelty of this guideline is that for the first time, both STEMI and non-ST elevation ACS (NSTE-ACS) are combined into 1 single document,” Prof. Borja Ibañez (Hospital Universitario Fundación Jimenez Diaz, Spain) pointed out [1]. The rationale for this approach is viewing unstable angina, non-STEMI, and STEMI as different presentations within the spectrum of ACS [1–3]. “We believe that, after the acute management and stabilisation of those patients, the majority will undergo a similar management,” Prof. Maria Rubini Gimenez (University of Leipzig, Germany) further explained.

The initial assessment that considers clinical context, stability of the patient, and ECG will lead to a working diagnosis that is then moved forward to a final diagnosis using further investigations with high-sensitivity cardiac troponin (hs-cTn) and possibly angiography and/or imaging. To rule non-STEMI in or out, the ESC algorithm with serial hs-cTn measuring at 0h/1h or 0h/2h is still recommended (class I).

Novelties in invasive treatment

As for the timing of invasive treatment in NSTE-ACS, there has been a revision for patients with at least 1 high-risk criterion: an early invasive strategy within 24h should be considered (class IIa). Other new or revised recommendations on invasive strategies include:
- intravascular imaging should be considered to guide percutaneous coronary intervention (PCI) (class IIa);
- intravascular imaging (preferably optical coherence tomography) may be considered for patients with ambiguous culprit lesions (class IIb); and
- for patients with suspected ACS, non-elevated (or uncertain) hs-cTn, no ECG changes, and no recurrence of pain, incorporating coronary computed tomography angiography or a non-invasive stress imaging test should be considered as part of the initial workup (class IIa).

For patients with in- or out-of-hospital cardiac arrest, routine immediate angiography after resuscitation is not recommended for haemodynamically stable patients without persistent ST-segment elevation (or equivalents) (class III). In this context, Prof. Ibañez also underlined that hypothermia is no longer advised for these patients, but temperature monitoring with active avoidance of fever is recommended (class I).

Also for ACS patients with multivessel disease, new recommendations have been issued:
- when presenting with cardiogenic shock, a staged PCI of non-infarct related artery (IRA) should be considered (class IIa); and
- for haemodynamically stable STEMI patients undergoing primary PCI, it is recommended that PCI of the non-IRA is based on angiographic severity (class I).

Antithrombotic therapy: a cornerstone of treatment

"One of the key aspects of managing patients with ACS is antithrombotic therapy," Dr John Joseph Coughlan (Mater Private Hospital, Ireland) stated. He pointed out that antiplatelet therapy and anticoagulation with 12 months of potent, P2Y12 inhibitor-based dual antiplatelet therapy (DAPT) remains the default recommended regimen for all patients with ACS (see Figure). In order to reduce bleeding risk, various new recommendations on alternative strategies have been issued:
- for patients who are event-free after 3–6 months of DAPT and who are not at high ischaemic risk, single antiplatelet therapy (preferably with a P2Y12 receptor inhibitor) should be considered (class IIa);
- P2Y12 inhibitor monotherapy may be considered as an alternative to aspirin monotherapy for long-term treatment (class IIb);
- for high-bleeding-risk patients, aspirin or a P2Y12 receptor inhibitor monotherapy after 1 month of DAPT may be considered (class IIb);
- for patients requiring oral anticoagulation, withdrawing antiplatelet therapy at 6 months while continuing oral anticoagulation may be considered (class IIb); and
- de-escalation of antiplatelet therapy in the first 30 days after an ACS event is not recommended (class III).

Figure: Recommended antithrombotic therapy for all ACS patients in the short- and long-term. Modified from [3]

ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy.
Special ACS situations
As for ACS complications and comorbidities, Prof. Margret Leosdottir (Skåne University Hospital, Sweden) focused on the new recommendations for left ventricular (LV) thrombus, diabetes, cancer, and older patients. Two recommendations were related to imaging:
- cardiac magnetic resonance imaging should be considered for patients with equivocal ECG images or in case of high clinical suspicion of LV thrombus (class IIa); and
- following an acute anterior MI, a contrast ECG may be considered for the detection of LV thrombus if the apex is not well visualised on ECG (class IIb).

“As for the management of patients with ACS and diabetes, there has been substantial progress in diabetes treatment since the publication of the 2017 STEMI and 2020 non-STEMI guidelines,” Prof. Leosdottir noted. A new recommendation has now been added: It is recommended to base the choice of long-term glucose-lowering treatment on the presence of comorbidities, including heart failure, chronic kidney disease, and obesity (class I).

Further new recommendations on comorbidities include:
- for frail older patients with comorbidities, a holistic approach is recommended to individualise interventional and pharmacological treatments, after careful evaluation of the risks and benefits (class I);
- for older ACS patients, especially those with a high bleeding risk, clopidogrel as the P2Y₁₂ receptor inhibitor may be considered (class IIb);
- an invasive strategy is recommended for cancer patients presenting with high-risk ACS with expected survival ≥6 months (class I);
- a conservative non-invasive strategy should be considered for ACS patients with poor cancer prognosis (i.e. with expected life survival <6 months) and/or very high bleeding risk (class IIa); and
- a temporary interruption of cancer therapy is recommended for patients in whom the cancer therapy is suspected to be a contributing cause of ACS (class I).

Various antiplatelet agents are not recommended for ACS patients with cancer: aspirin for patients with a platelet count <10,000/μL, clopidogrel for patients with a platelet count <30,000/μL, and prasugrel or ticagrelor for patients with a platelet count <50,000/μL (all class III).

With regard to long-term management, the new recommendation to intensify lipid-lowering therapy during the index ACS hospitalisation, for patients who were on lipid-lowering therapy before admission (class I), received special acknowledgement.

Last but not least, Prof. Leosdottir pointed to the new chapter on patient perspectives, indicating a strengthening of the focus on patient-centred care and shared decision-making in all aspects of medical care.

Heart failure: the 2023 update
Already 2 years after the last ESC Guidelines on heart failure (HF), a focused update has been issued. It lists new and changed recommendations on chronic and acute HF, as well as comorbidities.

"Since we published our full guideline 2 years ago, there has been a lot of new evidence that required an update, because there are changes required to patient management," Prof. Theresa McDonagh (King’s College Hospital, UK) explained the motivation for the update [1]. She pointed out the multitude of important trial results that have emerged after the censoring date of 31 March 2021 for the former guidelines.

Starting with chronic HF, Prof. Roy Stuart Gardner (Golden Jubilee National Hospital, UK) underlined that the treatment algorithm for the management of patients with HF with reduced ejection fraction (HFrEF) has not been changed: instead of a sequential approach, patients should be started on key disease-modifying therapy as quickly and safely as possible [2]. He also reported that there was a task force deliberation on an alteration of nomenclature from the 3 phenotypes of HF with preserved ejection fraction (HFpEF), HF with mildly reduced ejection fraction (HFrEFm), and HFrEF to only 2 types: HFrEF and HF with normal EF. This change was favoured by 71% but did not reach the necessary 75% consensus (see Table).

Table: Criteria defining the different phenotypes of heart failure [2]

<table>
<thead>
<tr>
<th>HFpEF</th>
<th>HFrEFm</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms ± signs</td>
<td>Symptoms ± signs</td>
<td>Symptoms ± signs</td>
</tr>
<tr>
<td>LVEF ≤40%</td>
<td>LVEF 41–49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>Objective evidence of cardiac structural and/or functional abnormalities consistent with tje presence of LV diastolic/raised LV filling pressures, including raised natriuretic peptides</td>
</tr>
</tbody>
</table>

HF, heart failure; HFpEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction.

Based on the results of the EMPEROR-Preserved (NCT03057951) and the DELIVER (NCT03619213) trials, 2 novel recommendations have been issued:

- an SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended for patients with HFmrEF, to reduce the risk of HF hospitalisation or cardiovascular (CV) death (class I); and
- an SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended for patients with HFpEF, to reduce the risk of HF hospitalisation or CV death (class I) [1–3].

**Acute heart failure: what is new?**

Prof. Alexandre Mebazaa (Hôpital Lariboisière, France) stressed that optimal treatment of HF may substantially prolong survival [2,3]. “We know that giving the 4 classes of drugs at the optimal dose can reduce all-cause mortality by more than 50%, however, you know that all around the world and there are no exceptions, less than 5% of the patients have a combination of the 4 classes at the target dose.” Prof. Mebazaa alluded to inhibitors of the renin-angiotensin system, aldosterone receptor antagonists, beta-blockers, and SGLT2 inhibitors. With regard to the now available, strong data concerning mortality and rehospitalisation for HF, a new recommendation has been issued:

- an intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following an HF hospitalisation is recommended, to reduce the risk of HF rehospitalisation or death (class I).

Prof. Mebazaa further advised particular attention should be paid to symptoms and signs of congestion, blood pressure, heart rate, NT-proBNP values, potassium concentrations, and estimated glomerular filtration rate to make sure that a patient is going in the right direction during the follow-up visits.

**Comorbidities: important to manage**

“There are some important comorbidities like diabetes, iron deficiency, and chronic kidney disease (CKD) that are strongly related with the pathophysiology of HF; all of them create a special metabolic milieu and together promote the progression of HF; therefore, they are of very high importance,” Prof. Ewa Jankowska (Wroclaw Medical University, Poland) explained [2,3]. Prof. Marianna Adamo (Civil Hospital of Brescia, Italy) focused on new recommendations for prevention with regard to diabetes and nephropathy, which are also based on new data from randomised-controlled trials as well as metaanalyses:

- for patients with type 2 diabetes (T2DM) and CKD, SGLT2 inhibitors (dapagliflozin or empagliflozin) are recommended, to reduce the risk of HF hospitalisation or CV death (class I); and
- for patients with T2DM and CKD, finerenone is recommended, to reduce the risk of HF hospitalisation (class I).

Iron deficiency in itself is seen as an important factor for patients with HF. “Treating iron deficiency with intravenous iron is not related to the direct effect of erythropoiesis. Patients who are not anaemic benefitted equally to those who are anaemic,” Prof. Jankowska stated. The amelioration of quality-of-life is an important factor in favour of iron repletion and recent results merited a class I recommendation. As for hard clinical endpoints, the outcomes were not quite as strong, leading to a class IIa recommendation:

- intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF and iron deficiency, to alleviate HF symptoms and improve quality-of-life (class I); and
- intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF and iron deficiency, to reduce the risk of HF hospitalisation (class IIa).

Prof. Jankowska furthermore stressed that oral iron does not improve exercise capacity in patients with HF.

STEP-HFpEF: Semaglutide safe and efficacious in HFpEF plus obesity

In patients with heart failure with preserved ejection fraction (HFpEF) and obesity, treatment with semaglutide resulted in greater weight loss and improved HF-related symptoms compared with placebo. Together with the favourable safety profile, semaglutide presents itself as a potentially practice-changing therapy in this patient population.

"Most patients with HFpEF are overweight or have obesity," stated Dr Mikhail Kosiborod (University of Missouri, MO, USA) [1]. "Since there are no approved therapies for the obesity phenotype of HFpEF and it has been demonstrated that the GLP-1 agonist semaglutide induces weight loss in overweight and obese individuals, the STEP-HFpEF trial was conducted" [1–3]. This phase 3 trial (NCT04788511) investigated the effects of 2.4 mg semaglutide, subcutaneously administered once weekly, on HFpEF symptoms and physical functioning in patients with the obesity HFpEF phenotype [3]. The double-blind trial randomised 529 adult patients 1:1 to the experimental arm or a placebo. The co-primary endpoints were the change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and the percentage change in body weight from baseline to week 52.

The mean change in KCCQ-CSS at week 52 was 16.6 points in the active treatment arm and 8.7 points in the placebo arm, representing a significant 7.8-point benefit for the semaglutide arm (95% CI 4.8–10.9; P<0.001; see Figure 1). Further, body weight was reduced by 13.3% in the semaglutide arm compared with 2.6% in the placebo arm, meeting this second primary endpoint (95% CI -11.9 to -9.4; P<0.001; see Figure 2). Participants receiving semaglutide also showed a significant improvement in 6-minute walking distance compared with those receiving placebo (mean difference 20.3 metres; 95% CI 8.6–32.1; P<0.001). At week 52, CRP levels had dropped to a ratio of 0.93 compared with baseline in the placebo arm and to a ratio of 0.56 compared with baseline in the semaglutide arm. Mean reductions from baseline NT-proBNP were approximately 5% and 21% in the placebo and semaglutide arms, respectively.

Serious adverse events (AEs) were more common in the placebo arm than in the semaglutide arm (26.7% vs 13.3%; P<0.001). This effect was mainly driven by a higher rate of cardiac disorders in the placebo arm (11.3% vs 2.7%; P=0.001). The AE rate of participants discontinuing treatment appeared to be higher in the experimental arm (13.3% vs 5.3%), mainly due to a difference in gastrointestinal AEs resulting in treatment discontinuations (9.5% vs 2.6%).

Discussant of the trial, Prof. Frank Ruschitzka (University Heart Center Zürich, Switzerland) congratulated the investigators on these potentially practice-changing results but wondered whether the effects of semaglutide on HFpEF symptoms are mainly driven by weight loss or by other mechanisms. He also warned that weight loss is not a great proxy for fat loss and that the loss of lean mass and the risk for sarcopaenia need to be further investigated. Finally, he stressed that the proportion of non-White individuals in the STEP-HFpEF trial was low and that the effects of semaglutide on the HFpEF with obesity phenotype need to be addressed in other ethnicities.

Figure 1: Change in KCCQ-CSS from baseline to week 52 [1]

Figure 2: Change in body weight from baseline to week 52 [1]

DICTATE-AHF: Early dapagliflozin to manage acute HF

Dapagliflozin on top of high-dose intravenous loop diuretics just missed its primary endpoint of improving diuretic efficiency in hospitalised patients with acute heart failure (HF). Nonetheless, the results of DICTATE-AHF seems to support the early initiation of dapagliflozin to facilitate decongestion and guideline-directed medical therapy optimisation in acute HF.

"Loop diuretics plus SGLT2 inhibitors have consistently displayed to improve outcomes in patients with HF," said Prof. Zachary Cox (Lipscomb University College of Pharmacy, TN, USA) [1]. "However, the safety and efficacy of early, in-hospital initiation of dapagliflozin have not yet been demonstrated." Prof. Cox highlighted that there have been some concerns with the safety of administering SGLT2 inhibitors very early in hospital. "Patients may be at risk for hypoglycaemia, ketoacidosis, genitourinary infections, and worsening renal function."

The open-label phase 3 DICTATE-AHF trial (NCT04298229) randomised 240 participants with acute HF within 24 hours after hospital admission 1:1 to dapagliflozin 10 mg daily plus structured usual care or usual care with protocolised diuretic titration only. The primary outcome was diuretic efficiency until day 5 or until hospital discharge, calculated by the cumulative weight change divided by cumulative loop diuretic dose and expressed as kg/40 mg intravenous furosemide equivalents.

The primary endpoint showed a trend of benefit for dapagliflozin with an OR of 0.65 (95% CI 0.41–1.01; P=0.06) compared with usual care; however, this did not meet statistical significance. Prof. Cox clarified that the cumulative weight change was identical for both arms, but that the median dose of cumulative loop diuretics was significantly lower in the dapagliflozin arm (560 mg vs 800 mg; P=0.006). Furthermore, 52% of the participants in the dapagliflozin arm had discontinued intravenous diuretics at day 5 compared with 33% of those in the usual care arm (P=0.006). Equal rates were observed for ‘time to discharge,’ showing that participants on dapagliflozin had a shorter time to discharge (P=0.007).

Finally, no differences were seen between both arms with regard to safety outcomes, such as worsening HF, readmission for acute decompensated HF, hypoglycaemia, genitourinary tract infections, ketoacidosis, or diabetes-related readmissions.

Although this modestly sized, open-label study did not meet its primary endpoint, it can be taken in the context of the totality of data for SGLT2 inhibitors. "The totality of the DICTATE-AHF data supports the early initiation of dapagliflozin in acute HF, to safely facilitate decongestion and optimisation of guideline-directed medical therapy," concluded Prof. Cox.

Natriuresis-guided diuretic therapy to facilitate decongestion in acute HF

The PUSH-AHF trial demonstrated that natriuresis-guided diuretic therapy outperformed placebo in terms of natriuresis and diuresis in patients with acute heart failure (HF). Moreover, it was a safe strategy; thus, claim the authors, these results are directly implementable into clinical practice.

"Quick and adequate decongestion in patients with acute HF remains difficult in today’s practice," said Dr Jozine ter Maaten (University of Groningen, the Netherlands) [1]. "The one-size-fits-all approach that is used falls short in many patients." Urinary sodium (natriuresis) may guide diuretic therapy to personalise therapy and improve decongestion. The pragmatic, single-centre, open-label, randomised-controlled PUSH-AHF trial (NCT04606927) assessed the effectiveness and safety of natriuresis-guided diuretic therapy in acute HF. Participants in the experimental arm (n=150) received a standardised starting dose of loop diuretics based on renal function and outpatient dose. If the dose was insufficient, defined as urinary sodium <70 mmol/L and diuresis <150 mL/hour, the bolus dose was doubled. If this still proved to be insufficient, hydrochlorothiazide, acetazolamide, or an SGLT2 inhibitor was added. Participants in the control arm (n=160) received the standard-of-care. The dual primary endpoints were 24-hour natriuresis and 180-day all-cause mortality or adjudicated HF hospitalisation.

The first primary endpoint was met, in favour of the natriuresis-guided arm, with an estimated difference of 63 mmol/L urinary sodium at 24 hours (95% CI 18–109;
The second primary endpoint was not met (HR 0.92; 95% CI 0.62–1.38; P=0.70). The effect of natriuresis-guided therapy on natriuresis was maintained at 48 hours (P=0.024). Furthermore, diuresis was improved at both 24 hours (P=0.0053) and 48 hours (P=0.014) in the experimental arm. Dr ter Maaten emphasised that natriuresis-guided therapy did not lead to electrolyte disorders or higher rates of renal or cardiac adverse events.

In summary, natriuresis-guided diuretic therapy was safe, improved natriuresis and diuresis in patients with acute HF. There was, however, no effect of this intervention on 180-day all-cause mortality or adjudicated HF hospitalisation. “The results of this trial are directly applicable as spot urinary sodium values are inexpensive and easy to obtain, as are the medications used in the treatment algorithm,” argued Dr ter Maaten. “Finally, these findings underscore the use of repeated spot urinary sodium assessments for personalised treatment targets as proposed by the ESC HF guidelines.”

HEART-FID: Is intravenous ferric carboxymaltose helpful in HFrEF with iron deficiency?

Although the HEART-FID trial narrowly missed its primary endpoint, the authors concluded that the totality of evidence on intravenous ferric carboxymaltose (FCM) supports the safety and clinical benefits of this therapy in patients with heart failure with reduced ejection fraction (HFrEF) and iron deficiency.

Dr Robert Mentz (Duke University, NC, USA) outlined that the AFFIRM-AHF and IRONMAN trials, as well as meta-analyses, indicated that intravenous iron reduces the risk of HF hospitalisations without a significant effect on mortality [1–3]. “More evidence is needed with respect to the effect of FCM on clinical outcomes.” The multicentre, double-blind, phase 3 HEART-FID trial (NCT03037931) randomised 3,065 participants with HFrEF and iron deficiency 1:1 to intravenous FCM or a placebo [4]. The primary endpoint was a hierarchical composite of all-cause mortality at 12 months, HF hospitalisations at 12 months, and change in 6-minute walking distance (6MWD) at 6 months.

The primary endpoint was not significantly different at the significance threshold that was pre-specified for the trial (P=0.019). The corresponding rates for the individual aspects of the primary endpoint were:
- all-cause mortality at 12 months: FCM 8.6% versus placebo 10.3%;
- HF hospitalisations at 12 months: FCM 13.3% versus placebo 14.8%; and
- change in 6MWD at 6 months: FCM +8 metres versus placebo +4 metres.

Treatment-emergent adverse event rates were similar in participants receiving FCM and those receiving placebo (27.0% vs 26.2%).

Despite its neutral results, the presenting author stated, “The HEART-FID trial is the largest study to evaluate the long-term safety and efficacy of intravenous FCM in patients with HFrEF and iron deficiency. FCM showed an acceptable safety profile and led to a modest, albeit non-significant, improvement in the primary endpoint.”


Meta-analysis: Does FCM improve clinical outcomes in HF?

A large, pooled analysis using individual participant data to investigate the effects of ferric carboxymaltose (FCM) on clinical outcomes in patients with heart failure (HF) and iron deficiency displayed a significant reduction of the composite of cardiovascular (CV) hospitalisation and CV death at 1 year of follow up. This effect was mostly driven by a reduction in hospitalisations.

“Iron deficiency occurs in 50–80% of the patients with HF,” said Prof. Piotr Ponikowski (Medical University Wroclaw, Poland) [1]. “Although the positive effect of intravenous FCM on exercise capacity and quality-of-life has been demonstrated, its effect on clinical outcomes is less clear.” Prof. Ponikowski and colleagues conducted a pooled analysis of patient-level data including randomised, double-blind, placebo-controlled trials that investigated the effect of FCM on prospectively recorded HF hospitalisations, CV death, and all-cause death for a minimum duration of 52 weeks, in patients with HF and iron deficiency.

The CONFIRM-HF (NCT01453608), AFFIRM-AHF (NCT02937454), and HEART-FID (NCT03037931; also presented at ESC 2023)
trials met the inclusion criteria [2–4]. “The meta-analysis included approximately 4,500 patients, with a mean age of 70 years, and about 40% of the patients were women,” added Dr Ponikowski. The co-primary endpoints were a composite of total CV hospitalisations and CV death through 52 weeks, and a composite of total HF hospitalisations and CV death through 52 weeks.

The endpoint of total CV hospitalisations and CV death was met, favouring FCM over placebo (rate ratio [RR] 0.86; 95% CI 0.75–0.98; P=0.029; see Figure). The endpoint of total HF hospitalisations and CV death just missed statistical significance but showed a trend towards a benefit for patients who were randomised to FCM compared with those on placebo (RR 0.87; 95% CI 0.75–1.01; P=0.076). Prof. Ponikowski added that these effects were driven by a reduction in CV hospitalisations (RR 0.83; 95% CI 0.73–0.96; P=0.009) and HF hospitalisations (RR 0.84; 95% CI 0.71–0.98; P=0.025) but not by a reduction in time to CV death (RR 0.97; 95% CI 0.80–1.17; P=0.72) or all-cause death (RR 0.93, 95% CI 0.78–1.10; P=0.39).

Furthermore, the subgroup analysis revealed one significant interaction effect: patients with transferrin saturation levels <15% benefitted significantly more from treatment with FCM compared with those on placebo (RR 0.87; 95% CI 0.75–1.01; P=0.076). Patients with transferrin saturation levels ≥24% (Pinteraction=0.019). Finally, an exploratory analysis suggested that patients with a higher cumulative dose at 6 months may benefit more from treatment with FCM than those with lower cumulative doses.

**Figure: Co-primary endpoint of total CV hospitalisations and CV death [1]**

<table>
<thead>
<tr>
<th>Study</th>
<th>FCM n/N (%)</th>
<th>PBO n/N (%)</th>
<th>Rate ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONFIRM HF</td>
<td>28/150 (18.7)</td>
<td>38/151 (25.2)</td>
<td>0.65 (0.37–1.14)</td>
<td></td>
</tr>
<tr>
<td>AFFIRM-AHF</td>
<td>218/558 (39.1)</td>
<td>252/550 (45.8)</td>
<td>0.85 (0.66–1.10)</td>
<td></td>
</tr>
<tr>
<td>HEART-FID</td>
<td>371/1529 (24.3)</td>
<td>391/1532 (25.5)</td>
<td>0.88 (0.75–1.05)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>617/2237 (27.6)</td>
<td>681/2233 (30.5)</td>
<td>0.84 (0.75–0.98)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Cl, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; PBO, placebo.

“Based on the results of our meta-analysis, FCM should be considered as an option to reduce the risk for CV or HF hospitalisations in patients with HF with reduced or mildly reduced left ventricular ejection fraction and iron deficiency,” concluded Prof. Ponikowski. “Further research is needed to select the appropriate patients for this therapy and to assess the potential benefits of re-dosing in the first 6 months of treatment.”


**Catheter ablation saves lives in end-stage HF with AF**

Catheter ablation outperformed medical therapy for treating atrial fibrillation (AF) in patients with end-stage heart failure (HF) in the CASTLE-HTx trial. This effect was mostly driven by a reduction in all-cause mortality in the ablation arm and could be explained by an improved left ventricular (LV) function and a decreased AF burden in patients who underwent ablation.

“Although we know that catheter ablation reduces mortality and worsening of HF in patients with HF and symptomatic AF, it is not yet established whether this effect translates to patients with end-stage HF eligible for heart transplant or LV assist device,” argued Prof. Christian Sohns (Heart and Diabetes Center NRW, Germany) [1,2]. To investigate this matter, the CASTLE-HTx trial (NCT04649801) randomised 194 participants with end-stage HF and symptomatic AF who were potential candidates for heart transplantation 1:1 to catheter ablation and guideline-directed medical therapy or medical therapy alone [3]. The primary outcome was a composite of all-cause mortality, LV assist device implantation, or urgent heart transplantation. The trial was terminated for efficacy earlier than planned, after 18 months of follow-up.

Ablation was superior to medical therapy in terms of the primary endpoint (HR 0.24; 95% CI 0.11–0.52; P<0.001). This effect was mainly driven by a reduction in death from any cause in the ablation arm (HR 0.09; 95% CI 0.01–0.70; P=0.005). LV assist device implantations (n=10 vs n=1) and urgent heart transplantations (n=6 vs n=1) both occurred more frequently in the medical therapy arm. Prof. Sohns showed that these effects can be explained by an improved LV function and a reduced AF burden in the ablation arm compared with the medical therapy arm (see Figure).
Figure: Impact on left ventricular function and AF burden [2]

In conclusion, ablation for AF led to fewer deaths, LV assist device implantations, and urgent heart transplantation in patients with end-stage HF, as compared with medical therapy alone.


**CRT upgrade benefits patients with HFrEF and an ICD**

An upgrade from an implantable cardioverter-defibrillator (ICD) to a cardiac resynchronisation therapy defibrillator (CRT-D) was associated with a reduced risk for cardiovascular and other adverse outcomes in patients with heart failure with reduced ejection fraction (HFrEF) and right ventricular (RV) pacing. Based on these results from the BUDAPEST CRT Upgrade trial, the authors believed that patients with HFrEF with a pacemaker or ICD and RV pacing should immediately receive a CRT upgrade. However, the sample size of this study was small and larger studies are needed to confirm these findings.

"It has not been established whether an upgrade from a pacemaker or an ICD to a CRT offers benefits for patients with HFrEF," said Dr Béla Merkely (Semmelweis University, Hungary) [1]. According to Dr Merkely, the lack of data on hard outcomes from large trials led to several modifications of CRT guidelines in the last decade. "This demonstrates the need for more robust evidence," he argued. "Furthermore," Dr Merkely claimed, "in 60% of the patients, an indicated upgrade is not performed or postponed to a later, often undetermined date."

The multicentre, randomised-controlled BUDAPEST CRT Upgrade trial (NCT02270840) evaluated the efficacy and safety of a CRT-D upgrade in patients with HFrEF and intermittent or permanent RV pacing who already had an ICD [1,2]. Participants had HFrEF, a prior pacemaker or ICD, RV pacing of 20–100%, and a paced QRS complex ≥150 ms (n=360) and were randomised 3:2 to a CRT-D upgrade or no upgrade. The composite primary endpoint was the first occurrence of HF hospitalisation, all-cause mortality, or <15% reduction in left ventricular end-systolic volume (LVESV) at month 12.

After 12 months, 78.9% of participants in the no-intervention arm had experienced a primary endpoint event, whereas only 32.4% of the participants in the CRT-D arm had one of the primary outcome events (adjusted OR 0.11; 95% CI 0.06–0.19; P<0.001). The secondary outcome of all-cause mortality or HF hospitalisation favoured the CRT-D arm over the no-intervention arm as well (adjusted HR 0.27; 95% CI 0.16–0.47; P<0.001). For mortality alone the adjusted HR was 0.52 (95% CI 0.23–1.19).

"These results show that patients with HFrEF with a pacemaker or ICD and intermittent or permanent RV pacing should receive a CRT upgrade without delay to reduce the risk for serious adverse events," according to Prof. Merkely. Even though the results of this open-label trial were impressive, larger studies are needed to confirm whether the investigated intervention really reduces mortality in this population.


**Traditional Chinese medicine successful in HFrEF**

In the Chinese QUEST trial, qiliqiangxin capsules decreased the risk of cardiovascular death and heart failure hospitalisation in patients with heart failure with reduced ejection fraction (HFrEF). The capsules were well tolerated, and the authors concluded that qiliqiangxin may be a novel approach in the management of patients with HFrEF.

"Qiliqiangxin has been used in traditional Chinese medicine for over 1,000 years," said Dr Xinli Li (First Affiliated Hospital of Nanjing Medical University, China). "This product has been shown to reduce NT-proBNP in patients with chronic HF [1]." According to Dr Li, qiliqiangxin upregulates PPAR-y and its coactivator PGC1-a, which inhibits ventricular remodeling. The current randomised-controlled phase 4 trial, named QUEST (ChiCTR1900021929), hypothesised that qiliqiangxin...
capsules on top of standard-of-care outperform placebo on top of standard-of-care in terms of cardiovascular outcomes in patients with HFrEF [2]. In total, 3,119 patients were randomised 1:1 to qiliqiangxin or a placebo. The primary outcome was the composite of cardiovascular death and hospitalisation for HF.

After a median of 18.3 months of follow-up, the primary endpoint was met, favouring participants in the qiliqiangxin arm over those in the placebo arm (HR 0.78; 95% CI 0.68–0.90; P<0.001). Moreover, qiliqiangxin reduced the risk of both hospitalisation for HF (HR 0.76; 95% CI 0.64–0.90; P=0.002) and cardiovascular death (HR 0.83; 95% CI 0.68–1.00; P=0.045) as individual endpoints.

The qiliqiangxin capsules were well tolerated and did not lead to an increase in adverse events (AEs), serious AEs, or discontinuations related to AEs, compared with placebo.

Prof. Carolyn Lam (Duke-National University of Singapore, Singapore) acknowledged that the QUEST trial adds rigorous scientific evidence for a traditional medicine that is potentially used by millions of patients with HF in China. She also said that the trial design and results bring up a couple of unanswered issues. “Since the rate of SGLT2 inhibitors and device therapy was very low in the study population, I wonder what the effect of qiliqiangxin on top of guideline-directed medical therapy (GDMT) including SGLT2 inhibitors and device therapy is,” she reasoned. “Also, since the prescribed doses of GDMTs are low in China, the effect of qiliqiangxin should be reviewed with different doses of GDMTs. Finally, we need to establish the interaction effect of this traditional medicine with other agents, such as digoxin, and study its effects in patients with HFmEF and HFpEF.”


Key Research on Prevention

Diagnostic tool doubles cardiovascular diagnoses in patients with COPD or diabetes

An easy-to-use diagnostic strategy more than doubled the number of new diagnoses of cardiovascular disease (CVD) in patients with chronic obstructive pulmonary disease (COPD) or type 2 diabetes. According to the authors, this diagnostic tool should be implemented in the management of patients with these conditions.

“Up to 40% of the patients with COPD or type 2 diabetes have unknown but treatable CVD,” outlined Dr Amy Groenewegen (University Medical Center Utrecht, the Netherlands) [1]. “These patients are often symptomatic.” To reveal CVD at an early stage in this population, Dr Groenewegen and colleagues evaluated a diagnostic strategy in primary care patients with COPD and/or type 2 diabetes.

The RED-CVD trial was a cluster-randomised trial including 25 practices and 1,216 participants [2]. The diagnostic intervention was a stepwise approach, starting with a symptom questionnaire, followed by step 2, a physical exam, NT-proBNP, and ECG evaluations, and step 3, a referral.

The primary outcome measure was newly detected CVD, including atrial fibrillation, heart failure, and coronary artery disease at 1 year of follow-up.

In the usual-care arm, 3.0% of the participants were diagnosed with a new CVD compared with 8.0% in the intervention arm (OR 2.83; 95% CI 1.62–4.95) [1]. Dr Groenewegen added that this effect was mainly driven by an increase in diagnoses of heart failure with preserved ejection fraction (3.2% vs 0.7%), atrial fibrillation (2.1% vs 0.8%), and relevant non-obstructive coronary artery disease (1.3% vs 0.2%) in the intervention arm.

The questionnaire showed that 70% of the participants reported having symptoms. Of the participants that continued to the next step, 25% had abnormalities in the physical exam, 10% had abnormalities on ECG, and 26% had newly elevated NT-proBNP levels. In total, 239 of the 607 participants (39%) in the intervention arm were referred based on abnormal findings in step 2.

“This easy-to-use diagnostic strategy led to a significant increase in diagnoses of new CVD in patients with COPD...
and/or type 2 diabetes, and should be considered to be implemented in the management of these patients in the primary care setting,” concluded Dr Groenewegen.


Inorganic nitrate strongly reduces CIN in high-risk patients undergoing angiography

Dietary inorganic nitrate significantly reduced contrast-induced nephropathy (CIN) in patients at risk for renal injury undergoing coronary angiography for acute coronary syndrome (ACS). Moreover, long-term renal and cardiovascular outcomes in the NITRATE-CIN trial were in favour of patients treated with inorganic nitrate as compared with placebo.

“Older patients with heart failure, chronic kidney disease, or diabetes undergoing angiography for ACS have an increased risk for CIN, a condition that potentially has severe consequences,” said Dr Dan Jones (Queen Mary University of London, UK) [1]. “Although the pathophysiology of CIN is not perfectly understood, it is known that the loss of nitric oxide plays an important role. Replacing this lost nitric oxide may therefore reduce the risk for CIN in these patients.”

The current double-blind, single-centre, phase 2 NITRATE-CIN trial (NCT03627130) enrolled 640 patients undergoing invasive coronary angiography for non-ST elevated ACS who were at risk for CIN. The study population had a mean age of 71.0 years, 26% of the participants were women, 46% had diabetes, 56% had chronic kidney disease with an eGFR <60 mL/min, and the mean Mehran score was 10. They were randomised 1:1 to a 5-day intervention with potassium nitrate (12 mmol/744 mg nitrate) or a placebo. The primary endpoint was the incidence of CIN as defined by the KDIGO criteria [2].

After a median follow-up of 12 months, CIN was observed in 30.5% of the participants in the placebo arm and 9.1% in the inorganic nitrate arm (P<0.0001) [1]. These results were consistent across troponin levels, Mehran risk scores, and diabetic status. However, participants who received prior organic nitrate (n=72) appeared to benefit less from the intervention than those who had not received prior organic nitrate (n=484; OR 0.65 vs OR 0.17; P_interaction =0.04).

Procedural myocardial infarction, a secondary endpoint, occurred in 12.5% and 4.1% of the participants in the placebo arm and inorganic nitrate arm, respectively (P=0.003). Furthermore, Dr Jones mentioned that renal outcomes at 3 months, major adverse cardiovascular events (MACE) at 1 year, and major adverse kidney events (MAKE) at 1 year all favoured participants in the inorganic nitrate arm over those in the placebo arm.

“These results could have important implications for the reduction of the burden of CIN worldwide,” according to Dr Jones. “However, studies powered for MACE and MAKE outcomes should be conducted to confirm these findings.”


Does colchicine prevent perioperative AF and MINS?

Treatment with colchicine did not significantly reduce atrial fibrillation (AF) or myocardial injury after non-cardiac surgery (MINS) in patients undergoing major, non-cardiac, thoracic surgery. Interestingly, there was a hypothesis-generating observed interaction effect between surgical approach and received study drug on the occurrence of clinically important AF, with those undergoing thoracoscopic surgery experiencing benefit from colchicine, whereas those undergoing non-thoracoscopic surgery did not.

“Perioperative AF and MINS are prognostically important adverse outcomes after major thoracic surgery,” outlined Dr David Conen (McMaster University, Canada) [1]. Dr Conen and his co-investigators evaluated the effects of oral colchicine on the incidence of clinically important perioperative AF and MINS in patients undergoing major, non-cardiac, thoracic surgery. The phase 3 COP-AF trial (NCT03310125) randomised 3,209 participants of at least 55 years of age who were scheduled for non-cardiac thoracic surgery with general anaesthesia 1:1 to colchicine 0.5 mg, starting from 4 hours pre-surgery, then twice daily for 10 days, or a matching placebo.

Clinically important perioperative AF occurred in 6.4% and 7.5% of the participants in the colchicine and placebo arms, respectively (HR 0.85; 95% CI 0.65–1.10; P=0.22). Similarly, no significant difference was seen in the incidence of MINS between those who received colchicine and those who received a placebo (18.3% vs 20.3%; HR 0.89; 95% CI 0.76–1.05; P=0.16). Secondary efficacy outcome measures also numerically
favoured the colchicine arm over the placebo arm but failed to display significant differences.

The occurrence of sepsis and infections was similar for participants on colchicine and those on placebo (6.4% vs 5.2%; HR 1.24; 95% CI 0.93–1.66; P=0.14). In contrast, non-infectious diarrhoea did appear more frequently in participants treated with the investigational agent (8.3% vs 2.4%; HR 3.64; 95% CI 2.54–5.22; P<0.001).

Finally, the authors reported a significant interaction effect between surgical approach and received study drug on the occurrence of clinically important AF (P_interaction<0.0001): those who received thoracoscopic surgery were less likely to experience clinically important AF if they were treated with colchicine instead of placebo (3.5% vs 6.5%; HR 0.53; 95% CI 0.36–0.77); if patients underwent non-thoracoscopic surgery, placebo appeared the preferred option in the prevention of clinically important AF (10.5% vs 16.0%; HR 1.59; 95% CI 1.07–2.35). This interaction is hypothesis generating and requires validation in future prospective studies.

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DAPT or clopidogrel monotherapy after stenting in high-risk East-Asian patients?

In East-Asian patients with acute coronary syndrome (ACS) who were at high risk for bleeding and ischaemic events and who completed 9 to 12 months of dual antiplatelet therapy (DAPT) after the implantation of a drug-eluting stent, a prolonged clopidogrel monotherapy treatment outperformed a continued DAPT regimen in terms of bleeding and major adverse cardiac and cerebrovascular events. The OPT-BIRISK trial adds data to the complex issue of antithrombotic therapy after ACS in the understudied East-Asian population.

“It remains a challenge to select the optimal antithrombotic therapy for patients with ACS who are at high risk for bleeding and ischaemic events,” said Prof. Yaling Han (General Hospital of Northern Theater Command, China) [1]. “Continued P2Y_12 inhibitor monotherapy after 9–12 months of DAPT may be a sound strategy for so-called bi-risk patients with ACS.” To test this regimen, patients with ACS who had ACS with high bleeding and ischaemic risk were treated with DAPT for 9–12 months after drug-eluting stent implantation and then randomised to clopidogrel monotherapy or continued DAPT with clopidogrel plus aspirin for 9 months. The primary endpoint of the OPT-BIRISK trial (NCT03431142) was the risk for BARC type 2, 3, or 5 bleeding during the 9-month follow-up.

The results demonstrated that BARC type 2, 3, or 5 bleeding events occurred more frequently in the DAPT arm than in the clopidogrel monotherapy arm (3.3% vs 2.5%; HR 0.75; 95% CI 0.57–0.97; P=0.03). This outcome was consistent across subgroups (e.g. age, sex, heart failure, diabetes, renal dysfunction) except in participants with anaemia, for whom the continued DAPT strategy appeared to lead to a reduced risk for bleeding events compared with the monotherapy arm (HR 2.17; P_interaction=0.04). Finally, major adverse cardiac and cerebrovascular events (MACCE) occurred more often in participants in the DAPT group (3.5% vs 2.6%; HR 0.74; 95% CI 0.57–0.96; P=0.02).

Prof. Renato Lopes (Duke University, NC, USA) congratulated the investigators for providing information on how to manage East-Asian patients with antithrombotic therapy after ACS. He mentioned that the patients had not had a clinical event in the last 9–12 months at the time of randomisation. “Therefore, the population is not likely to be the high-risk population the investigators intended to evaluate. Also, it is important to mention that the results were driven by a reduction in BARC 2, and not BARC 3 or 5 bleeding events, meaning a reduction in
less severe bleeding events in the monotherapy arm but not in severe bleeding events. Finally, the applicability of these results in non-Asian patients needs to be further investigated.”


The optimal duration of anticoagulation therapy in cancer patients with DVT
Cancer patients with isolated distal deep vein thrombosis (DVT) benefitted more from a 12-month regimen with edoxaban than from a 3-month treatment with this agent, with regard to venous thromboembolism (VTE). The bleeding risk was not significantly increased for patients on the prolonged anticoagulation regimen.

“Although there are guideline recommendations for the management of isolated distal DVT, the subgroup of cancer patients has not been well studied,” stated Dr Yugo Yamashita (Kyoto University, Japan). “No randomised-controlled trials have been conducted to establish the optimal duration of anticoagulation therapy in these patients.” The open-label, adjudicator-blinded ONCO DVT study (NCT03895502) compared a 12-month and a 3-month edoxaban treatment period in patients with cancer and newly diagnosed isolated distal DVT [1]. In total, 604 participants were randomised to 1 of the 2 study arms. The primary endpoint was symptomatic recurrent VTE or VTE-related death at 12 months.

Symptomatic recurrent VTE or VTE-related death occurred more frequently in participants who received 3 months of edoxaban therapy than in those who were randomised to the 12-month treatment period (8.5% vs 1.2%; OR 0.13; 95% CI 0.03–0.44; P<0.001; see Figure). There was no significant difference between the prolonged-treatment arm and the short-term treatment arm in the key secondary endpoint of major bleeding (10.2% vs 7.6%; OR 1.34; 95% CI 0.75–2.41). The subgroup analysis did not reveal any significant interaction effects.

In summary, cancer patients with isolated distal DVT had a reduced risk for symptomatic recurrent VTE or VTE-related death if they were treated with 12 months rather than 3 months of anticoagulation therapy.


Results of FRAIL-AF trial suggest increased bleeding risk with DOACs
According to the findings of the FRAIL-AF trial, switching frail patients with atrial fibrillation (AF) from a vitamin K antagonist (VKA) to a direct oral anticoagulant (DOAC) should not be considered without a clear indication. In contrast to the hypothesis of the research team, switching to a DOAC resulted in a significantly higher risk for bleeding among these patients.

Dr Linda Joosten (University Medical Center Utrecht, the Netherlands) argued that it is important to evaluate the use of anticoagulants for AF in frail patients since frail individuals comprise 12% of the population, the prevalence of AF in frail older people is high (18%), and the incidence of stroke in frail AF patients is remarkably higher than in non-frail AF patients (12.3% vs 3.9%) [1–3]. “The 2023 EHRA expert consensus statement on the management of arrhythmias in frailty syndrome states that the advantages of DOACs relative to VKAs are likely to be consistent in frail and non-frail AF patients,” said Dr Joosten [1]. “However, evidence for this statement is lacking.”

The FRAIL-AF trial investigated whether switching from a VKA to a DOAC reduced bleeding risk in frail older patients with AF, as compared with continuing treatment on a VKA [4]. Thus, the 1,330 enrolled participants were randomised 1:1 to either of these options. Dr Joosten pointed out that the population of the current trial was different from the standard populations tested in DOAC trials, with a mean age of 83 years, a median Groningen Frailty Indicator score of 4, and a median CHA2DS2-VASc score of 4. The primary endpoint of FRAIL-AF was major or clinically relevant non-major bleeding.
After 1 year of follow-up, the primary outcome data showed that participants who switched to a DOAC had an increased risk for bleeding compared with those who continued on a VKA (15.3% vs 9.4%; HR 1.69; 95% CI 1.23–2.32; P=0.0011). This effect appeared to be mainly driven by an increase in clinically relevant non-major bleedings in the DOAC arm (12.7% vs 7.4%; HR 1.77; 95% CI 1.24–2.52). Dr Joosten mentioned that there was no difference in the occurrence of thromboembolic events between VKA receivers and DOAC receivers (2.0% vs 2.4%; HR 1.26; 95% CI 0.60–2.61). All-cause mortality rates were also similar between both study groups (7.0% vs 6.7%).

Discussant Dr Isabelle van Gelder (University Medical Center Groningen, the Netherlands) mentioned that 50.2% of the participants in the DOAC group switched to rivaroxaban and that this DOAC has been associated with a higher risk for bleeding [5]. “However, I believe that the main explanation for the results is to be found in the constitution of the study population. These are frail patients, very different from the populations that were studied in the DOAC trials, and they take many medications. Polypharmacy has been associated with an increased risk for bleeding and DOACs are novel drugs that may come with unknown interaction effects with some of these medications [6].”


**Should we use anticoagulation in AHRE to prevent stroke?**

In a phase 3 trial, edoxaban did not reduce a composite outcome of stroke, systemic embolism, or cardiovascular death in patients with atrial high-rate episodes (AHRE), and it increased the risk for major bleeding. These

**NOAH-AFNET 6 trial results suggest that patients with AHRE are better managed without anticoagulation therapy until atrial fibrillation (AF) is diagnosed.**

Prof. Paulus Kirchhof (University Heart & Vascular Center Hamburg, Germany) and his colleagues hypothesised that the oral anticoagulant edoxaban would prevent stroke and systemic embolism in patients with AHRE [1,2]. From 206 sites across Europe, they enrolled 2,536 patients with AHRE, either older than 65 years and with at least 1 additional stroke risk factor or older than 75 years of age, and randomised them 1:1 to edoxaban or a placebo. The primary endpoint of this phase 3 trial, named NOAH-AFNET 6 (NCT02618577), was a composite of stroke, systemic embolism, or cardiovascular death. The trial was unanimously terminated after 184 of the planned 220 primary outcome events had occurred.

After a median follow-up of 21 months, 3.3% of the participants in the edoxaban arm experienced a primary outcome event compared with 4.0% in the placebo arm (adjusted HR 0.81; 95% CI 0.60–1.08; P=0.15). As expected, the safety outcome of major bleeding or death favoured the placebo arm over the edoxaban arm with 114 versus 149 events (HR 1.31; 95% CI 1.02–1.67; P=0.03). This effect was predominantly driven by a higher rate of major bleeding in the experimental arm (adjusted HR 2.10; P=0.002). “The stroke rates were low with or without anticoagulation (0.9% vs 1.1%),” noted Prof. Kirchhof, “and we can’t prevent what does not occur” [1].

Based on these results, the researchers suggest that patients with AHRE should not be managed with anticoagulation therapy until AF is confirmed by ECG. Also, novel methods are needed to estimate the risk of stroke in patients with rare atrial arrhythmias like AHRE.

OCTOBER trial: OCT-guided PCI improves clinical outcomes in bifurcation lesions

Optical coherence tomography (OCT)-guided percutaneous coronary intervention (PCI) was superior to angiography-guided PCI in reducing the risk of cardiovascular adverse events in patients with complex bifurcation lesions in the OCTOBER trial.

The OCTOBER trial (NCT03171311) assessed whether stepwise, OCT-guided PCI improved clinical outcomes compared with angiography-guided PCI in 1,201 patients with stable or unstable angina or non-ST-elevation myocardial infarction (NSTEMI) with true bifurcation lesions [1,2]. OCT was applied before stent implantation, after rewiring, and to perform a final evaluation. The primary outcome measure was a composite of cardiac death, target-lesion myocardial infarction (MI), or ischaemia-driven target-lesion revascularisation at 2 years. Dr Lene Nyhus Andreasen (Aarhus University, Denmark) presented the primary results.

In the OCT-guided PCI arm, 10.1% of the participants had a major cardiovascular event, compared with 14.1% in the angiography-guided PCI arm, thus meeting the primary endpoint (HR 0.70; 95% CI 0.50–0.98; P=0.035; see Figure). “The study was underpowered for the secondary outcomes, which were mainly the individual components of the primary outcome,” noted Dr Nyhus Andreasen. Cardiac death occurred in 1.4% and 2.6% of the participants in the experimental arm and the control arm, respectively (HR 0.53; 95% CI 0.22–1.25). Target-lesion MI was observed in 7.8% of the participants in the OCT-guided PCI arm and 8.5% of those in the angiography-guided PCI arm (HR 0.90; 95% CI 0.60–1.34). Ischaemia-driven target-lesion revascularisation was reported in 2.8% and 4.6% of the participants, numerically favouring the experimental arm (HR 0.60; 95% CI 0.32–1.13). Finally, the procedural safety did not differ between the 2 study arms.


Angiography vs OCT vs IVUS guidance for PCI: a network meta-analysis

A network meta-analysis including 20 randomised-controlled trials and data from 12,428 patients showed that intravascular imaging (IVI)-guided PCI outperformed angiography-guided PCI in terms of reducing target-lesion failures, all-cause mortality, and stent thrombosis. No differences were observed for optical coherence tomography (OCT)-guided compared with intravascular ultrasound (IVUS)-guided PCI and each individually against angiography.

Prof. Gregg Stone (Mount Sinai, NY, USA) and co-investigators conducted a ‘real-time’ network meta-analysis evaluating the effects of IVI-guided versus angiography-guided PCI and OCT-guided versus IVUS-guided PCI [1]. The primary endpoint was target-lesion failure, defined as cardiac death, target-vessel-related myocardial infarction (TVMI), or ischaemia-driven/clinically-driven target-lesion revascularisation (TLR). The authors included 20 randomised trials, with publication years between 2010 and 2023, totalling 12,428 patients.

Included were 18 trials (11,502 patients) that compared IVI guidance with angiography guidance. The primary endpoint was met for this comparison, favouring IVI guidance (RR 0.69; 95% CI 0.61–0.78; P<0.0001). All 3 components of the primary endpoint significantly favoured IVI guidance over angiography guidance: cardiac death (RR 0.54; 95% CI 0.40–0.74; P<0.0001); TVMI (RR 0.89; 95% CI 0.66–0.97; P=0.02); TLR

CI, confidence interval; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.
(RR 0.71; 95% CI 0.59–0.85; P=0.0001). Dr Stone added that IVI-guidance also significantly reduced all-cause death (RR 0.75; 95% CI 0.60–0.93; P=0.009) and stent thrombosis (RR 0.48; 95% CI 0.31–0.76; P=0.002) compared with angiography guidance. OCT-guided PCI was compared with IVUS-guided PCI in 4 trials (1,316 patients). No significant differences were reported between these 2 techniques (see Table).

"Future research is needed to determine which lesion types benefit most from IVI guidance, and whether there are subtle differences in outcomes between OCT- and IVUS-guidance of PCI procedures," Prof. Stone concluded.


Can aspirin be omitted after PCI in patients with high bleeding risk?

An aspirin-free strategy did not reduce major bleeding risk compared with a dual antiplatelet (DAPT) strategy, including aspirin, in the first month after patients with high bleeding risk underwent a percutaneous coronary intervention (PCI). However, the STOPDAPT-3 trial results suggested there may be an increased risk for coronary events in patients not receiving aspirin. The authors concluded that a DAPT strategy with aspirin and a P2Y12 inhibitor remains the standard-of-care in the first month after PCI.

In the first month following a PCI, the risk for major bleeding events with DAPT remains high in clinical practice, especially in patients with acute coronary syndrome (ACS) or a high bleeding risk [1]. To tackle this matter, Dr Masahiro Natsuaki (Saga University, Japan) and colleagues investigated the role of aspirin in this context. They hypothesised that omitting aspirin from a DAPT strategy could reduce the risk of bleeding in the first month after PCI in patients with ACS or patients with high bleeding risk without increasing the risk for cardiovascular events.

To test this hypothesis, the phase 4 STOPDAPT-3 study (NCT04609111) enrolled 6,002 patients with ACS or high bleeding risk undergoing PCI with an everolimus-eluting stent from 72 centres in Japan (mean age 71.6 years; 23% women) [2]. The participants were randomised to prasugrel (20 mg loading dose followed by 3.75 mg per day) plus aspirin (81–100 mg per day) or prasugrel monotherapy. Co-primary endpoints were BARC type 3, 4, or 5 bleeding and a composite of cardiovascular death, myocardial infarction (MI), definite stent thrombosis, or ischaemic stroke at 1 month.

Major bleeding occurred in 4.71% of the participants in the DAPT arm and 4.47% in the no-aspirin arm (HR 0.95; 95% CI 0.75–1.20; P=0.66), demonstrating that the omission of aspirin was not superior to a DAPT strategy in terms of bleeding risk. Next, the no-aspirin arm was non-inferior to the DAPT arm with regard to the composite outcome of cardiovascular events (4.12% vs 3.69%; HR 1.12; 95% CI 0.87–1.45; P_{non-inferiority}=0.01). "However, the risk for sub-acute stent thrombosis appeared to be higher in the no-aspirin arm (HR 3.40; 95% CI 1.26–9.23; P<0.05)," added Dr Natsuaki. Similarly, the risk for unplanned coronary revascularisation may be higher in the no-aspirin group (HR 1.83; 95% CI 1.01–3.30; P<0.05).

"The use of aspirin as a component of DAPT may have an additional protective effect on the vulnerable coronary lesions in the first month after PCI, without increasing the risk for major bleeding," argued Dr Natsuaki. "The DAPT approach remains the standard-of-care in the first month after PCI."

Prof. Marco Valgimigli (Cardiocentro Ticino Institute, Switzerland) commented that some questions remain to be answered. "For

<table>
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<tr>
<th>Outcome</th>
<th>N trials</th>
<th>N pts</th>
<th>N events</th>
<th>Direct estimate</th>
<th>% evidence</th>
<th>Indirect estimate</th>
<th>% evidence</th>
<th>Network estimate</th>
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<tr>
<td>TLF</td>
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<td>1316</td>
<td>48</td>
<td>0.89 (0.51–1.57)</td>
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<td>1.32 (1.00–1.73)</td>
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<tr>
<td>- Cardiac death</td>
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<td>3</td>
<td>1.32 (0.25–6.98)</td>
<td>15</td>
<td>1.12 (0.56–2.27)</td>
<td>85</td>
<td>1.15 (0.50–2.20)</td>
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<tr>
<td>- TV-MI</td>
<td>4</td>
<td>1316</td>
<td>14</td>
<td>0.97 (0.34–2.79)</td>
<td>14</td>
<td>1.06 (0.69–1.64)</td>
<td>86</td>
<td>1.05 (0.70–1.57)</td>
</tr>
<tr>
<td>- TLR</td>
<td>4</td>
<td>1316</td>
<td>34</td>
<td>0.78 (0.39–1.52)</td>
<td>25</td>
<td>1.51 (1.02–2.22)</td>
<td>75</td>
<td>1.28 (0.91–1.79)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
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<td>1316</td>
<td>4</td>
<td>0.93 (0.19–4.51)</td>
<td>26</td>
<td>1.15 (0.45–2.96)</td>
<td>74</td>
<td>1.09 (0.48–2.45)</td>
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<tr>
<td>All-cause death</td>
<td>4</td>
<td>1316</td>
<td>12</td>
<td>1.26 (0.44–3.62)</td>
<td>19</td>
<td>0.91 (0.55–1.55)</td>
<td>81</td>
<td>0.97 (0.61–1.52)</td>
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<tr>
<td>All MI</td>
<td>4</td>
<td>1316</td>
<td>21</td>
<td>1.26 (0.52–3.02)</td>
<td>17</td>
<td>1.12 (0.75–1.67)</td>
<td>83</td>
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<tr>
<td>TVR</td>
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<td>1.10 (0.67–1.80)</td>
<td>34</td>
<td>1.52 (1.07–2.17)</td>
<td>66</td>
<td>1.36 (1.02–1.82)</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; TLF, target-lesion failure; TLR, target-lesion revascularisation; TVR, target-vessel revascularisation.
example, what is the role of intravascular imaging guidance, which was routine in this study. And importantly, what is the role of peri-procedural versus post-procedural aspirin administration, an issue that was not resolved by the current trial.” Finally, it should be mentioned that this study utilised an ad hoc dose of prasugrel for the Asian study population.


Functional revascularisation outperforms culprit-only strategy in older MI patients

In the FIRE trial, physiology-guided complete revascularisation was superior to a culprit-only revascularisation strategy in older patients with myocardial infarction (MI) and multivessel disease.

Dr Simone Biscaglia (Ferrara University Hospital, Italy) emphasised that patients older than 75 years of age are poorly represented in trials evaluating revascularisation strategies. “Importantly, the risk of periprocedural complications is higher and prognostically impactful in this population, and the benefit of complete revascularisation has been questioned in older patients with MI” [1,2].

Therefore, the randomised-controlled FIRE trial (NCT03772743) compared a physiology-guided complete revascularisation with a culprit-only revascularisation strategy in patients older than 75 years of age with MI and multivessel disease [3,4]. The included participants (n=1,445) were randomised 1:1 to one of the treatment arms and the primary endpoint was a composite of death, MI, stroke, or ischaemia-driven revascularisation.

At 1 year follow-up, the data showed that participants in the complete-revascularisation arm had a reduced risk of experiencing a primary endpoint event compared with those in the culprit-only arm (15.7% vs 21.0%; HR 0.73; 95% CI 0.57–0.93; P=0.01; see Figure). Similar results were observed for the key secondary endpoint of cardiovascular death or MI (8.9% vs 13.5%; HR 0.64; 95% CI 0.47–0.88; P=0.005). Finally, the composite safety endpoint of contrast-associated acute kidney injury, stroke, or BARC type 3, 4, or 5 bleeding did not show a significant increase in these events in participants in the complete-revascularisation arm compared with those who were randomised to the culprit-only arm (22.5% vs 20.4%; HR 1.11; 95% CI 0.89-1.37; P=0.37).

“The results of the FIRE trial demonstrated that physiology-guided complete revascularisation reduces adverse cardiovascular outcomes,” said Prof. Vijay Kunadian (Newcastle University, UK), discussant of this trial. “These results may, however, not be generalisable to all older patients. We should be careful with frail patients, those with many co-morbidities, cognitive impairment, prior coronary artery bypass grafting, or left main disease in particular. Furthermore, we need to await the long-term results of this study and it should be investigated whether angiography-guided percutaneous coronary intervention would result in similar outcomes.”


No benefit of extracorporeal life support in MI plus cardiogenic shock

The addition of extracorporeal life support (ECLS) to standard medical therapy did not reduce all-cause mortality in patients with acute myocardial infarction (MI) and cardiogenic shock, challenging current guideline recommendations.

“Although the use of ECLS has been increasing in the context of treating infarct-related cardiogenic shock, there is insufficient evidence for its effect on mortality,” explained Prof. Holger Thiele (University of Leipzig, Germany) [1]. To evaluate ECLS in this setting, the ECLS-SHOCK trial (NCT03637205) randomised 420 patients with acute MI complicated by cardiogenic shock 1:1 to ECLS plus standard medical therapy or standard medical therapy only [2]. The primary endpoint was 30-day all-cause mortality.

No significant difference was observed in all-cause mortality between the ECLS arm and the control arm (47.8% vs 49.0%; RR 0.98; 95% CI 0.80–1.19; P=0.81). Prof. Thiele added that secondary outcomes such as arterial lactate, renal function, and simplified acute physiology score (SAPS II) confirmed that there was no difference between both treatment groups. However, there was an increased risk for moderate-to-severe bleeding in participants receiving ECLS compared with those in the control arm (23.4% vs 9.6%; RR 2.44; 95% CI 1.50–3.95; P<0.05). Similarly, the ECLS arm showed higher rates of peripheral ischaemic vascular complications requiring surgical or interventional therapy (11.0% vs 3.8%; RR 2.86; 95% CI 1.31–6.25; P<0.05).

The authors also performed a meta-analysis of the 4 trials investigating ECLS in this setting (i.e. ECLS-SHOCK 1, ECMO-CS, EURO SHOCK, and ECLS-SHOCK) and found no effect on all-cause mortality by omitting this therapy (OR 0.93; 95% CI 0.66–1.29) [3].

In conclusion, both the current ECLS-SHOCK trial and a meta-analysis including 4 randomised-controlled trials comparing ECLS to control failed to show that an ECLS strategy reduces all-cause mortality or other endpoints in patients with acute MI and cardiogenic shock. However, there was an increased bleeding rate in patients who were treated with ECLS. These findings question current guideline recommendations and the increasing use of mechanical circulatory support in patients with cardiogenic shock in clinical practice. These results question the recommendations of the current guidelines and suggest that ECLS should be used with restraint in patients after MI and complicating cardiogenic shock.


**Lp(a) and cardiovascular events: which test is the best?**

Mass spectrometry lipoprotein (a) (Lp[a]) assessment and immunoassay-based Lp(a) tests were equally prognostic for major adverse cardiovascular events (MACE) in patients with recent acute coronary syndrome (ACS) receiving placebo in the ODYSSEY OUTCOMES study. Furthermore, the tests performed similarly in terms of predicting MACE reductions in the active arm of the study, in which patients received the PCSK9 inhibitor alirocumab.

Prof. Michael Szarek (University of Colorado, CO, USA) explained that Lp(a) is a well-known risk factor for cardiovascular events and that it hampers the responsiveness to PCSK9 inhibitors [1]. However, it is not yet clear which Lp(a) assessment should be used to map these prognostic and predictive associations. In the phase 3 ODYSSEY OUTCOMES study (NCT01663402), patients with recent ACS (n=11,970) were randomised to treatment with the PCSK9 inhibitor alirocumab or placebo. In addition, baseline Lp(a) was measured by 3 different tests:

- Siemens N-latex nephelometric immunoassay (IA-mass; mg/dL)
- Roche TinaQuant turbidimetric immunoassay (IA-molar; nmol/L)
- semi-automated mass spectrometry (MS; mmol/L)

The investigators observed the value of these assessments for the prognosis of MACE in the placebo group and the prediction of MACE reductions in the alirocumab arm.

In the placebo arm, the associations of Lp(a) concentrations and MACE risk were nearly identical for the 3 different tests, implying that the different methods of measurement were equally precise for the prognostication of MACE (see Figure). Likewise, the 3 tests were similar in predicting MACE reductions following alirocumab therapy.

These data suggest that Lp(a) is an important risk predictor regardless of how measured and may enable easier application in broad populations.

**Figure: Prognosis of MACE according to Lp(a) concentrations in placebo arm [1]**

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1. Szarek M, et al. Two of a kind: mass and molar immunoassay-based lipoprotein (a) concentrations are similarly prognostic for MACE risk and predictive of alirocumab benefit in ODYSSEY OUTCOMES. ESC Congress 2023, 25–28 August, Amsterdam, the Netherlands.
Immediate or staged revascularisation in STEMI plus multivessel disease?

Immediate multivessel percutaneous coronary intervention (PCI) was non-inferior to staged multivessel PCI in patients with ST-elevation myocardial infarction (STEMI) and multivessel disease (MVD) who had received a successful PCI of the culprit artery, according to the results of the MULTISTARS AMI study.

The MULTISTARS AMI trial (NCT03135275) assessed whether immediate multivessel PCI was non-inferior to staged PCI (within 19 to 45 days) in haemodynamically stable patients with STEMI and MVD following successful PCI of the culprit artery [1]. The study randomised 840 participants 1:1 to immediate PCI of non-culprit lesions or staged PCI of non-culprit lesions. The primary outcome was a composite of all-cause death, non-fatal MI, stroke, unplanned ischaemia-driven revascularisation, or hospitalisation for heart failure at 52 weeks. Prof. Barbara Stähli (University of Zürich, Switzerland) presented the primary findings.

Immediate PCI was non-inferior to staged PCI (RR 0.52; 95% CI 0.38–0.72; P non-inferiority <0.0001). In fact, the risk for primary outcome events was significantly lower in the immediate PCI group (P=0.0004). Non-fatal MI (RR 0.36; 95% CI 0.16–0.80) and unplanned ischaemia-driven revascularisation (RR 0.42; 95% CI 0.24–0.74) appeared to occur more frequently in the staged PCI arm than in the immediate PCI arm. The results were consistent across subgroups. "Immediate PCI was non-inferior to staged PCI in patients with STEMI and MVD who underwent a successful primary PCI," concluded Prof. Stähli.

Prof. Robert Byrne (RCSI University, Ireland), discussant of the trial, pointed out that the observed difference in MI rates between the 2 study arms was not due to an increase of spontaneous (type 1) MI in the staged PCI group but related to a higher number of procedural MI in the staged PCI group (n=12 vs n=0). "This raises some questions in relation to ascertainment bias in the immediate PCI group, where it can be difficult to detect periprocedural MI," he argued. "Therefore, the results of the MULTISTARS AMI trial provide evidence, but not strong evidence, of benefit with routine immediate PCI during the index procedure as compared with staged outpatient PCI."


Other

Acoramidis improves survival and functional status in ATTR-CM

Acoramidis demonstrated clinical and functional benefits over placebo in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) in the ATTRibute-CM trial. The agent was well tolerated and survival rates in patients on acoramidis approached age-matched survival rates of individuals without ATTR-CM.

Acoramidis is an investigational, orally administered agent that aims to stabilise tetrameric transthyretin. The phase 3 ATTRibute-CM study (NCT03860935) randomised 631 participants with ATRR-CM (median age 78 years; 10% women; 10% variant TTR carriers) 2:1 to 800 mg twice-daily acoramidis or placebo [1]. Tafamidis use was allowed after 12 months and the primary endpoint was a hierarchical analysis of all-cause mortality, cumulative frequency of cardiovascular hospitalisations, change from baseline NT-proBNP, and change from baseline in 6-minute walking distance (6MWD). Prof. Julian Gillmore (University College London, UK) presented the findings.

At 30 months, the win ratio was 1.77 (95% CI 1.42–2.22; P<0.0001; see Figure) in favour of the acoramidis group, meeting the primary endpoint. In addition, participants on acoramidis saw a relative risk reduction (RRR) in all-cause mortality of 25%. For cardiovascular mortality, the RRR was even higher, at 30%. Furthermore, the relative risk for cardiovascular hospitalisation in the acoramidis arm was 0.50 compared with the placebo arm (95% CI 0.36-0.70; P=0.0001). There were significant differences in the other individual components of the primary endpoint as well,
namely the change in NT-proBNP (ratio of adjusted geometric mean fold-change 0.53; 95% CI 0.463–0.604; P<0.0001) and change in 6MWD (least squares mean difference of 39.64 m in favour of acoramidis; 95% CI 21.07–58.22; P<0.0001).

Figure: Primary outcome overall and by subgroups [1]

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients (%)</th>
<th>Win ratio</th>
<th>Win ratio (95% CI)</th>
<th>FS test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>611 (100.0)</td>
<td>—</td>
<td>1.772 (1.417–2.317)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>ATTR-CM Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ATTRm-CM</td>
<td>59 (9.7)</td>
<td>—</td>
<td>2.529 (1.303–4.911)</td>
<td>0.0061</td>
<td></td>
</tr>
<tr>
<td>ATTRwt-CM</td>
<td>552 (90.3)</td>
<td>—</td>
<td>1.756 (1.396–2.208)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP (pg/mL) ≤3000</td>
<td>401 (65.6)</td>
<td>—</td>
<td>1.787 (1.373–2.325)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP (pg/mL) &gt;3000</td>
<td>250 (34.4)</td>
<td>—</td>
<td>1.678 (1.160–2.626)</td>
<td>0.0060</td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²) &lt;45</td>
<td>94 (15.4)</td>
<td>—</td>
<td>1.410 (0.849–2.341)</td>
<td>0.1841</td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²) ≥45</td>
<td>517 (84.6)</td>
<td>—</td>
<td>1.797 (1.452–2.226)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age &lt;78</td>
<td>299 (48.9)</td>
<td>—</td>
<td>2.052 (1.489–2.829)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age ≥78</td>
<td>312 (51.1)</td>
<td>—</td>
<td>1.499 (1.098–2.045)</td>
<td>0.0107</td>
<td></td>
</tr>
<tr>
<td>NYHA Class I, II</td>
<td>512 (83.8)</td>
<td>—</td>
<td>1.892 (1.479–2.419)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>99 (16.2)</td>
<td>—</td>
<td>1.150 (0.652–2.030)</td>
<td>0.692</td>
<td></td>
</tr>
</tbody>
</table>

The rates of treatment-emergent adverse events (TEAEs) were comparable for the acoramidis group (98.1%) and the placebo group (97.6%). Serious TEAEs appeared to be somewhat more frequent in the placebo arm (54.6% vs 64.9%).

Prof. Gillmore concluded that the ATTRibute-CM trial showed that acoramidis was safe and efficacious in patients with ATTR-CM, delivering survival and functional benefits for this population.


Expedited transfer to a specialised centre does not improve cardiac arrest outcomes

Patients with resuscitated out-of-hospital cardiac arrest (OHCA) without ST elevation did not benefit from immediate transfer to a specialised cardiac arrest centre compared with a transfer to the nearest emergency department in terms of survival or neurological outcomes. These were the main results of the ARREST trial.

“There are regional differences in cardiac arrest survival due to variations in infrastructure, resources, and personnel,” Dr Tiffany Patterson (King’s College London, UK) pointed out [1]. “The standard-of-care for patients with resuscitated OHCA is to transfer them to the nearest emergency department. However, post-arrest care may best be delivered at a specialised centre.” The ARREST trial (NCT03880565) assessed whether transferring patients with resuscitated non-ST elevated OHCA to a specialised centre improves their chance of survival compared with delivery to the nearest emergency department [1,2]. The study included 32 emergency departments and 7 specialised cardiac arrest centres in London. Ambulance paramedics randomised pre-hospital patients (n=862) 1:1 to either a transfer to the nearest emergency department or a transfer to a specialised care centre. The primary outcome was 30-day all-cause mortality.

At 30 days, no differences were observed between the standard-of-care/emergency department group and the cardiac arrest centre group in terms of 30-day all-cause mortality (risk ratio 1.00, 95% CI 0.90–1.11; P=0.96). Secondary outcomes, such as 3-month mortality and neurological outcomes at discharge, confirmed that transfer to a specialised cardiac arrest centre did not result in significant health benefits for patients.

1. Patterson T, et al. ARREST Trial: expedited transfer to a cardiac arrest centre for non-ST elevation OHCA. Hot Line Session 5, ESC Congress 2023, 25–28 August, Amsterdam, the Netherlands.

ARAMIS: Can anakinra alleviate acute myocarditis?

The IL-1 receptor antagonist anakinra added to standard-of-care did not increase the number of days free from myocarditis complications in low-risk patients with acute myocarditis. However, the authors noted that larger trials are needed to evaluate anti-inflammatory strategies in high-risk patients.

"Experimental studies and case reports suggest that IL-1β inhibition could be effective in acute myocarditis," said Prof. Mathieu Kerneis (Sorbonne University, France) [1]. The ARAMIS trial (NCT03018834) randomised 120 participants with acute myocarditis to standard-of-care plus anakinra (once daily 100 mg, subcutaneously administered) or to standard-of-care plus placebo. The primary endpoint was the number of days alive and free from myocarditis complications at 28 days post-discharge.

The participants were treated for a median of 2 days. The median of days free from complications was 31 in the...
placebo group and 30 in the anakinra group (P=0.17). Although the cardiovascular event rate appeared to be higher in the placebo arm (16.7% vs 10.5%), the study was not powered for this endpoint. Finally, no particular safety issues emerged for the treatment with anakinra. Serious adverse events occurred in 12.1% of the participants in the anakinra arm and 10.2% in the placebo arm.

Discussant Dr Enrico Ammirati (Niguarda Hospital, Italy) emphasised that the ARAMIS trial reflects the situation in the real world. "Most patients with acute myocarditis are at low risk of events. However, other randomised-controlled trials are needed to assess anakinra or other immunosuppressive drugs in high-risk patients with acute myocarditis."


Minimising atrial pacing does not reduce the risk for AF in sinus node disease

The risk for atrial fibrillation (AF) was not reduced with minimised atrial pacing in patients with sinus node disease who underwent a first-time pacemaker implantation, according to the DANPACE II trial. In fact, a base pacing rate of 40 bpm without rate-adaptive pacing increased the risk for syncope.

"Sinus node disease and AF often coexist," stated Dr Mads Brix Kronborg (Aarhus University, Denmark) [1]. "In patients with sinus node disease, a higher percentage of atrial pacing has been linked to an increased risk of AF. Whether this increased risk is caused by abnormal prolongation and propagation of atrial depolarisation induced by pacing or whether it may result from an increased need for pacing in more progressive atrial disease is not known."

The current DANPACE II trial was designed to determine whether minimising atrial pacing reduces the risk of AF in patients with sinus node dysfunction. Participants (n=539) with sinus node dysfunction undergoing first-time pacemaker implantation were randomised 1:1 to pacing programmed to a base rate of 60 bpm with rate-adaptive pacing (DDDR-60) or pacing programmed to a base rate of 40 bpm without rate-adaptive pacing (DDD-40). The included patients were remotely monitored for 2 years. The primary endpoint was the first device-detected episode of AF lasting over 6 minutes.

The median percentage of atrial pacing was 1% in the DDD-40 arm and 49% in the DDDR-60 arm. However, this reduced atrial pacing did not result in a decreased incidence of AF >6 minutes (46% in both arms; log-rank P=0.83). Furthermore, AF >6 hours was observed in 36% of the participants in the DDD-40 group and 32% of those in the DDDR-60 group (log-rank P=0.35). The corresponding results for AF > 24 hours were 26% for the DDD-40 arm and 21% for the DDDR-60 arm. Syncope or pre-syncope occurred more frequently in the DDD-40 arm (22% vs 13%; log-rank P=0.01). Also, the rate of crossovers was higher in the DDD-40 arm at 23%, compared with 3% in the DDDR-60 arm (log-rank P<0.001).

In conclusion, a reduction in atrial pacing did not lead to a reduction in the incidence of AF in patients with sinus node dysfunction who received a first pacemaker but resulted in a higher rate of syncope.