Medicom International Conference Series in Cardiology

ESC Congress 2021

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PEER-REVIEWED CONFERENCE REPORT

2021 ESC Clinical Practice Guidelines

Essential messages for the 4 new ESC Clinical Practice Guidelines heart failure, valvular heart disease, cardiac pacing and resynchronisation, and cardiovascular disease prevention explore the implications for clinical practice.

read more on PAGE 3

EMPEROR-Preserved

Patients with heart failure with preserved ejection fraction are a high-risk population with few proven therapies. The landmark EMPEROR-Preserved trial offered hope; empagliflozin treatment provided a 21% reduction in CV death and hospitalisation.

read more on PAGE 10

Thromboprophylaxis in COVID-19

The MICHELLE trial found that thromboprophylaxis with rivaroxaban post-discharge benefitted COVID-19 patients. Individuals with moderate-to-high risk scores for venous thromboembolism showed a 67% risk reduction.

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

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Letter from the Editor

Prof. Marc P. Bonaca

Dear colleagues,

Thank you very much for your interest in the ESC 2021 Medicom Conference Report. This ESC Congress saw a rich mix of guideline updates, hotline sessions and innovative science. You will find summaries of new Guidelines introduced on heart failure, valvular disease, cardiac resynchronization, and prevention.

Key hotlines were presented including the awaited data on empagliflozin and its effects in patients with heart failure with preserved ejection fraction, a high-risk population with few proven therapies. Additional hotlines covered blood pressure control, management of patients after cardiac arrest, app-based interventions, and more data on the effects of polypills in primary prevention. Additional presentations also covered key topics such as COVID-19, vascular disease, and valvular heart disease.

We hope that you will find the enclosed summaries of great interest. Through our independent review process, we strive to provide informative and balanced summaries in a succinct and approachable format with the hopes that you can learn of some of the top scientific presentations from this important meeting. Unfortunately, with space limitations, we are unable to capture all presentations but we have provided a selection that we hope provides a sense of key learnings. Thank you again and please accept our best wishes for a safe and healthy season.

Sincerely,

Marc Bonaca, MD MPH

Biography

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

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

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

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2021 ESC Clinical Practice Guidelines

2021 ESC Guidelines on Heart Failure

Substantial revisions have been made by the Task Force for the diagnosis and treatment of acute and chronic heart failure (HF) of the European Society of Cardiology (ESC). Among them, an indication for SGLT2 inhibitors for all HF patients with reduced ejection fraction (HFrEF) and the introduction of the new phenotype of HF with mildly reduced EF (HFmrEF).

After 5 years and with the emergence of abundant valuable evidence, the 2021 ESC Guidelines on HF comprise major changes to those published in 2016. Where overlapping, guidelines were harmonised. The new recommendations, which include a multitude of treatment modifications, have also redefined a phenotype from HF with mid-range EF to HF with mildly reduced EF as a new concept [1]. "After the diagnosis of heart failure is confirmed, the guidelines recommend classification by left ventricular (LV) EF into those with a reduced EF of 40% or less, those with a mildly reduced EF above 40% but less than 50%, and those with a preserved EF of 50% or more" explained Prof. Carolyn Lam (Duke-NUS Medical School, Singapore) [2]. She added, "importantly for all forms, the presence of a clinical syndrome of HF is a prerequisite." The rationale behind this new category is that patients with mildly reduced EF could benefit from treatment with medications indicated for those with reduced EF (HFrEF). This is reflected in a 'may be considered' class 2b recommendation for angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers, mineralocorticoid receptor antagonists (MRA), and the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan [1,2]. More details and practical guidance for the clinical practice are provided in the online supplementary material published with the guidelines [1].

Management before and after hospital discharge

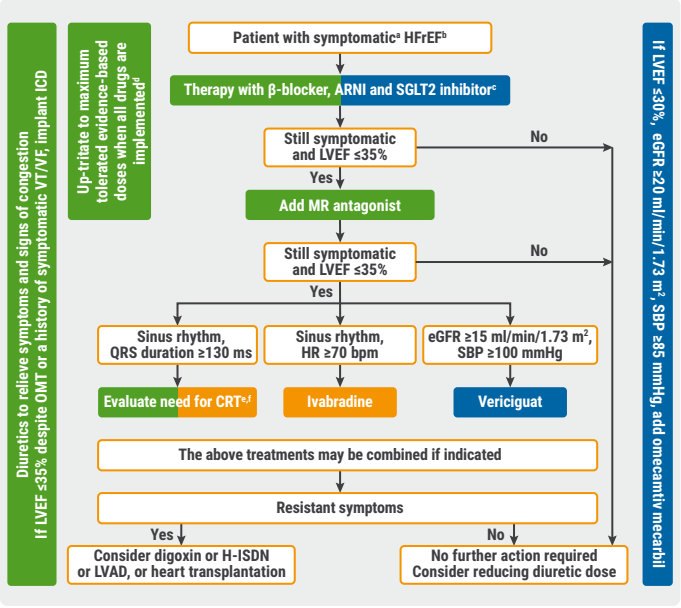
The importance of optimal HF treatment before leaving the hospital accompanied by subsequent out-patient management shortly afterwards has also been acknowledged with 3 new class-1 recommendations:

- It is recommended that patients hospitalised for HF should be carefully evaluated to exclude persistent signs of congestion before discharge and to optimise oral treatment.
- It is recommended that evidence-based oral medical treatment should be administered before discharge.
- An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance, and start and/or up-titrate evidence-based therapy [1].

Patients with HFrEF

The medication for HFrEF is now based on a triplet of ACEI/ARNI, β-blockers, and MRA that should be up-titrated to clinical trial dosages or as tolerated if no contraindication is present (see Figure) [1,3].

Figure: Treatment algorithm for patients with HFrEF [4]



aNYHA class II-IV; bLVEF <40%, cβ-blocker is recommended; dif not contraindicated; eCRT is recommended if QRS ≥130 ms and LBBB (in sinus rhythm); fCRT should/may be considered if QRS ≥130 ms with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular pacing.

AF, atrial fibrillation; ARNI, angiotensin receptor/neprilysin inhibitor; bpm, beats per minute; CRT, cardiac resynchronisation therapy; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; H-ISDN, hydralazine-isosorbide dinitrate; HR, heart rate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVAD, left ventricle assist device; LVEF, left ventricle ejection fraction; MR, mineralocorticoid receptor; NYHA, New York Heart Association; OMT, optimal medical therapy; SBP, systolic blood pressure; SGLT2 sodium-glucose co-transporter-2; VT/VF, ventricular tachycardia/ventricular fibrillation.

Furthermore, with the introduction of SGLT2 inhibitors, a new class of drugs has been added in a general class-1 recommendation after clear evidence in clinical trials:

- Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalisation and death.

Additionally, in a special population with HFrEF, vericiguat received a new class-2b recommendation:

- Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACEI (or ARNI), a β-blocker and an MRA to reduce the risk of CV mortality or HF hospitalisation.

In 2021, ESC is calling for a change in treatment that moves away from lengthy sequential approaches of care to on-time strategies that focus on keeping people out of the hospital and from experiencing complications from HFrEF, such as chronic kidney disease (CKD). Considering that roughly 40% of patients with HF also have CKD or diabetes, the recommendation to apply the new first-line treatments underscores the importance of managing multiple risks, addressing the underlying pathophysiology of cardiovascular, metabolic, and renal diseases.

Early initiation in the shortest time possible with the 4 key drug therapies ACE-I, β-blockers, MRAs and ARNI (sacubitril/valsartan, class 2b) and personalising the approach based on comorbidities at the first-line is a significant step forward. Diuretics can be applied based on volume load. All HF patients with type 2 diabetes should be treated with an SGLT2 inhibitor; the choice between empagliflozin or dapagliflozin (both class 1a) is up to the attending physician.

Comorbidities in heart failure

Important changes have been incorporated for the treatment of several cardiovascular and non-cardiovascular diseases found in HF patients with chronic coronary syndrome:

- In patients suitable for surgery, coronary artery bypass graft (CABG) should be considered as the first-choice revascularisation strategy, especially if they have diabetes and for those with multivessel disease (class 2a).
- In LV assist device candidates needing coronary revascularisation, CABG should be avoided if possible (class 2a).
- Coronary revascularisation may be considered to improve outcomes in patients with HFrEF, chronic coronary syndrome, and coronary anatomy suitable for revascularisation, after careful evaluation of the individual risk-benefit ratio, including coronary anatomy, comorbidities, life expectancy, and patient's perspectives (class 2b).
- PCI may be considered as an alternative to CABG, based on Heart Team evaluation, considering coronary anatomy, comorbidities, and surgical risk (class 2b) [1,5].

In patients who have diabetes as well as HF, recommendations also concern the inclusion of SGLT2 inhibition:

- SGLT2 inhibitors (i.e. canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin) are recommended in patients with type 2 diabetes at risk of CV events to reduce hospitalisations for HF, major CV events, end-stage renal dysfunction, and CV death (class 1).
- SGLT2 inhibitors (i.e. dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with type 2 diabetes and HFrEF to reduce hospitalisations for HF and CV death.

Furthermore, screening and treating iron deficiency merited new recommendations:

- It is recommended that all patients with HF are periodically screened for anaemia and iron deficiency with a complete blood count, serum ferritin concentration, and transferrin saturation.
- Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalised for HF and with LVEF ≤50% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with transferrin saturation <20% to reduce the risk of HF hospitalisation.

Since clinical trials have also revealed the possibility that an efficacious treatment for amyloidosis might lead to heart failure, 2 new class 1-recommendations have been added for this patient population:

- Tafamidis is recommended in patients with genetic testing proven hereditary transthyretin-cardiomyopathy and NYHA class I or II symptoms to reduce symptoms, CV hospitalisation and mortality.
- Tafamidis is recommended in patients with wild-type transthyretin cardiac amyloidosis and NYHA class I or II symptoms to reduce symptoms, CV hospitalisation, and mortality.

In addition, a new class-1 recommendation has been introduced recommending heart transplant consideration for patients with advanced HF who are refractory to medical/device therapy and who do not have absolute contraindications [1,6].

As a final remark on the 2021 Heart Failure Guidelines, guideline co-author Prof. Marco Metra (University of Brescia, Italy) called his fellow cardiologists to action: "now, we have new evidence, we have new guidelines from the ESC, and it's our task to implement them in our clinical practice" [7].

1. McDonagh TA, et al. Eur Heart J 2021;42(36):3599–3726.
2. Lam CS. Classification of HF and diagnosis and treatment of HFmrEF and HFpEF. Session: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, ESC Congress 2021, 27–30 August.

3. Gardner RS. New recommendations for the treatment of HFrEF. Session: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, ESC Congress 2021, 27–30 August.
4. Dębska-Kozłowska A, et al. Heart Fail Rev 2021;May 29. DOI:10.1007/s10741-021-10120-x.
5. Adamo M. New recommendations for comorbidities. Session: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, ESC Congress 2021, 27–30 August.
6. Chioncel O. Advanced and acute heart failure. Session: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, ESC Congress 2021, 27–30 August.
7. ESC TV at #ESCCongress 2021 – 2021 ESC Guidelines on Heart Failure.

2021 ESC/EACTS Guidelines on Valvular Heart Disease

Based on a substantial amount of new evidence, the experts of the European Society of Cardiology (ESC) and the European Association for Cardiothoracic Surgery (EACTS) have developed new guidance for the treatment of valvular heart disease (VHD). Experienced experts in special centres are seen as an indispensable part of decision-making.

The new guidelines on VHD highlight the importance of an integral approach to patients with VHD within a Heart Valve Centre of excellence that is interlinked with a Heart Valve Clinic, able to provide guideline-directed therapy [1,2]. As an overarching principle, decision-making should be in the hands of a Heart Team consisting of various specialists including interventional cardiologists, cardiac surgeons, and cardiovascular anaesthesiologists. Based on clinical and imaging assessments, the Heart Team will consider local resources, risks versus benefits, treatment options, and goals of the individual patients.

Aortic valve disease

In severe aortic regurgitation, there is a new recommendation for surgery in asymptomatic patients with a left ventricular end-systolic diameter (LVESD) of >50mm or LVESD >25mm/m^2 body surface area (BSA) or resting left ventricular ejection fraction (LVEF) of ≤50% [1,2]. Furthermore, a new class 2b recommendation indicates that surgery may be considered in asymptomatic patients with LVESD >20mm/m^2 BSA or resting LVEF ≤55% if surgery is at low risk (see Figure).

In aortic stenosis, interventions should now be considered in asymptomatic patients with severe aortic stenosis and an LVEF <55% without any other cause (class 2a). A consideration for intervention should also be given in these cases with an LVEF >55%, a normal exercise test, and low procedural risk if there is either very severe stenosis (mean gradient ≥60mmHg or Vmax ≥5m/sec), or severe calcification and Vmax progression ≥0.3m/sec/year, or markedly elevated BP levels in repeated measurements that do not have other explanations [1–3].

Figure: Recommendations on surgery indication in severe aortic regurgitation in 2017 vs 2021. Modified from [1]

New or Revised	Recommendations in 2017 version	Class	Recommendations in 2021 version	Class
Recommendations on indications for surgery in severe aortic regurgitation				
Revised	Surgery is indicated in asymptomatic patients with resting enjetion fraction ≤50%	I	Surgery is recommended in asymptomatic patients with LVESD >50 mm or LVESD >25mm/m^2 BSA (in patients with small body size) or resting LVEF ≤50%.	I
	Surgery should be considered in asymptomatic patients with resting ejection fraction >50% with severe dilatation: LVEDD >70 mm or LVESD >50 mm (or LVESD >25mm/m^2 BSA in patients with small body size).	IIa		
New			Surgery may be considered in asymptomatic patients with LVESD >20mm/m^2 BSA (in patients with small body size) or resting LVEF ≤55%, in surgery at low risk	IIb
Revised	Heart Team discussion is recommended in selected patients in whom aortic repair may be a feasible alternative to valve replacement.	I	Aortic valve repair may be considered in selected patients at experienced centres when durable results are expected.	IIb

When it comes to deciding which surgical approach should be preferred, Prof. Bernard David Prendergast (St Thomas' Hospital, UK) stated that surgical valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) are both excellent treatment options for patients with aortic stenosis. "The choice between the interventions must be based upon Heart Team evaluations of all patients. In straightforward situations, surgery is recommended for younger patients (<75 years) at lower surgical risk and for patients when transfemoral TAVI is not possible, and the patient remains operable. TAVI is preferred in older patients ≥75 years and in those of inoperable or high surgical risk," he summarised the new recommendations. "The mode of intervention in all scenarios should be determined by a multifactorial assessment in individual patients, followed by a Heart Team recommendation that is discussed with the patient who can make an informed treatment choice," Prof. Pendergast added.

Mitral valve disease

As for mitral regurgitation (MR), the new guidelines make a clear distinction between primary and secondary mitral valve regurgitation [1,2,4]. The revised guidelines advise surgery for

asymptomatic patients with a preserved LV function (LVEF >60%), LVESD <40mm (class 1) and atrial fibrillation (AF) secondary to MR or pulmonary hypertension (class 2a) [2]. The left atrial volume of >60ml/m^2 or diameter of >55mm remains key and an emphasis on centre experience to ascertain durable results is unchanged.

For secondary MR, the new recommendations are:

- Valve surgery/intervention is recommended only in patients with severe secondary MR who remain symptomatic despite guideline-directed treatment and has to be decided by structural collaborative Heart Team (class 1).
- In symptomatic patients with concomitant coronary artery or other cardiac disease requiring treatment who are judged not appropriate for surgery by the Heart Team based on their individual characteristics, percutaneous coronary intervention (and/or TAVI) possibly followed by transcatheter edge-to-edge repair (TEER) should be considered (class 2a).

There also is a revision for the patients without concomitant disease that upgraded TEER from 2b to 2a, as TEER should be considered in selected symptomatic patients not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to therapy.

Tricuspid valve disease

Indications for intervention in tricuspid regurgitation have been broadened [1]. A new recommendation has been issued in favour of transcatheter treatment of symptomatic secondary severe tricuspid regurgitation comprising a 'may be' consideration in inoperable patients at a Heart Valve Centre with expertise in the treatment of tricuspid valve disease (class 2b).

A new development for the tricuspid valve is early surgery for asymptomatic or mildly symptomatic patients with isolated primary regurgitation and right ventricular dilatation. It is recognised that delayed intervention yields poor outcomes including durability. This is a class 2a indication that is not applicable to those with left-sided disease (recommend early left-sided management) [2].

Antithrombotic management

Several changes in recommendations concerning the antithrombotic treatment in the perioperative and post-operative period of prosthetic valve implantation or valve repair have been included in the 2021 ESC/EACTS guidelines on VHD [1,5]. Prof. Davide Capodanno (University of Catania, Italy) called attention to the following new entries:

- In patients with no baseline indications for oral anticoagulation (OAC), low-dose aspirin or OAC using a vitamin K antagonist (VKA) should be considered for the first 3 months after surgical intervention of an aortic biological heart valve (class 2a).
- For stroke prevention in AF who are eligible for OAC, DOACs are recommended in preference to VKA for patients with aortic stenosis, aortic regurgitation, and mitral regurgitation.
- Left atrial appendage occlusion should be considered to reduce thromboembolic risk in patients with AF and a CHADVASC 2 ≥2 undergoing valve surgery (class 2a).
- Direct oral anticoagulants (DOAC) should be considered over VKA after 3 months following surgical implantation of a biological heart valve in patients with atrial fibrillation (class 2a).
- DOACs may be considered over VKA within 3 months following surgical implantation of a biological heart valve in mitral position in patients with atrial fibrillation (class 2b).

Concerning the postoperative period after TAVI, 4 more management recommendations were added:

- OAC is recommended lifelong for TAVI patients who have other indications for OAC (class 1).
- Lifelong single-antiplatelet therapy is recommended after TAVI in patients with no baseline indication for OAC (class 1).
- Routine use of OAC is not recommended after TAVI in patients without baseline indication for OAC (class 3).
- Anticoagulation should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients at least until resolution (class 2a).

1. Vahanian A, et al. Eur Heart J 2021;28 Aug. DOI:10.1093/eurheartj/ehab395.
2. Delagado V. Timing and indication of intervention in asymptomatic patients with valvular heart disease. Session: 2021 ESC/EACTS Guidelines for the management of valvular heart disease, ESC Congress 2021, 27–30 August.
3. Pendergast BD. Mode of intervention in aortic stenosis. Session: 2021 ESC/EACTS Guidelines for the management of valvular heart disease, ESC Congress 2021, 27–30 August.
4. Praz F. Mode of intervention in mitral regurgitation. Session: 2021 ESC/EACTS Guidelines for the management of valvular heart disease. ESC Congress 2021, 27–30 August.
5. Capodanno D. Anticoagulation/avoid stroke in patients with valvular heart disease. Session: 2021 ESC/EACTS Guidelines for the management of valvular heart disease, ESC Congress 2021, 27–30 August.

2021 ESC Guidelines on Cardiac Pacing and Cardiac Resynchronisation Therapy

A plethora of new evidence has accumulated since the publication of the previous ESC pacing guidelines in 2013. The 2021 Guidelines on cardiac pacing and cardiac resynchronisation therapy include a few novel sections, such as evaluating patients before pacing, physiologic pacing, implantation, and perioperative management.

In his talk on general indications for pacing, Prof. Jean-Claude Deharo (Hospital La Timone of Marseille, France) introduced the new section included in the 2021 Guidelines on the evaluation of the patient with suspected or documented bradycardia, or conduction system disease, including novel diagnostic tools and what tests to perform in specific situations [1,2]. A simple but systematic approach is recommended, consisting of history, physical examination, ECG, and cardiac imaging. The next tests depend on the result of this evaluation:

- In patients with bradycardia or cardiac conduction disorders that occur during sleep, polysomnography/sleep study is recommended (class 1).
- In patients with early onset of progressive cardiac conduction disease (<50 years) or a family history of inherited cardiac conduction disorder, genetic testing is recommended (class 2a.
- In patients with clinical suspicion of potential causes of bradycardia, further laboratory tests should be performed (class 1).
- In patients with suspected structural heart disease, scars or cardiomyopathy, further imaging (i.e. cardiac magnetic resonance, computed tomography, or positron emission tomography) is advised (class 2a).
- In patients with unexplained syncope and bifascicular block, electrophysiologic study (EPS) or exercise testing (ET) for an exertion-induced block should be considered (class 2a); an empirical pacemaker is recommended in elderly and frail patients.
- In patients with syncope and sinus bradycardia, EPS may be considered when non-invasive tests have failed to show a correlation between syncope and bradycardia (class 2b);
- In patients with suspected or recurrent reflex syncope, carotid sinus massage is recommended (class 1); and tilt table should be considered for patients with recurrent reflex syncope (class 2a) finally.
- In patients with exercise-induced symptoms, ET is recommended.

"If you do not have a diagnosis after following this scheme, long-term ambulatory electrocardiographic monitoring is recommended dependent on frequency of symptoms," Prof. Deharo elaborated.

There are also a few new recommendations for cardiac pacing in patients with bradycardia and conduction system disease (all class 1):

- Pacing is indicated in symptomatic patients with the bradycardia-tachycardia form of sinus node dysfunction (SND) to correct bradyarrhythmias and enable pharmacological treatment unless ablation of the tachyarrhythmia is preferred.
- Pacing is indicated in patients with atrial arrhythmia (mainly AF) and permanent or paroxysmal third- or high-degree atrioventricular block (AVB) irrespective of symptoms.
- In patients with SND and dual-chamber pacemakers, it is recommended to minimise unnecessary ventricular pacing through programming.

Physiologic pacing is a whole new section in the guidelines, with growing evidence on His corrective pacing.

Prof. Christophe Leclercq (University Hospital of Rennes, Hospital Pontchaillou, Rennes, France) pointed out that several indications for cardiac resynchronisation therapy (CRT) in heart failure have been modified in agreement with the ESC Heart Failure Guidelines task force [3]:

- For example, in candidates for implantable cardioverter defibrillator (ICD) who have a CRT indication, implantation of a defibrillator with cardiac resynchronisation therapy (CRT-D) is recommended (class 1).
- However, patients with a CRT indication can either receive a CRT-D or a CRT-pacemaker (CRT-P). Factors in favour of choosing CRT-P include age, short life expectancy, and major comorbidities.

Prof. Haran Burri (University Hospital of Geneva, Switzerland) covered the 2021 recommendations on the management of patients with pacemakers in specific conditions, namely after acute myocardial infarction (AMI), cardiac surgery, and transcatheter aortic valve implantation (TAVI) [4]. Implantation of a permanent pacemaker after an AMI is indicated with the same recommendations as in the general population when atrioventricular block does not resolve within a waiting period of at least 5 days after AMI. Most often, atrioventricular block resolves spontaneously within a few days and only a minority of patients require permanent pacing after AMI. "This is why we should wait for at least 5 days before we consider pacing," Prof. Burri explained. The recommended waiting time before permanent pacemaker implantation in case of SND after cardiac surgery or heart transplantation is 6 weeks.

In the past few years, a lot of new data has become available on TAVI. The 2021 Guidelines make a class I recommendation for permanent pacing in patients with complete or high-degree atrioventricular block persisting for 24 to 48 hours after TAVI and those with new-onset alternating bundle branch block.

In contrast, ambulatory ECG monitoring or electrophysiologic study is recommended for patients with new post-TAVI left bundle branch block with a QRS over 150 ms or PR interval over 240 ms with no further prolongation during more than 48 hours post-procedure (class 2). The same recommendations are given for patients after TAVI with pre-existing conduction abnormalities with prolongation of QRS (>20 ms) or PR (>20 ms). There are many predictors given in the guidelines for permanent pacing after TAVI. Compared with the 2013 guidelines, more pacemaker patients can now undergo MRI.

Prof. Christoph Starck (German Heart Center Berlin, Germany) focused his talk on the novel guideline sections implantation, perioperative management, and long-term management [5]. Although mortality is low after the implantation of a pacemaker and cardiac resynchronisation therapy, any complications are as high as 5–15%. The most frequent complications are infections. Thus, administration of preoperative antibiotic prophylaxis within 1 hour of skin incision is recommended to reduce the risk of cardiovascular implantable electronic device (CIED) infections (class 1).

Numerous pragmatic recommendations are given on how to reduce complications. For example, the pacemaker device is placed in a pocket created under the skin, and the new guidelines state that rinsing the device pocket with saline before wound closure should be considered. Use of antibiotic-eluting envelopes is recommended in patients undergoing a re-intervention CIED procedure (class 2). Chlorhexidine alcohol should be considered over povidone-iodine alcohol (class 2a) Permanent pacemaker implantation should not be done in patients with a fever but should be delayed until the fever has been absent for at least 24 hours to reduce the risk of later device infection.

Follow-up for routine pacemaker and cardiac resynchronisation therapy, either in person alone or combined with remote device management is crucial: "Focus of all recommendations is minimising complication risk," Prof. Starck concluded.

1. Glikson M, et al. Eur Heart J 2021;42(35):3427–3520.
2. Deharo JC. Evaluation and general indications for pacing. Session: 2021 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy, ESC Congress 2021, 27–30 August.
3. Leclercq C. CRT, conduction system and alternative site pacing. Session: 2021 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy, ESC Congress 2021, 27–30 August.
4. Burri H. Pacing in specific conditions. Session: 2021 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy, ESC Congress 2021, 27–30 August.
5. Starck Ch. Implantation, complications, perioperative and long-term management. Session: 2021 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy, ESC Congress 2021, 27–30 August.

2021 ESC Guidelines on Cardiovascular Disease Prevention

Estimation of cardiovascular disease risk remains a cornerstone in the new 2021 ESC Guidelines. A novel stepwise treatment intensification approach with age-specific thresholds is recommended to control risk factors.

The new 2021 Guidelines on Cardiovascular Disease (CVD) Prevention were presented by Prof. Frank Visseren (Guidelines Task Force Chair; University Medical Center Utrecht, the Netherlands) at the ESC Congress 2021 and published simultaneously in the European Heart Journal [1,2]. "We wanted to make more personalised CVD prevention guidelines instead of a one-size-fits-all and focus more on the elderly," said Prof. Visseren in his overview of the new guidelines.

The most important changes in the 2021 CVD Prevention Guidelines include:

- A stepwise approach to individualised CVD prevention.
- Applying the SCORE2 and SCORE2-OP for 4 geographic regions.
- Age-specific risk thresholds in seemingly healthy people.
- Estimation of lifetime CVD risk and treatment benefit as an option.
- Shared decision making by taking patient-specific conditions, preferences, (lifetime) CVD risk, and treatment benefit into account.
- Recommendations on the environment.
- Signalling potential cost issues.

The SCORE2 tool now considers the risk of non-fatal and fatal heart attacks and strokes, rather than just the risk of fatal events as in the previous SCORE tool. The SCORE2 algorithm can be found in the freely available ESC CVD Risk app. The separate SCORE2-OP is applied for people aged 70 years and over.

Categories of individuals considered for prevention

Recommendations on CVD prevention are given in a stepwise approach, divided in 4 categories:

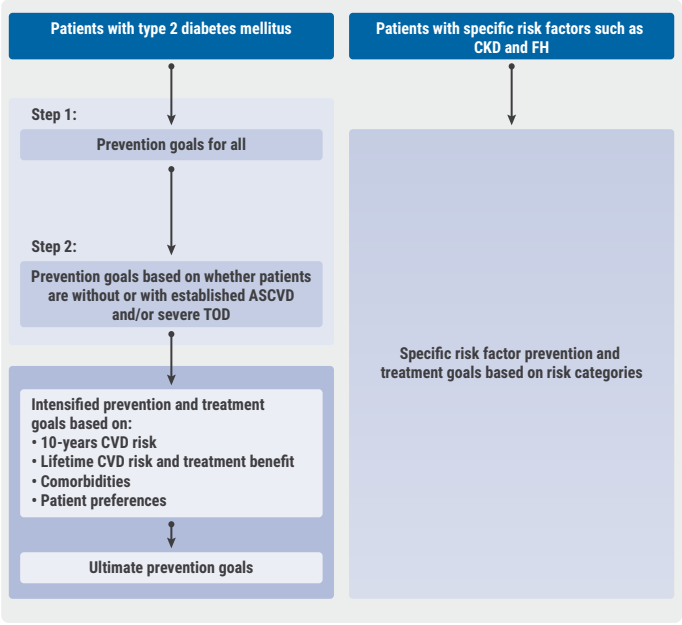
1. Seemingly healthy people.
2. Patients with established atherosclerotic cardiovascular disease (ASCVD).
3. Patients with diabetes mellitus (DM).
4. Patients with specific risks, such as familial hypercholesterolaemia or chronic kidney disease.

Notably, the new guidelines stratify countries into 4 risk levels: low risk, moderate risk, high risk, and very high risk.

In addition, geographic risk regions were introduced due to the known west-east and north-south gradient of CV risk in Europe.

The guidelines include a flowchart in which step 1 indicates prevention goals for all, and step 2 indicates intensified prevention and treatment goals necessary due to individual risk factors (see Figure 1). "Estimation of lifetime CVD risk and treatment benefit was included because the older you are, the less you can gain; when you start young, your risk reduction is much larger," Prof. Visseren explained.

Figure 1: Examples of a stepwise approach to risk stratification and treatment option in patients with diabetes and special risk factors. Modified from [1]



ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; FH, familial hypercholesterolaemia; TOD, target organ damage.

Novel risk thresholds according to age in seemingly healthy persons

Prof. Yvo Smulders (VU Universiteit Medical Center, the Netherlands) discussed the prevention in apparently healthy people [3]. "The flowcharts in the guidelines present a general approach," he said. In STEP 1, all apparently healthy persons should stop smoking, receive lifestyle recommendations, and their systolic blood pressure (SBP) should be <160 mmHg. Further requirements are dependent on the age group and the estimated 10-year CVD risk.

Decisions on risk-factor treatment are dependent both on the individual CVD risk and the age group. In healthy persons with a very high CVD risk, risk-factor treatment is generally recommended, in contrast to those with low-to-moderate risk. "The new guidelines want you to briefly stop and think before you start treatment," Prof. Smulders said. So-called risk modifiers, such as stress symptoms and psychosocial stress should be considered. In the elderly, polypharmacy, frailty, and comorbidity have to be taken into account

Prof. Naveed Sattar (University of Glasgow, Scotland) pointed out 2 important new recommendations for type 2 diabetes: those with concomitant heart failure with reduced ejection fraction should be treated with an SGLT2 inhibitor due to the proven outcome benefits [4]. For those recently diagnosed with diabetes who are motivated to try, considerable weight loss combined with low-calorie diets followed by food reintroduction and weight-maintenance phases is recommended as this can lead to DM remission.

Anti-inflammatory therapy for patients with established ASCVD

As Dr David Carballo (Geneva University Hospitals, Switzerland) pointed out, a novel recommendation in the 2021 Guidelines is anti-inflammatory therapy with low-dose colchicine (0.5 mg o.d.) for patients with established ASCVD [5]. Finally, novel content is added to draw attention to environmental exposures with CVD risk-modifying potential including air and soil pollution, above threshold noise levels, and effects of climate change.

1. Visseren FLJ, et al. Eur Heart J 2021;42(34):3227–3337.
2. Visseren FLJ. Introduction, novel concepts in the 2021 ESC prevention guidelines. Session: 2021 ESC Guidelines on Cardiovascular Disease Prevention, ESC Congress 2021, 27–30 August.
3. Smulders Y. Management of ASCVD risk in apparently healthy people. Session: 2021 ESC Guidelines on Cardiovascular Disease Prevention, ESC Congress 2021, 27–30 August.
4. Sattar N. Management of ASCVD risk in people with diabetes mellitus. Session: 2021 ESC Guidelines on Cardiovascular Disease Prevention, ESC Congress 2021, 27–30 August.
5. Carballo D. Management of ASCVD risk in patients with established ASCVD and on a population level. Session: 2021 ESC Guidelines on Cardiovascular Disease Prevention, ESC Congress 2021, 27–30 August.

Best of the Hotline Sessions

Empagliflozin: First drug with clear benefit in HFpEF patients

As the first positive study about a treatment drug in heart failure with preserved ejection fraction (HFpEF), EMPEROR-Preserved is considered a landmark trial. Besides a relevant 21% reduction in the primary composite outcome, key secondary endpoints results were also significant [1,2].

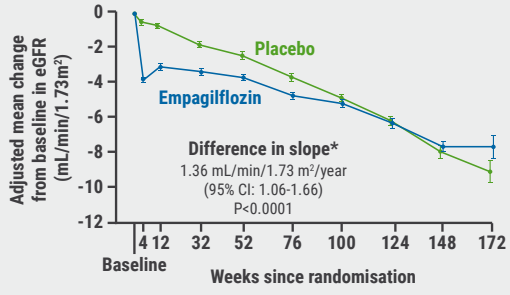
"We are about to have one of the most exciting clinical trials, I think, we've seen in a long time presented here in this Hotline-session at the ESC 2021-Digital experience and I have to say that I cannot think of any trial been more anticipated than the EMPEROR-Preserved trial," session chair Prof. John McMurray (University of Glasgow, Scotland) introduced EMPEROR-Preserved (NCT03057951) [1]. The trial aimed to assess empagliflozin as add-on to standard of care for HFpEF patients. It included 5,988 patients with HFpEF who had been hospitalised for HF within the last 12 months or were diagnosed with structural heart disease and ejection fraction (EF) over 40%. EMPEROR-Preserved was conducted as a multinational trial at 622 different sites in 23 countries worldwide.

After randomisation, participants with NYHA class II–IV and eGFR ≥20 mL/minute/1.73 m^2 were treated with either 10 mg of empagliflozin daily or placebo and followed over a median time of 26 months. "The primary endpoint of the study was a composite of cardiovascular death and HF hospitalisation and the 2 key secondary endpoints are the first and recurrent adjudicated HF hospitalisation and the slope of change in the estimated GFR for these patients over time," explained principal investigator Prof. Stefan Anker (Charité University Hospital, Germany). The baseline characteristics included a mean age of about 72 years, 45% women, a mean eGFR of 60.6 mL/minute/1.73 m^2, and 49% of patients had diabetes. Prof. Anker pointed out that when it came to underlying medication, the study subjects were in many ways treated similarly to HF patients with reduced EF with ≥80% under inhibition of the renin-angiotensin-aldosterone system and more than 80% on β-blockers.

The results showed event rates of 415 (6.9/100 patient-years) in the empagliflozin and 511 (8.7/100 patient-years) in the placebo group. This led to a significant hazard ratio (HR) of 0.79 (95% CI 0.69–0.90; P=0.0003), with a 21% relative risk reduction overall. Interestingly, this significant treatment difference was present from day 18 on. Evaluating the single components of the primary endpoint showed that the benefit was mainly driven by the reduction in first hospitalisation (HR 0.71; 95% CI 0.60–0.83) and not by a decrease in cardiovascular death (HR 0.91; 95% CI 0.76–1.09).

The analysis of 13 pre-specified subgroups like diabetes status, sex, and EF corroborated the beneficial effect of the empagliflozin treatment. Also, the findings for the secondary endpoint of first and recurrent hospitalisation for HF demonstrated a 27% relative risk reduction (HR 0.73; 95% CI 0.61–0.88; P=0.0009). Furthermore, the decline of kidney function over time was significantly reduced with empagliflozin (P<0.0001), and in patients whose kidney function was re-evaluated 23–42 days after the double-blind treatment, the eGFR was less reduced in the empagliflozin cohort compared with the placebo group (see Figure). Empagliflozin also proved beneficial in terms of health-related quality of life and change in NYHA class. "EMPEROR-Preserved is the first trial to show unequivocal clinical benefits with a drug in patients with HFpEF," Prof. Anker commented on the results.

Figure: Results in terms of the slope of decline in eGFR over time [1]



In 3176 patients, eGFR was reassessed at the end of the trial 23-42 days after the withdrawel of double-blind therapy, thus allowing unconfounded assessment of the effects of treatment. Over 28 months, eGFR deteriorated by

-5.7 mL/min 1.73 m² on placebo **-3.3 mL/min 1.73 m² on Empagliflozin** **P<0.0001**

* Analysed based on on-treatment data.

1. Anker SD. EMPEROR-Preserved: effect of empagliflozin on cardiovascular death and heart failure hospitalisations in patients with heart failure with a preserved ejection fraction, with and without diabetes. Hot Line Session, ESC Congress 2021, 27–30 August.
2. Anker SD, et al. N Engl J Med 2021; Aug 27. DOI:10.1056/NEJMoa2107038.

CardioMEMS: neutral outcome but possible benefit prior to COVID-19

In the prospective GUIDE-HF trial, even heart failure (HF) patients with mild symptoms (i.e. NYHA class II) appeared to benefit from haemodynamic-guided HF management with an implantable device. However, a significant effect could only be seen in the pre-pandemic era.

The rationale of haemodynamic-guided HF management is that the addition of information about pulmonary artery pressure to clinical signs and symptoms may allow for improved HF management as elevated or increasing pulmonary artery pressure predicts congestion [1]. The multicentre, single-blind, prospective GUIDE-HF (NCT03387813) trial assessed this approach in 1,022 patients in Canada and the USA with NYHA class II–IV HF and either a hospitalisation for HF within the preceding 12 months or elevated natriuretic peptides (i.e. B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide) within 30 days. Prof. JoAnn Lindenfeld (Vanderbilt University Medical Center, TN, USA) presented the findings, which were simultaneously published in *The Lancet* [2,3].

All participants underwent implantation of the wireless haemodynamic monitoring device (CardioMEMS). Previously, this device demonstrated a 28% reduction of HF hospitalisations in NYHA III patients in the CHAMPION trial (NCT00531661) [4]. In the GUIDE-HF trial, patients were then randomised 1:1 to either a treatment group, managed with provider remote access to the haemodynamic data, or a control group, managed without provider access to these data. The primary endpoint was a composite of cumulative HF hospitalisations, urgent HF visits, and mortality during a median follow-up of 11.7 months.

There were 253 primary endpoint events among 497 patients in the haemodynamic-guided management group and 289 in 503 patients in the control group. In the overall analysis, the primary endpoint was reduced by 12% in the treatment group. This difference failed to meet statistical significance (HR 0.88; 95% CI 0.74–1.05; P=0.16).

Interestingly, a pre-specified COVID-19 sensitivity analysis including the primary endpoint up to 13 March 2020 (the date of the national COVID emergency declaration in the USA) showed a different result: 177 primary events occurred in the intervention group and 224 events in the control group. This translated into a 19% reduction in primary endpoint events in the treatment group (HR 0.81; CI 0.66–1.00; P=0.049). This difference in primary events almost disappeared during COVID-19, with a 21% decrease in the control group relative to pre-COVID-19, virtually no change in the treatment group, and no difference between groups (HR 1.11; 95% CI 0.80–1.55; P=0.53). Again, HF hospitalisations were not reduced by haemodynamic-guided management (HR 0.83; 95% CI 0.68–1.01; P=0.064) in the overall study analysis but were lower in the pre-COVID-19 impact analysis (HR 0.72; 95% CI 0.57–0.92; P=0.007). Neither urgent HF visits nor mortality were reduced independently with treatment in the overall or pre-COVID-19 analyses. "This was a very safe device," Prof. Lindenfeld said. Of the 1,022 participants, 1,014 (99%) had freedom from device- or system-related complications.

"The results suggest that the benefits of haemodynamic-guided management in reducing HF hospitalisations extend to patients with NYHA class II symptoms and to those with elevated natriuretic peptides, independent of prior HF hospitalisations in all ejection fractions. The COVID-19 pandemic clearly affected the outcomes of GUIDE-HF," Prof. Lindenfeld concluded; however, given the overall neutral finding, additional studies are needed to clarify the utility of this approach.

1. Abraham WT, Perl L. J Am Coll Cardiol 2017;70:389–398.
2. Lindenfeld J. GUIDE-HF: haemodynamic-guided management of heart failure – randomised arm primary outcomes. Hot Line Session, ESC Congress, 27–30 August.
3. Lindenfeld J, et al. Lancet 2021;398:991–1001.
4. Abraham WT, et al. Lancet 2016;387:453–461.

Cardiac arrest without ST-elevation: instant angiogram does not improve mortality

Immediate versus delayed angiography in survivors of an out-of-hospital cardiac arrest (OHCA) was assessed within the TOMAHAWK study. The results failed to determine an advantage of the early procedure on 30-day all-cause mortality [1,2].

About 2 third of resuscitated OHCA patients without primarily obvious non-cardiac pathology do not present ST-elevation on the ECG [3]. Pros and cons of an instant coronary angiogram in these patients are still under debate [1,2]. The TOMAHAWK study (NCT02750462) hypothesised that the unselected immediate angiogram would be advantageous for OHCA patients compared with a delayed/selective angiogram. The trial randomised 554 patients over 30 years of age from various sites in Germany and Denmark who

met the inclusion criteria of documented OHCA with return of spontaneous circulation (ROSC). ST-elevation in the ECG was among the reasons for exclusion. The primary endpoint was defined as all-cause mortality at 30 days.

The median age in the cohort was 70 years, roughly 38% had a prior diagnosis of coronary artery disease, and more than 50% presented a shockable first monitored rhythm. The timespan from OHCA to return ROSC was 15 min in both study groups. In the immediate group, 95.5% received an angiogram that was performed within 3 hours after OHCA, while 62.2% of the delayed group patients were taken to the Cath lab at a median of 46.9 hours after their arrest.

Overall, there was no significant difference between the arms in the primary endpoint (HR 1.28; 95% CI 1.00–1.63). "If you take the composite of all-cause mortality or severe neurological deficit, this actually becomes statistically significant, yet not accounted for multiple testing; so, this is just hypothesis generating," Prof. Steffen Desch (University Heart Center Lübeck, Germany) highlighted one of the key secondary outcomes. Several relevant subgroups were also assessed without reaching statistical significance.

Although this has to be considered a neutral trial, discussant Prof. Susanna Price (Royal Brompton Hospital, UK) stressed that it answered an important question [4]. "It gives me information that is useful regarding the opportunity to minimise harm, which is a lot of what critical care is about. So, we do not necessarily have to move these patients very acutely when they just come into the ED. This has implications for resource utilisation, but it also has implications for mobilising patients around the hospital during COVID 19," she underlined.

1. Desch S. TOMAHAWK: Immediate angiography after out-of-hospital cardiac arrest. Hot Line Session, ESC Congress 2021, 27–30 August.
2. Desch, S. N Engl J Med 2021;29 Aug. DOI:1056/NEJMoa2101909.
3. Dumas F, et al. Circ Cardiovasc Interv. 2010;3(3):200-207.
4. Price S. TOMAHAWK – Discussant review. Hot Line Session, ESC Congress 2021, 27–30 August.

Older hypertensive patients benefit from intensive blood pressure control

Blood pressure management with systolic blood pressure (SBP) target below 130 mmHg led to a 26% reduction of adverse cardiovascular (CV) events in patients over 60 years in the multicentre, randomised controlled STEP trial [1,2]. Importantly, lowering <130 mmHg did not result in more serious adverse incidents.

"As the population is ageing, hypertension management among older patients has been increasingly discussed," said Prof. Jun Cai (FuWai Hospital, China) pointing out that previous trials led to distinct conclusions. "This study is important because it addresses a very simple question: When treating BP in older people, how low should we go?" expressed the trial discussant Prof. Bryan Williams (University College London, UK) [3].

STEP (NCT03015311) investigated intensive BP treatment from 110 mmHg to <130 mmHg as SBP target versus standard therapy with SBP between 130 mmHg and <150 mmHg. The study enrolled 8,511 patients between 60–80 years of age who had no history of a prior stroke. BP medications consisted of olmesartan, amlodipine, and hydrochlorothiazide. The measuring of BP was either performed by trained personnel in an office setting or at home with a smartphone app as a monitoring device. Furthermore, various examinations were executed at baseline and throughout the control visits including ECG, echocardiography, and cognitive function testing.

The primary outcome was a composite of multiple adverse CV events (i.e. stroke, acute coronary syndrome, revascularisation, decompensation of heart failure, atrial fibrillation, CV mortality). Baseline findings of the study population included a mean age of 66.2 years, just over half of the participants were women, and about 19% had diabetes.

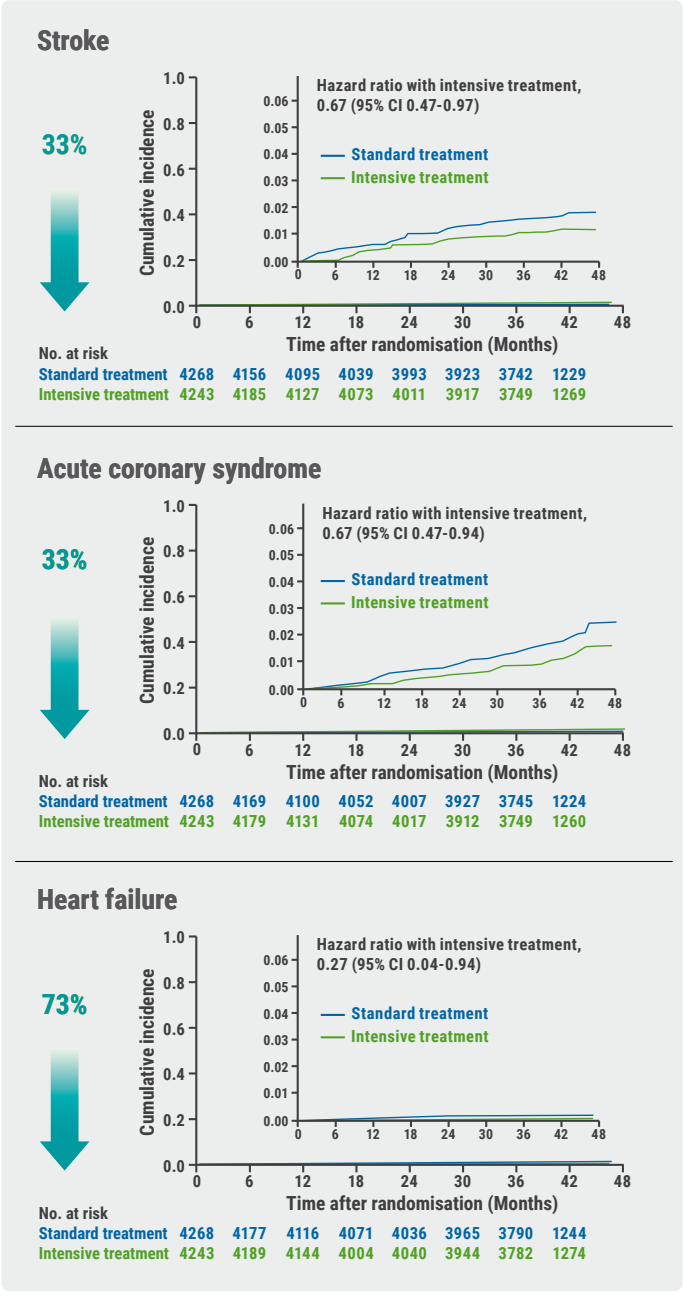
"After randomisation, the 2 treatment strategies resulted in a rapid and sustained between-group difference in SBP," Prof. Cai pointed out. Over a median follow-up of 3.34 years, the event rate for the primary outcome was 3.5% on intensive treatment and 4.6% on standard therapy. Intensive treatment reduced the likelihood of primary outcome by 26% (HR 0.74; 95% CI 0.60–0.92; P=0.007). Prof. Cai highlighted that the intensive BP lowering approach provided a significant 33% reduction in stroke and acute coronary syndrome, 28% in major adverse cardiac events, and 73% reduction in heart failure (see Figure on the next page). However, no significant decrease was seen in all-cause mortality, atrial fibrillation, or coronary revascularisation. "The beneficial effects of the intensive treatment were consistent across our prespecified subgroup analysis, including age older than 70 or not, sex, baseline SBP levels, previous diabetes and 10-year Framingham risk score," said Prof. Cai.

As for safety outcomes, there was a significant difference in the rate of hypotension events (3.4% intensive group

vs 2.6% standard group; P=0.03), but none concerning dizziness, severe events such as syncopes or fractures, nor deterioration of renal function. "The STEP results support that the SBP target in older patients should be set lower than 130 mmHg for better CV benefits without increasing serious adverse events as well as renal injuries," concluded Prof Cai.

1. Cai J. STEP Study: Intensive vs. standard blood pressure control among older hypertensive patients. Hot Line Session, ESC Congress 2021, 27–30 August.
2. Zhang W, et al. N Eng J Med 2021;Aug 30. DOI:10.1056/NEJMoa2111437.
3. Willams B. STEP Study – Discussant review. Hot Line Session, ESC Congress 2021, 27–30 August.

Figure: Intensive blood pressure lowering is beneficial in various secondary outcomes. Modified from [1]



Antagonising the mineralocorticoid receptor beneficial for patients with diabetes and CKD

The multinational FIGARO-DKD trial investigated the effect of the mineralocorticoid receptor antagonist finerone on cardiovascular outcomes in patients with mild-to-moderate chronic kidney disease (CKD) and type 2 diabetes. Finerenone decreased cardiovascular morbidity and mortality and kidney disease progression [1,2].

"I think many of us know that patients with CKD and diabetes have a high risk of hospitalisation for heart failure (HF) and cardiovascular death. In fact, patients who have both CKD and type 2 diabetes have a 3-fold risk of having HF compared with patients with diabetes alone," explained Prof. Bertram Pitt (University of Michigan School of Medicine, MI, USA) [1].

The phase 3 FIGARO-DKD trial (NCT02545049) investigated whether the non-steroidal mineralocorticoid-receptor antagonist finerenone would reduce the cardiovascular risk in these patients [1,2]. After a run-in phase of 4–16 weeks, during which the renin-angiotensin system inhibition therapy of the patients was optimised, the study randomised 7,437 adults to finerenone 10 mg/20 mg daily or placebo. Among the inclusion criteria was an eGFR ≥25 ml/min/1.73 m², urine albumin-to-creatinine ratio (UACR) ≥30–≤5,000 mg/g and a serum potassium of ≤4.8 mmol/L. The primary endpoint was composed of cardiovascular death, non-fatal myocardial infarction, and hospitalisation HF. Secondary composite endpoints looked at a decrease in eGFR of ≥40% and ≥57% or renal death, as well as the development of end-stage renal disease.

The study cohort had a mean age of 64 years, a mean type 2 diabetes duration of 14.5 years with a mean HbA1c of 7.7% and included 31% women. All participants had a renin-angiotensin system blocker, 71% received statins, 48% β-blockers, and 51% calcium antagonists. Importantly, at least 60% of patients with a preserved eGFR had albuminuric CKD with a UACR of ≥30mg/g. Prof. Pitt reminded his colleagues not to forget to screen for UACR even when eGFR is normal.

The risk for the primary endpoint was significantly reduced in the finerenone arm of the study by 13%, demonstrated by a hazard ratio of 0.87 (95% CI 0.76–0.98; P=0.026). "I'd like to emphasise that this was primarily driven by a 29% reduction in hospitalisation for HF," stated Prof. Pitt. The composite kidney outcome of a ≥40% reduction was non-significant

(P=0.069). "However, the more reliable and classic endpoint, a greater than 57% reduction in eGFR, an endpoint that has been used in many renal trials, was significantly reduced and, most importantly for our patients, the progression to end-stage renal disease was also significantly reduced. So, significantly less dialysis and end-stage renal disease," highlighted Prof. Pitt.

The overall adverse-event profile was balanced between the groups, but hyperkalaemia occurred about twice as often in the finerenone group (10.8%) compared with the placebo group (5.3%). Of note, only 1.2% of patients on finerenone had to discontinue the medication due to hyperkalaemia.

"Together, the results of FIGARO-DKD and the previous FIDELIO-DKD (NCT02540993) allow us to say pretty confidently: finerenone provides kidney and CV benefits across the spectrum of patients with CKD and type 2 diabetes," Prof. Pitt concluded.

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2. Pitt B. N Engl J Med 2021;Aug 28. DOI:1056/NEJMoa2110956.

Late-Breaking Science in Heart Failure

Valsartan seems to attenuate hypertrophic cardiomyopathy progression

The phase 2 VANISH trial assessed whether valsartan could decelerate the disease course of hypertrophic cardiomyopathy (HCM). The positive results demonstrated a slower relative cardiac remodelling in those treated with the sartan.

"HCM is typically diagnosed by identifying unexplained left-ventricular (LV) hypertrophy and the prevalence in the general population is roughly 1 in 500," Prof. Carolyn Ho (Brigham and Women's Hospital, MA, USA) outlined. Prof. Ho stated that familial HCM is caused by known genetic variants in about 65% of cases [1]. Results of pre-clinical trials have pointed to TGF-β neutralisation antibodies or sartans as a possibility to prevent LV hypertrophy and fibrosis in HCM [2,3]. Thus, the VANISH trial (NCT01912534) investigated whether disease evolution could be reduced by valsartan treatment in early sarcomeric HCM [1,4].

The presented primary analysis cohort included 178 patients who all initially received valsartan in an active run-in period with up-titration to a dose of 320 mg in adults or 80 to 160 mg in children (depending on age and weight). Upon completion, the participants were randomised to further treatment with valsartan or placebo until the study ended after 2 years. All patients were aged between 8 and 45 years and had a (likely) sarcomeric variant with NYHA class I-II, a maximal LV wall thickness (LVWT) of 12–25 mm and no signs of obstruction.

The mean age of the cohort was around 23 years with 43% of participants under the age of 18 and 39% women. Baseline maximal LVWT ranged between 8.1 and 8.2 (z-score) or 16.4 and 17.9 mm in the placebo and valsartan group, respectively.

"In developing the primary endpoint, we carefully considered the challenges we would face in demonstrating a treatment response. Mainly, we recognised that the magnitude of the impact of valsartan was unknown, our participants were healthy and asymptomatic at enrolment and, therefore, clinical events would be extremely rare," Prof. Ho stated. She further explained that the researchers for this reason strove to interrogate disease biology rather than traditional clinical outcomes by identifying moderate effects in 9 different cardiac metrics. These consisted of markers for myocardial injury and stress, morphology, and function. The effect size was then defined as change in composite z-score at 2 years compared with baseline.

The results showed a positive trial with a between-group difference of 0.231 (P=0.001), which stood for a relative amelioration in cardiac remodelling. "In the individual components, improvement was most marked for NT-ProBNP level, LV end-diastolic volume and e' velocity, each individually significant after adjusting for covariates," said Prof. Ho. Within the analysis of pre-specified subgroups, valsartan led to all in all consistent effects, with the most pronounced benefit in subjects with LVWT less than the median z-score of 7.3. However, treatment with valsartan

did not result in significant amelioration of left atrial volume index or LV mass index.

Prof. Ho stressed that treatment with valsartan was safe with no excess of adverse events, no instances of hypotension, hyperkalaemia, or renal insufficiency. "The VANISH trial suggested that there is an opportunity to attenuate disease progression in sarcomeric HCM with a widely available and well-tolerated medication," she concluded.

1. Ho CY. VANISH Trial Results. Late-Breaking Science in Heart Failure, ESC Congress 2021, 27–30 August.
2. Teekakirikul P, et al. J Clin Invest. 2010;120(10):3520–9.
3. Raja AA, et al. Circ Heart Fail. 2019;12(12):e006231.
4. Ho CY, et al. Nat Med 2021;Sept 23. DOI:10.1038/s41591-021-01505-4.

Dapagliflozin reduces incidence of sudden death in HFrEF patients

A novel analysis of DAPA-HF investigated the efficacy of dapagliflozin on ventricular arrhythmia (VA), resuscitated cardiac arrest (RCA), and sudden death. The results showed a significantly reduced likelihood for the composite outcome by 21% [1,2].

The majority of sudden deaths are of cardiac aetiology and most of them are associated with arrhythmias [3]. Thus, the DAPA-HF (NCT03036124) trial evaluated dapagliflozin's efficacy to prevent adverse outcomes of heart failure (HF) in patients with HF and reduced ejection fraction (HFrEF) [4]. The previously published main results showed a 26% risk reduction of the composite primary endpoint of cardiovascular death or worsening of HF. DAPA-HF included 4,744 patients with a left ventricular ejection fraction (LVEF) ≤40% and an NT-proBNP ≥600pg/mL who were in NYHA class II–IV. The mean age was 67 years, mean LVEF 31%, 45% suffered from diabetes, and 41% from chronic kidney disease. "Background HF therapy was very good," Dr James Curtain (University of Glasgow, Scotland) stated referring to a high percentage of patients on renin-angiotensin-aldosterone inhibition, β-blocker, and mineralocorticoid receptor antagonists (MRA).

The primary outcome of this new analysis consisted of a composite of VA, resuscitated cardiac arrest, or sudden death. Furthermore, sensitivity analyses were performed, with composites that excluded non-sustained ventricular tachycardia or included only more serious VAs and predictors of the primary outcome were identified. Dr Curtain outlined that "315 patients or 6.6% of the total study cohort experienced a primary outcome event of which the majority, 64%, were adjudicated sudden death. VA accounted for 33% of the primary outcome events and there were 8 RCAs."

Comparing patients without a primary outcome event with those who were subject to VA, resuscitated cardiac arrest, or sudden death, the latter were significantly more often men, had a history of prior VA, a lower LVEF, and had a lower eGFR. Also, primary outcome events were more likely to occur in those on a loop diuretic or having a defibrillating device.

Among the significant independent predictors of VA, resuscitated cardiac arrest, or sudden death were male sex, higher NTproBNP, history of VA or myocardial infarction. The risk of a primary outcome event was reduced by higher values of LVEF, systolic blood pressure, or serum sodium.

"Dapagliflozin compared with placebo reduced the incidence of the primary outcome VA, RCA, or sudden death by 21% with an HR of 0.79 and P-value of 0.037," said Dr Curtain. He further elaborated that the results of the competing risk analysis including all-cause death were effectively the same with an incidence reduction by 20%. In his summary, Dr Curtain also pointed out that the effect of dapagliflozin was generally consistent across key subgroups and within several sensitivity analyses examining composites excluding non-sustained ventricular tachycardia or including only more serious VA.

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2. Curtain JP, et al. Eur Heart J 2021;27 Aug. DOI:10.1093/eurheartj/ehab560.
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4. McMurray JJV, et al. N Engl J Med 2019;381:1995-2008.

Late-Breaking Science in Hypertension

Smartphone app improves BP control independent of age, gender, and BMI

A digital tool including 6 non-pharmacological interventions was tested in patients with early-stage hypertension in the HERB-DH1 study. Participants using the app were able to lower their blood pressure (BP) and implement positive lifestyle interventions [1,2].

The International Society of Hypertension has highlighted the need for population-level initiatives to reduce the global burden of elevated BP. Digital therapeutics is an emerging branch of medicine that utilises technology-based software algorithms or applications. These digital therapeutics could be beneficial in improving BP level and control. To test this, the HERB system was developed, a new interactive smartphone app designed to help users make intensive and consistent lifestyle modifications to reduce BP.

The HERB app includes 6 non-pharmacologic interventions: sleep condition, salt intake, alcohol reduction, exercise, body-weight control, and stress management. Patients in the intervention group measured their BP at home, and doctors were able to monitor the patient´s data on the web and interact with them when necessary.

The prospective, randomised, controlled HERB-DH1 study included participants aged 20 to <65 years who were diagnosed with essential hypertension (i.e. office SBP 140–179 mmHg, and/or DBP 90–109 mmHg). Details regarding the design of the HERB-DH1 study were previously published [3]. The 24-hour SBP of the participants had to be ≥130 mmHg by ambulatory BP measurement at screening. All participants were antihypertensive mediation-naïve for more than 3 months. The digital therapeutics group (n=199) using the app and standard lifestyle modification was compared with a control group (n=191) that received standard lifestyle modification only. Antihypertensive drugs were available if needed according to the guidelines in both groups. The primary outcome was the change in 24-hour systolic BP by ABPM at 12 weeks.

"At 12 weeks, there was a reduction of morning home SBP by 10.6 in the intervention group and by 6.2 in the control group, which was highly statistically significant," emphasised Prof. Kazuomi Kario (Jichi Medical University, Japan). Although there were marked individual differences in patient´s responses at 12 weeks, patients using the app were generally doing better than those in the control group.

A subgroup analysis revealed that patients benefited from the app independent of age, sex, and BMI. Those with a 24-hour SBP by ambulatory blood pressure monitoring at baseline from ≥145 mmHg had a significantly better effect from the intervention than the others (P<0.001). The app adherence was always >95%. Patients in the app group also lost significantly more body weight and a lower percentage needed antihypertensive medication compared with the control group.

Prof. Kario concluded that the HERB-DH1 study highlighted that digital tools, such as the HERB system, have the potential to contribute to individual-level initiatives for patients with early-stage hypertension by facilitating the implementation and effectiveness of lifestyle modification messages and behaviours.

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2. Kario K, et al. European Heart Journal, ehab559. DOI:10.1093/eurheartj/ehab559.
3. Kario K, et al. J Clin Hyperten 2020;22:1713–722.

QUARTET demonstrates that simplicity is key in BP control

The QUARTET study showed that simple, single-step strategies can improve blood pressure (BP) control. In this study, a quadruple combination of hypertensive agents in tiny doses was more effective than standard monotherapy [1,2].

Many factors impede BP control: most patients need at least 2 medications, treatment inertia is common, and patients have concerns regarding adverse events. Prof. Clara Chow (University of Sydney, Australia) pointed to a previous pilot study of her team that suggested that simplified strategies using low-dose, single-pill combinations might be a way to overcome barriers to BP control. In this study including 55

patients, a single pill with a quarter dose was more effective than monotherapy with a usual dose [3]. "This study was the rationale to perform the double-blind, randomised controlled QUARTET (ANZCTR 12616001144404) study," Prof. Chow explained.

The primary objective of QUARTET was to determine whether hypertension management starting with a single pill containing quarter-standard doses of 4 types of BP lowering medicines ('quadpill') is more effective than an approach that starts with standard-dose monotherapy. The quadpill used contained a quarter dose of irbesartan, amlodipine, indapamide, and bisoprolol. Included patients were either untreated or received a monotherapy. They were randomised to initial quadpill (n=300) or monotherapy with irbesartan (n=291). Patients who failed to achieve the BP goal on their assigned therapy were treated with additional medication.

Extended cohorts were assessed after 52 weeks. "The majority (84%) was on the quadpill alone after 12 weeks. At 52 weeks, 79% were on the quadpill alone compared with 57% in the control arm," Prof. Chow said. Up-titration occurred in 15% of the intervention group and 40% of control by 12 weeks.

After 12 weeks, the primary outcome of unattended office BP was lower in the initial quadpill group by 6.9 mmHg (95% CI 4.9–8.9; P<0.001) compared with patients receiving irbesartan monotherapy in the intention-to-treat analysis (P<0.0001). BP control was achieved by 76% of patients taking the quadpill versus 58% in the control group (BP<140/90 mmHg; RR 1.3; 95% CI 1.2–1.5; P<0.0001)

The quadpill remained superior until the end of the trial after 1 year. In the subgroup of 417 patients who stayed in the study for 52 weeks, patients taking the quadpill had a 7.7 mmHg lower systolic BP compared with the controls (95% CI 5.2–10.3 mmHg; P<0.0001), and 81% of patients taking the quadpill compared with 62% in the control group achieved BP control.

At 12 weeks, there were 7 (3%) versus 3 (1%) severe adverse events in the intervention versus control group. In addition, there were no excess adverse event-related treatment withdrawals (4.0% vs 2.4%, P=0.27).

"Starting on ultra-low-dose combination is more effective than the usual way of starting patients on 1 medication first. We were excited that we got patients to BP control so quickly," Prof. Chow concluded.

1. Chow CK. The effectiveness and tolerability of ultra-low-dose quadruple combination in treatment of hypertension – A multicentre double-blind randomised trial. Late-breaking science in hypertension, ESC Congress 2021, 27–30 August.
2. Chow CK. Lancet;28 Aug. DOI:1016/S0140-6736(21)01922-X.
3. Chow CK, et al. Lancet 2017;389:1035–42.

Salt substitutes: a successful strategy to improve blood pressure

In the real-world DECIDE-Salt trial, a salt substitute was a safe and effective way to lower salt intake that led to a significant reduction in systolic blood pressure (BP) [1]. In contrast, a stepwise approach to reduce salt in the diet failed to lower salt intake.

The DECIDE-Salt study (NCT03290716) investigated strategies to lower dietary sodium intake, which might improve BP control. The study included 1,612 individuals (≥55 years) from 48 residential care facilities in China whose mean baseline BP was 138.6/81.4 mmHg and explored different ways of salt reduction regarding the influence on BP (i.e. primary endpoint) and cardiovascular events (i.e. secondary endpoint). Details of the study design were previously published [2]. Safety outcomes included hyperkalaemia, hypokalaemia, and impaired renal function.

In one group, usual salt was replaced by salt substitute in facility kitchens; in the other group, either salt or salt substitute was step-by-step reduced to 60% of the original salt content at baseline. Baseline characteristics of the participants were comparable in both groups. Prof. Yangfeng Wu (Peking University Clinical Research Institute, China) explained that a commercial salt substitute was used consisting of 62.5% NaCl, 25% KCL, 12.5% dried food flavourings, and traces of amino acids. Usual salt consisted of over 99% NaCl. Both were Iodine-fortified and provided to the facilities.

Compared with usual salt, the salt substitute led to reductions in mean systolic BP (-7.14 mmHg; 95% CI -10.49 to -3.79; P<0.0001) and mean diastolic BP (-1.91 mmHg; 95% CI -3.58 to -0.24; P=0.0251). In contrast, there was no significant influence of restricted supply versus usual supply of sodium on systolic BP.

Notably, a 40% reduction was seen in the relative risk of major CV events in the salt substitute group (HR 0.60; 95% CI 0.38–0.96; P=0.0318). Again, progressive restriction of salt/substitute did not influence this outcome. Mean 24-hour urinary sodium excretion in participants with progressive restriction of salt/substitute supply was not significantly

reduced (-5.7 mmol; 95% CI -24.7 to 13.3; P=0.5551) compared with usual supply. Neither salt reduction strategy influenced the risk of total mortality.

Moreover, the salt substitute was associated with an increase in mean serum potassium and the incidence of biochemical hyperkalaemia compared with usual salt (relative risk [RR] 2.67; 95% CI 1.18–6.05; P=0.0189). "We noted a higher risk of hyperkalaemia but no increased risk of hyponatraemia," Prof. Wu explained. In addition, only 2 patients had constantly elevated serum potassium levels, and there were no deaths attributed to hyperkalaemia. The risk of hypokalaemia was lower with the salt substitute compared with usual salt (RR 0.23; 95% CI 0.06–0.89; P=0.0334).

Prof. Wu concluded that the salt substitute reduced BP and cardiovascular events with decent safety. Although the salt substitute increased the risk of biochemical hyperkalaemia, no evidence of associated adverse clinical outcomes emerged. In contrast, stepwise restriction of salt/salt substitute supplied to facility kitchens did not meaningfully reduce sodium intake, and hence had no impact on BP or CV events.

1. Wu Y. Impact of salt substitute and stepwise reduction of salt supply on blood pressure in residents in senior residential facilities: Main results of the DECIDE-Salt trial. Late-breaking trials in hypertension. ESC Congress 2021, 27–30 August.
2. Jin A, et al. Am Heart J 2020;226:198–205.

Late-Breaking Science in Prevention

NATURE-PCSK9: Vaccine-like strategy successful in lowering CV events

In the NATURE-PCSK9 study, a yearly vaccine-like approach with PCSK9 small-interfering RNA reduced cardiovascular events by up to two thirds. The motto 'the earlier the better' also holds true for low-density lipoprotein (LDL) reduction [1].

Atherosclerosis is caused by the accumulation of LDL (ApoB) particles that become trapped within the artery wall over time [2]. A previous study has shown a cumulative benefit of long-term exposure to lower LDL (ApoB) levels [3]. Accordingly, individuals who inherit LDL-lowering variants of the PCSK9 gene are known to have large reductions in lifetime risk of cardiovascular events.

In a previous study, a single dose of a PCSK9 small-interfering RNA (siRNA) led to a durable reduction of LDL concentrations over 1 year ranging from 29.5% to 38.7% [4]. "The availability of a yearly dose of siRNA directed against PCSK9 allows us to use this strategy in a vaccine-like approach," explained Prof. Brian Ference (University of Cambridge, UK).

The primary objective of the NATURE-PCSK9 study was to compare the potential clinical benefit of a yearly vaccine-like strategy using siRNA beginning at age 30, 40, 50, or 60 years (expected to result in a 36% LDL reduction) with usual care on the lifetime risk of major coronary events. "Ideally, this would be done in a randomised controlled trial, but this is not feasible over a time period of 50 years," Prof. Ference said. Thus, the NATURE-PCSK9 trial estimated the clinical benefit and optimal timing of a PCSK9 siRNA vaccine-like strategy using data from the PCSK9 variants that the siRNA was designed to mimic to anticipate the expected outcome.

Included in the analysis were 445,765 participants enrolled in the UK Biobank without a diagnosis of atherosclerotic CV disease, diabetes, or cancer before the age of 30 years. The cumulative exposure to lower LDL in mmol-years precisely predicted the observed benefit from lifelong lower LDL due to PCSK9 partial loss of function, but also the benefit observed from lowering LDL with a PCSK9 inhibitor confirming the cumulative exposure hypothesis for LDL.

The vaccine-like strategy to lower LDL has the potential to dramatically reduce the lifetime risk of cardiovascular events by up to two-thirds – depending on baseline LDL and age at which therapy is started. Overall, the vaccine-like approach demonstrated a sustained 34% time-averaged LDL reduction. Each decade earlier that LDL lowering was initiated was associated with an increasingly greater proportional reduction in lifetime risk. A hazard ratio [HR] of

0.48 was calculated when LDL lowering began at 30 years of age, an HR of 0.54 for LDL lowering beginning at 40 years, an HR of 0.63 for LDL lowering from 50 years, and an HR of 0.73 for LDL lowering from 60 years. Moreover, patients with greater baseline LDL had a greater effect. Similar stepwise increased reductions in the lifetime risk of major CV events and the individual components of the composite outcomes were observed with each decade of earlier initiation of LDL-lowering therapy for both men and women.

The NATURE-PCSK9 study found that a vaccine-like strategy to reduce LDL using a once-yearly dose of a PCSK9 siRNA could markedly reduce the lifetime risk of CV events; the effect being greater the earlier the LDL-lowering siRNA therapy is initiated.

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2. Ray KK, et al. JAMA Cardiol 2019;4:1067–1075.
3. Ference BA, et al. J Am Coll Cardiol 2015;65:1552–61.
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Polypill: A successful tool in primary prevention

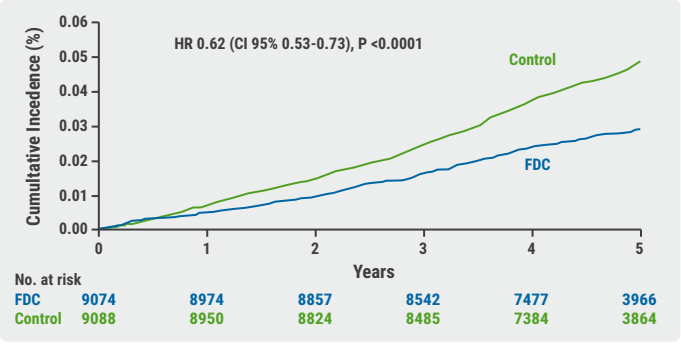
Findings of a meta-analysis of 3 large, randomised controlled trials suggest that fixed-dose combination treatments are able to prevent cardiovascular (CV) death, myocardial infarction (MI), stroke, and revascularisation [1,2]. Regimens containing aspirin resulted in the largest effects.

"Strategies that avoid a high proportion of first CV events are critical to reducing global CV disease (CVD) burden," said Prof. Philip Joseph (McMaster University, Canada) [1]. Fixed-dose combination (FDC) treatment could substantially reduce CV risk, but more data is needed to quantify its efficacy. The so-called polypill in a single formulation usually contains 2+ blood pressure-lowering agents, a statin, and in some cases, aspirin. In a meta-analysis of long-term, randomised controlled trials (each including >1,000 participants >2 years follow-up), Prof. Joseph and his colleagues tested different FDC strategies versus controls for primary prevention. The primary objective was the prevention of a composite of CV death, MI, stroke, or revascularisation. In addition, the impact on individual CV outcomes and the difference between regimens with and without aspirin was evaluated.

Data from 3 large RCTs of FDC in primary prevention was included in the analysis: the TIPS-3 trial (NCT01646437), the HOPE-3 trial (NCT00468923), and the Polylran trial (NCT01271985) [3-5]. With 18,162 participants in these trials, this meta-analysis is the largest study to date showing the effect of polypill therapy in CVD prevention.

"There was a large difference in the primary outcome: with FDC, we saw a 38% reduction [versus control]. This became apparent within 1 year of follow-up and the curves continued to diverge," Prof. Joseph said (see Figure). Likewise, single events were markedly reduced with a reduction of MI by 48%, a reduction of stroke by 42%, and a reduction of CV death by 35%. The polypill led to marked changes in risk factors: after a follow-up time of 2.1 years, LDL concentrations in the FDC group were 22.6 mg/dl (0.58 mmol/L) lower than in the control group. After this time, systolic blood pressure showed a mean difference of 4.7 mmHg in favour of the polypill.

Figure: The primary endpoint of CV death, MI, stroke, or revascularisation [1]



CI, confidence interval; FDC, fixed-dose combination; HR, hazard ratio.

"The largest effects were seen in combinations that included aspirin, but the others were still very important," Prof. Joseph said. Aspirin-containing regimens led to a reduction of CVD by 47%, a reduction of MI by 53%, and stroke by 51%. A subgroup analysis revealed that the benefit of FDC was most prevalent in the elderly (>66 years).

The analysis found no significantly elevated risk of haemorrhagic stroke or fatal bleeding, but a numerically increased risk of gastrointestinal bleedings was seen that failed to achieve statistical significance. Only 37 participants had to be treated with an aspirin-containing regimen to prevent 1 event of the primary outcome; in the total group, the number needed to treat was 51. Thus, Prof. Joseph advocated FDC treatment as a key strategy in primary CVD prevention.

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4. Yusuf S, et al. N Engl J Med 2016;374:2021–2031.
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Important Results in Special Populations

VOYAGER PAD: Fragile or diabetic patients also benefit from rivaroxaban

Two pre-specified analyses of the VOYAGER PAD study in special populations showed that treatment benefit was evident in all subgroups with low-dose rivaroxaban in patients with symptomatic peripheral artery disease (PAD) who had just undergone peripheral artery revascularisation [1,2]. Both patients with diabetes and fragile patients gain a net benefit from treatment.

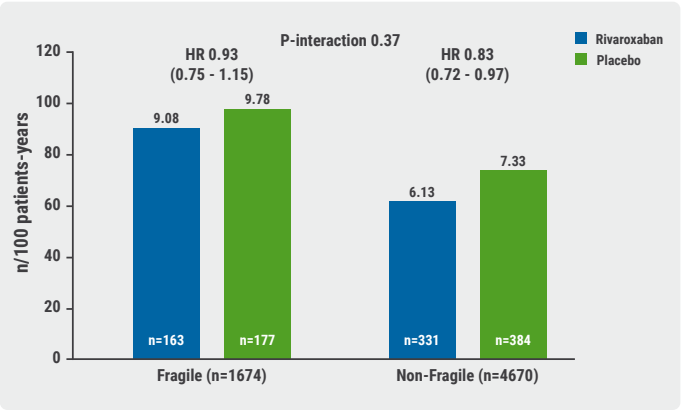
VOYAGER PAD (NCT02504216) included nearly 6,600 patients with symptomatic PAD who underwent peripheral artery revascularisation and demonstrated that the combined antithrombotic regimen of rivaroxaban plus aspirin was safe and effective for reducing the composite endpoint of acute limb ischaemia, major amputation of a vascular cause, myocardial infarction, ischaemic stroke, and cardiovascular death in this patient population with an absolute risk reduction of 2.6%. To assess whether this treatment benefit extends to subpopulations, 2 pre-specified analyses were performed in patients with diabetes and fragile patients. Both analyses were presented by Prof. Cecilia Low Wang (University of Colorado, CA, USA).

Participants with diabetes at baseline had a different baseline risk with more hypertension, coronary artery disease, a worse kidney function and more clopidogrel use compared with non-diabetics. "We found that among the placebo group the Kaplan Mayer estimate of the primary outcome at 3 years was 22.5% in those with diabetes and 18.2% in non-diabetes," Prof. Low Wang said. There was also a dramatic difference between diabetics and non-diabetic patients in all-cause mortality: 12.9% of patients with diabetes compared with 9.6% of patients without diabetes randomised to placebo died within 3 years. The hazard ratio for the primary endpoint in patients with diabetes was 0.94, which was consistent with the overall population. The P-value of interaction for diabetes was not significant (0.16). "This analysis shows that the efficacy of rivaroxaban was consistent regardless of diabetes status at baseline," Prof. Low Wang explained.

Prof. Low Wang also presented a pre-specified analysis of fragile patients, defined as age >75 years, weight ≤50 kg, and/or baseline eGFR <50 ml/min. Of the VOYAGER PAD participants, 26% were fragile according to this definition. Compared to the other participants, they were less frequently treated surgically.

A higher percentage of fragile patients reached the primary endpoint compared with the non-fragile group. However, similar to the participants with diabetes, the benefit was the same regardless of fragile status (see Figure).

Figure: VOYAGER PAD primary endpoint by fragile status [2]



Higher risk of TIMI major bleedings

A higher rate of discontinuation was observed in the diabetes population, which may have attenuated the observed benefit in the intention-to-treat analysis. However, the risk of TIMI major bleeding was significantly greater in patients with diabetes, possibly driven by the different baseline risk associated with bleeding. A higher percentage of patients with diabetes had a high bleeding risk at baseline compared with non-diabetics. As Prof. Low Wang emphasised, one should be aware that there were very few events of major bleedings overall. No major differences were seen in intracranial or fatal bleeding between the groups.

Similarly, fragile patients had a higher rate of ischaemic events and TIMI major bleedings, but there was no difference in intracranial or fatal bleeding. Overall, there was still a 6:1 benefit-risk ratio.

Although both diabetes and fragility are associated with a higher percentage of patients achieving the primary outcome and higher bleeding risk, therapy with rivaroxaban should be considered in these subgroups because its efficacy and safety of rivaroxaban are consistent regardless of these factors.

1. Low Wang C. VOYAGER PAD – rivaroxaban in symptomatic PAD with and without comorbid diabetes. Latest science in special populations, ESC Congress 2021, 27–30 August.
2. Low Wang C. Risk profile and the efficacy and safety of rivaroxaban in fragile PAD patients after revascularisation: Insights from VOYAGER PAD. Latest science in special populations, ESC Congress 2021, 27–30 August.

COVID-19 and the Heart

Rivaroxaban improves clinical outcomes in discharged COVID-19 patients

The multicentre MICHELLE trial found that thromboprophylaxis with rivaroxaban over 5 weeks after discharge was beneficial for COVID-19 patients. Individuals with moderate-to-high risk scores for venous thromboembolism (VTE) showed a 67% risk reduction in a composite of clinical outcomes [1].

"There is a clear indication of in-hospital pharmacological thromboprophylaxis for every patient with COVID-19 after bleeding risk assessment; however, there is no consensus on the role of extended thromboprophylaxis," stated Prof. Eduardo Ramacciotti (Santa Casa School of Medicine, Brazil) [1–3]. Thus, the MICHELLE trial (NCT04662684) was designed to shed light on a possible advantage of prolonged antithrombotic prophylaxis with rivaroxaban for COVID-19 patients after discharge from hospital [1].

The randomised controlled, open-label study analysed 318 patients that were allocated to treatment with 10 mg of rivaroxaban daily or placebo over 35 days. The enrolled adult COVID-19 patients had previously received a standard-dose thromboprophylaxis during hospital stay of ≥3 days and presented with a thromboembolism risk score of ≥4, or a risk score of 2/3 in combination with an initial D dimer >500 ng/mL in the modified IMPROVE VTE risk score. The primary outcome was a composite of several clinical and imaging-based parameters at day 35 (i.e. symptomatic VTE, VTE-related death, VTE detected at bilateral lower limb venous duplex scan and CT-pulmonary angiogram, symptomatic arterial thromboembolism, myocardial infarction, non-haemorrhagic stroke, major adverse limb event, and cardiovascular death). The baseline characteristics were balanced overall in the study arms. The mean age was between 56.4 and 57.8 years, around 40% were women, and 37.7–38.4% had an IMPROVE VTE score of ≥4.

The results of the primary outcome revealed a relative risk reduction of 67% for those receiving rivaroxaban (RR 0.33; 95% CI 0.13–0.90; P=0.03) compared with placebo. The corresponding number needed to treat equalled 16. "When we broke down the components of the primary outcome, we could see that the primary outcome occurrence was basically driven by pulmonary embolism, either asymptomatic or symptomatic, and fatal pulmonary embolism in the control group," said Prof. Ramacciotti. Regarding safety, no major bleedings happened in either study arm, and event rates were low in both groups, even for a composite of adverse consequences due to major, non-major, and other bleedings (rivaroxaban 2.51%; placebo 1.89%).

"In patients discharged after hospitalisation due to COVID-19 with increased IMPROVE VTE score, thromboprophylaxis with rivaroxaban 10 mg once daily for 35 days improved clinical outcomes without increasing bleeding, compared with no out-of-hospital anticoagulation," Prof. Ramacciotti concluded.

1. Ramacciotti E. The Michelle trial: Medically ill hospitalised patients for COVID-19 thrombosis extended prophylaxis with rivaroxaban therapy. Late-breaking trials – COVID 19, ESC Congress 2021, 27–30 August.
2. Spyropoulos AC, et al. J Thromb Haemost. 2020;18(8):1859–1865.
3. Moores LK, et al.Chest. 2020;158(3):1143–1163.

COVID-19: Thromboembolic risk reduction with therapeutic heparin dosing

The risk of major thromboembolic events in hospitalised COVID-19 patients was significantly reduced when thromboprophylaxis was given at a therapeutic dose of heparin instead of standard therapy. Within the HEP-COVID trial, this advantage was only found in non-ICU patients [1].

"Despite universal thromboprophylaxis with standard heparin, 'breakthrough thrombotic events' occur," stated Prof. Alex Spyropoulos (Northwell Health, NY, USA). The HEP-COVID trial (NCT04401293) was designed to investigate thromboprophylaxis in high-risk, hospitalised patients with COVID-19, as the optimal regime for this population is still unknown. The study included 253 adult patients hospitalised with COVID-19 requiring oxygen supplementation, who had either D-dimer of 4x the upper normal limit or a sepsis-induced coagulopathy (SIC) score of ≥4. They were randomised to 2 subgroups of ICU and non-ICU treatment and further to subcutaneous enoxaparin 1mg/kg twice daily or standard-of-care / intermediate-dose heparin (SOC group) over 10+4 days or until discharge. Before discharge, a compression ultrasound was performed of the lower extremities. The primary composite

efficacy endpoint consisted of venous thromboembolism (VTE), arterial thromboembolic events (ATE), and all-cause mortality after 30 days. The principal safety outcome was major bleeding.

The mean age of the modified intention-to-treat population was 66 years. Over 50% of participants were men, and the mean body mass index was around 30 kg/m2. Among the most frequent VTE risk factors were a history of VTE or cancer. The mean SIC score was 2.3 in both groups and D-dimer in the enoxaparin arm was 3,837 ng/mL versus 3,183 ng/mL in the SOC group. About one-third of the study subjects required ICU care and the mean length of in-patient care was close to 12 days.

The results demonstrated a relative risk (RR) of 0.68 (95% CI 0.49–0.96; P=0.0273) for the primary composite efficacy outcome with a 13.2 absolute risk reduction in favour of enoxaparin. Looking at ICU and non-ICU strata, the effect was driven by the non-ICU group with a RR of 0.46 (95% CI 0.27–0.81; P=0.0042), yet no significance in the ICU stratum (RR 0.92; 95% CI 0.62–1.39). The components VTE+ATE also revealed a significant risk reduction of 63% (P=0.0003), but all-cause mortality showed only a numerical between-group difference.

"The principal safety outcome of major bleeding occurred in 2 patients in the standard-dose group and 6 patients in the therapeutic-dose group with an incidence of 1.6% and 4.7%, and this was not statistically significant," said Prof. Spyropoulos. In summary, he stressed that this trial was the first to show the superiority of a therapeutic dose of low-molecular-weight heparin over SOC thromboprophylaxis with overall low rates of bleeding in those selected for the trial.

1. Spyropoulos AC. The HEP-COVID Trial. Latest Science in COVID-19, ESC Congress 2021, 27–30 August.

Long COVID symptoms – Is ongoing cardiac damage the culprit?

Residual symptoms after COVID-19 are of global interest. Prolonged cardiopulmonary alterations are common past 4 weeks after infection; however, patients' complaints do not always match objective findings [1].

"The National Institute for Health and Care Excellence in the United Kingdom has defined long COVID as a persistence of symptoms beyond 4 weeks and has subdivided this into 2 categories: the 'ongoing symptomatic phase,' which refers to symptoms up to 12 weeks and the 'post-COVID-19 syndrome,' which refers to symptoms that persist beyond 12 weeks," stated Dr Betty Raman (John Radcliffe Hospital, University of Oxford, UK) [1]. There is a vast multiplicity of patient-reported COVID-19 symptoms beyond 4 weeks, among which fatigue is most common [2–4]. Other widespread symptoms include shortness of breath, headaches, brain fog, and cardiopulmonary symptoms such as chest pain or palpitations. A poorly understood but not rare syndrome in long COVID is postural orthostatic tachycardia. Long COVID patients not only experience a marked reduction in quality of life, but a substantial part is also not able to return to work and normal exercise [1].

Results from a meta-analysis of over 4,000 hospitalised COVID-19 patients, found some sort of myocardial injury in about one-third of patients [5]. An imaging investigation demonstrated, for example, wall motion impairment, right ventricular dysfunction, and pericardial effusion in hospitalised COVID-19 patients [6]. Retrospective cohort studies revealed a 3-fold risk of major adverse cardiac events and a 2 to 3-fold risk of cardiomyopathy in patients after the acute phase of COVID-19 versus a comparator group without COVID-19 [7,8]. There is also prospective data from several smaller cohort studies with hospitalised COVID-19 patients [1]. "All of them do reveal some burden, albeit small, of ongoing cardiac damage in patients being followed up," Dr Raman explained. Data from cardiopulmonary exercise testing has furthermore found that the main aetiology for reduced exercise tolerance seems to stem from a muscular cause, not cardiopulmonary.

In summary, Dr Raman pointed out that post-acute cardiovascular sequelae are seen for up to 6 months from infection. "However, there does appear to be a dissociation between symptoms experienced by patients and objective abnormalities on cardiopulmonary testing and in the long-term, one must be vigilant of complications of long COVID, in particular the effects of chronic inflammation and endothelial dysfunction, but also the rising epidemic of obesity due to inability of people to become physically active and return to work. This highlights the need for more aggressive risk factor modification in patients recovering from COVID-19," she concluded.

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2. Ghosn J, et al. Clin Microbiol Infect. 2021;27(7):1041.e1-1041.e4.
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6. Giustino G, J Am Coll Cardiol. 2020;76(18):2043–2055.
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ESC Spotlight of the Year 2021: Sudden Cardiac Death

Breathing problems: the most frequently reported symptom before cardiac arrest

A Danish study revealed that breathing problems, not chest pain, are the most frequently reported symptom by patients with subsequent out-of-hospital cardiac arrest [1]. The most common symptom pair consisted of breathing problems and paleness. Yet, patients with breathing issues were less likely than those reporting chest pain to receive an emergency medical response.

Early identification of individuals at risk of out-of-hospital cardiac arrest remains challenging because little is known about the symptoms presented when contacting an emergency unit prior to an event. The study presented by Mr Filip Gnesin (Nordsjaellands Hospital, Denmark) intended to take a closer look at this important issue.

Mr Gnesin and his team identified patients from the Danish Cardiac Arrest Registry who experienced an out-of-hospital cardiac arrest from 2016 through 2018 and had phoned the Copenhagen Emergency Medical Services up to 24 hours before their arrest. The researchers systematically evaluated these pre-arrest calls and noted symptoms reported by the caller, who could be the patient or a bystander. Finally, these patients were linked to nationwide databases to collect other data such as survival.

Of 4,071 patients with an out-of-hospital cardiac arrest, 481 (11.8%) made a pre-arrest call. The median age of patients with pre-arrest calls was 74 years and 40.1% were women. The most reported symptoms were breathing problems (59.4%), confusion (23.0%), unconsciousness (20.2%), chest pain (19.5%), and paleness (19.1%).

The most commonly occurring symptom pairs were breathing problems in combination with paleness (14.5%), confusion (14.1%), unconsciousness (13.5%), sweating (13.0%), and chest pain (11.9%), respectively. An urgent medical response was dispatched in 68.7% of calls reporting breathing problems compared with 83.0% reporting chest pain.

Mr Gnesin said: "More than 10% of patients experiencing an out-of-hospital cardiac arrest had a phone call to the emergency medical services up to 24 hours before their arrest either made by themselves or a bystander. Breathing difficulty was the most common complaint and much more common than chest pain. Despite this, compared to chest pain, patients with breathing issues were less likely to receive emergency medical help and more likely to die within 30 days after the arrest. These findings indicate that breathing problems are an underrated warning sign of cardiac arrest" [2].

Mr Gnesin concluded that creating awareness of breathing problems as a common early symptom of cardiac arrest may contribute, together with more research, to identifying more characteristics specific to cardiac arrest so that early intervention might be possible.

1. Gnesin F. Symptoms reported in calls to emergency medical services 24 hours prior to out-of-hospital cardiac arrest. Session: Coronary Artery Disease (Chronic)/ Chronic Coronary Syndromes ePosters. ESC Congress 2021, 27–30 August.
2. Gnesin F. Press conference 'Preventing sudden cardiac death.' ESC Congress 2021, 27–30 August.

Lay responders can improve survival in out-of-hospital cardiac arrest

Swift assistance of lay responders to cardiac arrest victims is associated with improved survival: patients in a recent study had a 28% higher likelihood of being alive at 30 days. This result can be explained by higher cardiopulmonary resuscitation and defibrillator use [1,2].

"Our study suggests that when emergency medical services incorporate members of the public into their systems, cardiac arrest victims are more likely to survive," said study author Dr Martin Jonsson (Karolinska Institute, Sweden).

Lay-responder systems (e.g. dispatch of the public to a cardiac arrest) are increasingly implemented around Europe, in particular in indications where time is of key importance. Previously, studies have found an association between these systems and survival after out-of-hospital cardiac arrest. A Swedish study including 8,513 cardiac arrests at 4 different

study sites (i.e. 2 in Sweden, 1 in the Netherlands, and 1 in Switzerland) supported the usefulness of this approach.

The study included all out-of-hospital cardiac arrests occurring in 2016 through 2019 in 4 areas. Data from the 2 most populous regions in Sweden (i.e. Stockholm, Västra Götaland) were collected from the Swedish cardiopulmonary resuscitation (CPR) register. Information from North Holland, the Netherlands, was obtained from the ARREST database, and the Ticino Cardiac Arrest Registry was used for Ticino, Switzerland.

The system for dispatch of lay responders worked as follows: the public could sign up as lay responders via a mobile phone app/internet. They were then registered in a database and the system tracks their location. When the dispatch centre receives a call about a cardiac arrest, the dispatcher can activate the system. If lay responders are near the cardiac arrest location, they receive a notification from the app with instructions to run and perform CPR or find an automated external defibrillator (AED).

Activation of lay-responders was compared with a control group regarding the use of CPR, use of AEDs, and 30-day survival following a cardiac arrest in the community. The analyses were adjusted for age, sex, location, witnessed status, emergency medical services response time, and time of day.

In 3,410 of a total of 8,513 cases, lay responders were dispatched to the victim using a smartphone application, while a lay responder was not dispatched in 5,103 cases. When lay responders were dispatched, there was a 28% higher chance of CPR (risk ratio [RR] 1.28; 95% CI 1.12–1.45; P=0.0002), and a 56% higher chance of AED use (RR 1.56; 95% CI 1.02–2.39; P=0.0390). "Most importantly, we saw a 28% higher likelihood of being alive at 30 days," Dr Jonsson said during the presentation (95% CI 1.10–1.48; P=0.0012).

"Our study demonstrates the benefits of including the general public in the emergency response to a suspected cardiac arrest. Every second counts in these situations and lives can be saved with rapid use of AEDs and CPR," Dr Jonsson concluded.

1. Jonsson M. Dispatch of lay-responders is associated with bystander cardiopulmonary resuscitation, bystander defibrillation and 30-day survival following an out-of-hospital cardiac arrest. ESC Congress 2021, 27–30 August.
2. Jonsson M. Dispatch of lay-responders is associated with bystander cardiopulmonary resuscitation, bystander defibrillation and 30-day survival following an out-of-hospital cardiac arrest. Press conference, ESC Congress 2021, 27–30 August.