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ESC Congress 2020

European Society of Cardiology

29 AUGUSTUS - 1 SEPTEMBER 2020

PEER-REVIEWED CONFERENCE REPORT

ESC 2020 Clinical Practice Guidelines

This year's Guidelines cover non-ST-segment elevation acute coronary syndromes, atrial fibrillation, adult congenital heart disease, and sports cardiology and physical activity in patients with cardiovascular disease.

read more on PAGE 3

EMPEROR-Reduced Trial

EMPEROR-Reduced showed that empagliflozin reduces cardiovascular death or hospitalisation for heart failure in patients with a reduced ejection fraction, as compared with placebo, regardless of diabetes.

read more on PAGE 8

AKCEA-APOCIII-L_{Rx} Study

The AKCEA-APOCIII-L_{Rx} study showed that targeting apoC-III mRNA resulted in dose-dependent reductions of apoC-III, triglyceride levels, and other atherogenic lipoproteins compared with placebo in patients with hypertriglyceridaemia.

read more on PAGE 18

MEDICOM MEDICAL PUBLISHERS

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

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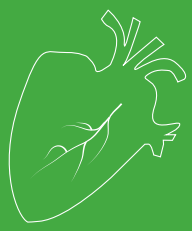

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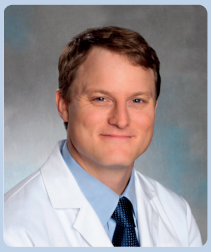
Letter from the Editor



Prof. Marc Peter Bonaca

Dear Reader,

We thank you for your attention and know this is a challenging time for all. It is also a challenging time for the dissemination of cutting-edge science and guidelines as we are forced to transition to novel forms of communication.

In this regard, we hope that the following report is a helpful and informative summary of the recent European Society of Cardiology Virtual Congress. You will find a summary of recent guideline updates, summaries of selected Hot Line Presentations, and key updates on COVID and Cardiovascular disease.

We hope that this reference helps to keep you informed and we are grateful for your readership. Most of all, we hope that all of you, your families and loved ones are safe and healthy and we thank all of you helping to care for the global community for your contributions.

Best,
Marc P. Bonaca

Biography

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

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

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

Conflict of Interest Statement:
Grant support to BWH from AstraZeneca, MedImmune, Merck, Pfizer
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2020 ESC Clinical Practice Guidelines

2020 Atrial Fibrillation Guidelines

The new 2020 atrial fibrillation (AF) guidelines advocate that patients with AF and their medical team should practice shared decision-making regarding treatment choices. The new guidelines were a collaboration between the European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS).

The new 2020 guidelines were presented at the ESC Congress 2020 by Prof. Gerhard Hindricks (Guidelines Task Force Chair; Heart Centre Leipzig, Germany), and published simultaneously online in the *European Heart Journal* [1,2]. "Patients want to be involved in decisions about their care and their preferences should be respected," said Prof. Hindricks.

Central to the new guidelines is an individualised approach to the Atrial fibrillation Better Care (ABC) pathway:

- **A**nticoagulation/Avoid stroke refers to anticoagulation medication for the prevention of stroke where risk is indicated.
- **B**etter symptom management strives to manage heart rate and heart rhythm with medications and procedures.
- **C**ardiovascular and Comorbidity optimisation covers high blood pressure management and lifestyle changes including smoking cessation, weight management, and exercise.

An individualised care plan should be formulated to address patient preferences and physical characteristics. Prevention of stroke remains an essential component for most patients. This year's update gave additional consideration to specific patient characteristics. For example, pregnant women with AF taking warfarin should avoid vaginal delivery, and endurance athletes are at higher risk for AF, but those participating in contact sports should avoid oral anticoagulants due to bleeding risk.

Accumulating data concerning population screening to identify people with previously undiagnosed AF suggests pre-symptomatic intervention to prevent stroke in these individuals is effective. Wearable devices (e.g. smart wrist bands coupled with smartphone apps) are a remarkable breakthrough, but the guidelines caution that many are not clinically validated for AF detection. A summary of changes in the guidelines from 2016 to 2020 are summarised in the Table.

1. Hindricks G, et al. 2020 ESC Guidelines on Atrial Fibrillation. 2020 New ESC Guidelines, ESC Congress 2020, 29 Aug.
2. Hindricks G, et al. Eur Heart J. 2020;ehaa612.DOI:10.1093/eurheartj/ehaa612.

Table: Summary of AF Guideline changes from 2016 to 2020 [2]

Recommendations about integrated AF management			
2020	**Class[a]**	**2016**	**Class[a]**
To optimise shared decision-making about specific AF treatment option(s) in consideration, it is recommended that: • Physicians inform the patient about advantages/limitations and benefit/risks associated with considered treatment option(s); and • Discuss the potential burden of the treatment with the patient and include the patient's perception of treatment burden in the treatment decision.	I	Placing patients in a central role in decision-making should be considered in order to tailor management to patient preferences and improve adherence to long-term therapy.	IIa
Recommendations for the prevention of thrombo-embolic events in AF			
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up.	I	Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding.	IIa
In patients on VKAs with low time in INR therapeutic range (e.g. TTR<70%), recommended options are: • Switching to a NOAC but ensuring good adherence and persistence with therapy; or • Efforts to improve TTR (e.g. education/counseling and more frequent INR checks).	I IIa	AF patients already on treatment with a VKA may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contraindications to NOAC (e.g. prosthetic valve).	IIb

AAD, antiarrhythmic drug; AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OSA, obstructive sleep apnoea; PCI, percutaneous coronary intervention; PRO, patient-reported outcome; VKA, vitamin K antagonist therapy.

[a]Class of recommendation.

Continue on the next page

Table: Summary of AF Guideline changes from 2016 to 2020 [2] (continued)

Recommendations for rhythm control/catheter ablation of AF			
2020	**Class[a]**	**2016**	**Class[a]**
AF catheter ablation after drug therapy failure			
AF catheter ablation for PV1 is recommended for rhythm control after one failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with: • Paroxysmal AF; • Persistent AF *without* major risk factors for AF recurrence; or • Persistent AF *with* major risk factors for AF recurrence.	I	Catheter or surgical ablation should be considered in patients with symptomatic persistent or long-standing persistent AF refractory to AAD therapy to improve symptoms, considering patient choice, benefit and risk, supported by an AF Heart Team.	IIa
First-line therapy			
AF catheter ablation: • Is recommended to reverse LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, independent of their symptom status. • Should be considered in selected AF patients with HFrEF to improve survival and reduce HF hospitalisation.	I IIa	AF ablation should be considered in symptomatic patients with AF and HFrEF to improve symptoms and cardiac function when tachycardiomyopathy is suspected.	IIa
Techniques and technologies			
Complete electrical isolation of the pulmonary veins is recommended during all AF catheter-ablation procedures.	I	Catheter ablation should target isolation of the pulmonary veins using radiofrequency ablation or cryothermy balloon catheters.	IIa
If patient has a history of CTI-dependent atrial flutter or if typical atrial flutter is induced at the time of AF ablation, delivery of a CTI lesion may be considered.	IIb	Ablation of common atrial flutter should be considered to prevent recurrent flutter as part of an AF ablation procedure if documented or occurring during the AF ablation.	IIa
Lifestyle modifications and other strategies to improve outcomes of ablation			
Weight loss is recommended in obese patients with AF, particularly those who are being evaluated to undergo AF ablation.	I	In obese patients with AF, weight loss together with management of other risk factors should be considered to reduce AF burden and symptoms.	IIa
Recommendations for stroke risk management peri-cardioversion			
In patients with AF undergoing cardioversion, NOACs are recommended with at least similar efficacy and safety as warfarin.	I	Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter.	IIa
Recommendations for stroke risk management peri-catheter ablation			
After AF catheter ablation, it is recommended that: • Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation; and • Long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure.	I	All patients should receive oral anticoagulation for at least 8 weeks after catheter ablation.	IIa
Recommendations for long-term antiarrhythmic drugs			
Amiodarone is recommended for long-term rhythm control in all AF patients, including those with HFrEF. However, owing to its extracardiac toxicity, other AADs should be considered first whenever possible.	I	Amiodarone is more effective in preventing AF recurrences than other AAD, but extracardiac toxic effects are common and increase with time. For this reason, other AAD should be considered first.	IIa
Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with AF			
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.	I	BP control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding.	IIa
Physical activity should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote AF.	IIa	Moderate regular physical activity is recommended to prevent AF, while athletes should be counseled that long-lasting intense sports participation can promote AF.	I
Optimal management of OSA may be considered, to reduce AF incidence, AF progression, AF recurrences, and symptoms.	IIb	OSA treatment should be optimised to reduce AF recurrence and improve AF treatment results.	IIa
Recommendation for stroke prevention in AF patients after ICH			
In AF patients at high risk of ischaemic stroke, (re-)initiation of OAC, with preference for NOACs over VKAs in NOAC-eligible patients, should be considered in consultation with a neurologist/stroke specialist after: • A trauma-related ICH; • Acute spontaneous ICH (which includes subdural, subarachnoid, or intracerebral haemorrhage), after careful consideration of risks and benefits.	IIa	Catheter or surgical ablation should be considered in patients with symptomatic persistent or long-standing persistent AF refractory to AAD therapy to improve symptoms, considering patient choice, benefit and risk, supported by an AF Heart Team.	IIb
Recommendations for postoperative AF			
Long-term OAC therapy to prevent thrombo-embolic events may be considered in patients at risk for stroke with post-operative AF after cardiac surgery, considering the anticipated net clinical benefit of OAC therapy and informed patient preferences.	IIb	Long-term anticoagulation should be considered in patients with AF after cardiac surgery at risk for stroke, considering individual stroke and bleeding risk.	IIa

AAD, antiarrhythmic drug; AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OSA, obstructive sleep apnoea; PCI, percutaneous coronary intervention; PRO, patient-reported outcome; VKA, vitamin K antagonist therapy.

[a]Class of recommendation.

Reprinted from Hindricks G, et al. Eur Heart J. 2020 [Epub ahead of print]. Copyright 2020, with permission from Oxford University Press.

2020 Non-ST-Segment Elevation Acute Coronary Syndromes Guidelines

In their first update in 5 years, Prof. Jean-Phillippe Collet (Pitié-Salpêtrière Hospital, France) presented the European Society of Cardiology guidelines on non-ST-segment elevation acute coronary syndromes (NSTE-ACS) [1]. He stressed 5 key points: (1) the new workflow for diagnosis of suspected NSTE-ACS; (2) non-invasive imaging in low-risk patients; (3) a new risk stratification model; (4) the timing of antithrombotic treatment; and (5) the 3 new sections on myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA), spontaneous coronary artery dissection, and quality indicators in NSTE-ACS care.

The guidelines were published online simultaneously in the *European Heart Journal* together with a companion question-and-answer document [2,3]. The guidelines are aimed at the treatment and diagnosis for "patients with acute chest discomfort but no persistent ST-segment elevation ACS, who exhibit ECG changes that may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudo-normalisation of T waves; or their ECG may be normal" [2].

Firstly, the new streamlined workflow for diagnosis of suspected NSTE-ACS includes the use of high-sensitivity troponin. Prof. Collet remarked, "In these guidelines, we have implemented the use of high-sensitivity troponins everywhere with the 0/1-hour algorithm, when available." Recent evidence summarised in the guidelines supports the value of high-sensitivity troponin to signal MI within 2 hours.

Secondly, non-invasive imaging in low-risk patients should be the preferred approach. "If you rule out the diagnosis of MI but there is still a suspicion of underlying disease, you may use CT angiography. It's very helpful," Prof. Collet said. It avoids invasive angiography in around 30% of cases, and has moved up to a class I, level A recommendation to exclude ACS when there is a low-to-intermediate likelihood of coronary artery disease and troponin tests or ECG results are normal or inconclusive.

Thirdly, risk stratification has been overhauled to simplify timely triage and intervention. The previous 4 risk groups have been simplified to 3. Patients who require a trip to the cath lab within 2 hours fall into the *very-high risk* group. *High-risk* patients require invasive management within 24 hours—during this time CT angiography may be performed. *Low-risk* patients are those for whom invasive management is selective.

The fourth take-home message presented by Prof. Collett is the timing of antithrombotic treatment, possibly the most controversial of the changes. The advice is to "avoid pre-treatment" when invasive management will be performed anyway, Prof. Collet stressed. "This is an important recommendation. We do not want to use potent $P2Y_{12}$ inhibitors when the diagnosis of NSTEMI is not established in terms of coronary anatomy." The evidence from several trials were pooled to support this recommendation.

Lastly, entirely new guidelines have been prepared for special populations, including MINOCA, spontaneous coronary artery dissection, and quality indicators in NSTE-ACS care, including diagnosis, care pathway, and medical intervention. To summarise, new key recommendations for NSTE-ACS are listed below [2]. The major changes in recommendations from 2015 to 2020 are summarised in the Table.

Diagnosis

- As an alternative to the ESC 0/1-hour algorithm, it is recommended to use the ESC 0/2-hour algorithm with blood sampling at 0 and 2 hours, if a high-sensitivity cardiac troponin (hs-cTn) test with a validated 0/2-hour algorithm is available.
- It is not recommended to routinely measure additional biomarkers, such as CK, CK-MB, h-FABP, or copeptin, in addition to hs-cTn for diagnostic purposes.

Risk stratification

- To gain prognostic information, measuring BNP or NT-proBNP plasma concentrations should be considered.

Antithrombotic treatment

- Prasugrel should be considered for NSTE-ACS patients who proceed to PCI.
- Routine pre-treatment with a $P2Y_{12}$ receptor inhibitor is not recommended for patients in whom the coronary anatomy is not known and for whom early invasive management is planned.
- In patients with NSTE-ACS who cannot undergo an early invasive strategy, pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered depending on bleeding risk.
- De-escalation of $P2Y_{12}$ inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may

be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgement or guided by platelet function testing or CYP2C19 genotyping depending on the patient's risk profile and availability of respective assays.

- In patients with AF (CHA_2DS_2-VASc score ≥1 in men and ≥2 in women), after a short period of triple antithrombotic therapy (up to 1 week from the acute event), DAT is recommended as the default strategy using a DOAC at the recommended dose for stroke prevention and single oral antiplatelet agent (preferably clopidogrel).
- Discontinuation of antiplatelet treatment in patients treated with OACs is recommended after 12 months.
- DAT with an OAC and either ticagrelor or prasugrel may be considered as an alternative to triple antithrombotic therapy with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used.

Invasive treatment

- An early invasive strategy within 24 hours is recommended in patients with any of the following high-risk criteria:
  - diagnosis of NSTEMI;
  - dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischaemia;
  - transient ST-segment elevation; or
  - a GRACE risk score of >140.
- A selective invasive strategy after appropriate ischaemia testing or detection of obstructive CAD by coronary CT angiography is recommended in low-risk patients.
- Delayed, as opposed to immediate, angiography should be considered in haemodynamically stable patients without ST-segment elevation successfully resuscitated after an out-of-hospital cardiac arrest.
- Complete revascularisation should be considered in NSTE-ACS patients without cardiogenic shock and with multivessel CAD.
- Complete revascularisation during index PCI may be considered in NSTE-ACS patients with multivessel disease.
- Fractional flow reserve-guided revascularisation of non-culprit NSTE-ACS lesions may be used during index PCI.

1. Collet JP, et al. 2020 ESC Guidelines on non-ST-segment evaluation acute coronary syndromes. 2020 New ESC Guidelines, ESC Congress 2020, 30 Aug.
2. Collet JP, et al. Eur Heart J. 2020;ehaa575. DOI:10.1093/eurheartj/ehaa575.
3. Barbato E, et al. Eur Heart J, ehaa601.DOI:10.1093/eurheartj/ehaa601.

Table: Key changes from 2015 to 2020 in NSTE-ACS recommendations. Modified from [2]

2015	Class	2020	Class
Diagnosis			
A rapid rule-out protocol at 0 and 3 hours is recommended if hs-cTn tests are available.	I	A rapid rule-out and rule-in protocol with blood sampling at 0 and 3 hours should be considered if an hs-cTn test with a validated 0/3-hour algorithm is available.	IIa
MDCT coronary angiography should be considered as an alternative to invasive angiography to exclude ACS when there is a low-to-intermediate likelihood of CAD and when cardiac troponin and/or ECG are inconclusive.	IIa	Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding.	I
Rhythm monitoring up to 24 hours or PCI (whichever comes first) *should be considered* in NSTEMI patients at low risk for cardiac arrhythmias.	IIa	Rhythm monitoring up to 24 hours or to PCI (whichever comes first) is *recommended* in NSTEMI patients at low risk for cardiac arrhythmias.	I
Rhythm monitoring for >24 hours should be considered in NSTEMI patients at intermediate-to-high risk for cardiac arrhythmias.	IIa	Rhythm monitoring for >24 hours is recommended in NSTEMI patients at increased risk for cardiac arrhythmias.	I
Risk assessment			
It is recommended to use established risk scores for prognosis estimation.	I	GRACE risk score models should be considered for estimating prognosis.	IIa
Pharmacological treatments			
Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/h for up to 4 hours after the procedure) is recommended as an alternative to UFH plus GP IIb/IIIa inhibitors during PCI.	I	Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients at high risk of ischaemic events and without increased risk of major or life-threatening bleeding.	IIb
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	IIb	Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/h for up to 4 hours after the procedure) is recommended as an alternative to UFH plus GP IIb/IIIa inhibitors during PCI.	IIa

ACS, acute coronary syndromes; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ECG, electrocardiogram/electrocardiography; GP, glycoprotein; GRACE, Global Registry of Acute Coronary Events; hs-cTn, high-sensitivity cardiac troponin; i.v., intravenous; MDCT, multidetector computed tomography; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

2020 Sports Cardiology and Exercise in Cardiovascular Patients Guidelines

Moderate physical activity is necessary and safe for people with cardiovascular (CV) conditions, according to the first sports and exercise guidelines released by the European Society of Cardiology. Clinicians should encourage people with heart disease to exercise moderately most days so that they accumulate at least 150 minutes of exercise per week. Those who are obese, diabetic, or have high blood pressure may benefit most from strength-building exercise such as lifting weights at least 3 times a week, plus moderate or vigorous aerobic exercise. Endurance sports and competitive athletes may require special monitoring and modifications.

Prof. Antonio Pelliccia (Institute of Sports Medicine and Science, Italy) presented the new ESC Guidelines, which will be the benchmark recommendations for future guidelines [1]. The guidelines have included the most current research in exercise in patients with CV disease. Where possible, these new guidelines align with existing ESC Guidelines for the investigation, risk assessment, and management of individuals with cardiovascular diseases to promote exercise programmes and sports participation.

In the first sections, evidence is weighed regarding recreation and competitive sports in the general population, with estimated incidences of CV death in both younger and older athletes with no history of health problems or putative congenital heart syndromes.

The bulk of the guidelines examine evidence of exercise in the clinical setting in patients with CV diseases. The chance of exercise triggering cardiac arrest or heart attack is extremely low, but clinicians should aim to monitor activity intensity and suggest modifications when needed. Special attention is also given to data supporting recommendations for individuals with obesity, hypertension, dyslipidaemia, or diabetes. Importantly, an entire concluding chapter is dedicated to gaps in existing evidence, which may serve as hypothesis-generating for future research.

1. Pelliccia A, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. 2020 New ESC Guidelines, ESC Congress 2020, 31 Aug.
2. Pelliccia A, et al. Eur Heart J. 2020;ehaa605. DOI:10.1093/eurheartj/ehaa605/5898937.

2020 Adult Congenital Heart Disease Guidelines

The spectrum of adult congenital disease is so broad that the European Society of Cardiology 2020 guidelines for the management of adult congenital heart disease has a particularly challenging scope. Prof. Helmut Baumgartner (University Hospital Münster, Germany) presented the new guidelines, which were simultaneously published online in the *European Heart Journal* [1,2].

Below are the 10 most relevant changes in the 2020 version of these guidelines.

1. The 2020 guidelines recommend that for low- and intermediate-risk patients with repaired simple lesions and precapillary pulmonary hypertension, treatment should include initial oral combination therapy or sequential combination therapy. High-risk patients should receive initial combination therapy including parenteral prostanoids (Class I).
2. Initial endothelin receptor antagonist monotherapy should be considered for Eisenmenger patients with reduced exercise capacity (i.e. 6-minute hall walk distance <450 m), followed by step-up combination therapy if patients do not improve (Class IIa).
3. There are new recommendations for atrial septal defect (ASD) closure in patients with Qp:Qs >1.5:1 based on calculated pulmonary vascular resistance, stratified by Wood units.

4. Individuals with lesions associated with pulmonary valve regurgitation and no native outflow tract should receive catheter intervention if anatomically feasible (Class I).
5. Pulmonary valve replacement should be considered in asymptomatic patients with severe pulmonary regurgitation and/or right ventricular (RV) outflow tract obstruction, in the presence of progressive RV dilatation to RV end-systolic volume index ≥80 mL/m^2, and/or RV end-diastolic volume index ≥160 mL/m^2, and/or progression of tricuspid regurgitation to at least moderate (Class IIa).
6. There are new updated recommendations for tricuspid valve replacement for severe tricuspid regurgitation in congenitally corrected transposition of the great arteries.
7. Patients with Fontan circulation should receive regular liver imaging (i.e. ultrasound, computed tomography, cardiac magnetic resonance) (Class IIa). Anticoagulation is a recommended addition to treatment when the individual has, or has had, atrial thrombus, atrial arrhythmias, or thromboembolic events (Class I). Furthermore, women with a Fontan circulation and any complication are counselled against pregnancy (Class I).
8. Endothelin receptor antagonists and phosphodiesterase-5 inhibitors may be considered in selected patients with Fontan circulation and elevated pulmonary pressures/resistance in the absence of elevated ventricular end-diastolic pressure (Class IIa).
9. Selected tetralogy of Fallot patients with multiple risk factors for sudden cardiac death (i.e. left ventricular dysfunction, non-sustained, symptomatic ventricular tachycardia [VT], QRS duration >180 ms, extensive RV scarring on CMR, or inducible VT at programmed electrical stimulation) should be considered as candidates for an implantable cardioverter-defibrillator (Class IIa).
10. An implantable cardioverter-defibrillator may also be considered in patients with advanced single or systemic RV dysfunction (ejection fraction systemic RV <35%) in the presence of additional risk factors (Class IIb).

In conclusion, substantial practice-changing changes have been implemented into the new guidelines for many manifestations of adult congenital heart disease.

1. Baumgartner H, et al. 2020 ESC Guidelines on adult congenital heart disease. 2020 New ESC Guidelines. ESC Congress 2020, 1 Sept.
2. Baumgartner H, et al. Eur Heart J. 2020;ehaa554.DOI:10.1093/eurheartj/ehaa554.

Hot Line Presentations

SGLT2 inhibitor improves cardiovascular outcomes in heart failure patients

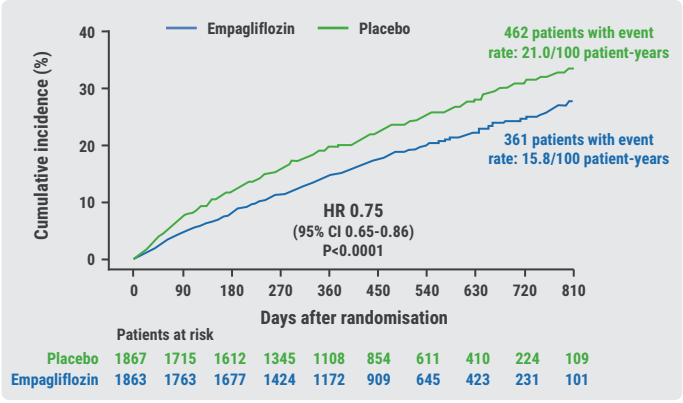
Findings from the phase 3 EMPEROR-Reduced trial show that the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin reduces cardiovascular death or hospitalisation for heart failure (HF) in patients with a reduced ejection fraction, as compared with placebo [1-3]. These cardiovascular improvements were independent of the presence of diabetes mellitus.

Previously, the DAPA-HF trial showed that the SGLT2 inhibitor dapagliflozin reduced the risk of cardiovascular death or hospitalisation for heart failure in patients with reduced ejection fraction, regardless of whether they had diabetes [4]. That trial primarily enrolled patients (n=4,744) with mild-to-moderate degrees of left ventricular systolic dysfunction and increases in natriuretic peptide levels. More evidence was needed on the effects of SGLT2 inhibitors in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.

The EMPEROR-Reduced trial, presented by Dr Milton Packer (Baylor University Medical Center, USA), evaluated empagliflozin in 3,730 patients with mild, moderate, or severe chronic heart failure (i.e. class II, III, or IV) due to poor systolic function of the left ventricle (ejection fraction ≤40%) with or without diabetes type 2 diabetes (49.8% had diabetes). They randomly received empagliflozin (10 mg once daily) or placebo, in addition to appropriate treatments for heart failure.

The primary outcome of EMPEROR-Reduced was a composite of cardiovascular death or hospitalisation for worsening heart failure. During a median of 16 months, a primary outcome event occurred in 19.4% of patients in the empagliflozin group and in 24.7% in the placebo group (HR 0.75; 95% CI 0.65-0.86; P<0.001; see Figure). This effect of empagliflozin was consistent in patients regardless of the presence of diabetes.

Figure: Primary endpoint analysis for EMPEROR-Reduced [1]



The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group compared with the placebo group (P<0.001). In addition, empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.

The EMPEROR-Reduced results confirm the DAPA-HF outcome that SGLT2 inhibitors have clinically important benefits and are well tolerated. According to Dr Packer, the findings from both trials now provide compelling evidence that SGLT2 inhibitors should be added to currently recommended treatments for patients with and without diabetes with chronic heart failure and a reduced ejection fraction.

1. Packer M. EMPEROR-Reduced: Empagliflozin in heart failure with a reduced ejection fraction, with and without diabetes. Hot Line 1, ESC Congress 2020, 29 Aug.
2. Packer M, et al. New Engl J Med. 2020; August 29. DOI: 10.1056/NEJMoa2022190.
3. Zannad F, et al. The Lancet. 2020; August 30. DOI: 10.1016/S0140-6736(20)31824-9.
4. McMurray JJ, et al. N Engl J Med. 2019 Nov 21;381(21):1995-2008.

First-in-class cardiac myosin inhibitor effective in obstructive hypertrophic cardiomyopathy

Recent results from the multicentre, phase 3 EXPLORER-HCM trial highlight the benefits of a disease-specific treatment for patients with obstructive hypertrophic cardiomyopathy. Mavacamten, a first-in-class cardiac myosin inhibitor, improved exercise capacity, left ventricular outflow tract (LVOT) obstruction, NYHA functional class, and health status in this patient population [1,2].

Hypertrophic cardiomyopathy is characterised by primary left ventricular hypertrophy. Core pathophysiological features include hypercontractility, diastolic dysfunction, and dynamic LVOT obstruction. Patients with obstructive hypertrophic cardiomyopathy are often symptomatic and can have atrial fibrillation, heart failure, and malignant ventricular arrhythmias.

Current treatment for obstructive hypertrophic cardiomyopathy is symptomatic and includes β-blockers, non-dihydropyridine calcium channel blockers, and disopyramide. However, these drugs do not address the underlying molecular mechanisms of hypertrophic cardiomyopathy and do not modify its natural history. In addition, they are often inadequate or poorly tolerated. Invasive septal reduction therapy, such as surgical septal myectomy and alcohol septal ablation, can effectively help patients with drugrefractory symptoms. However, these invasive procedures carry inherent risks and require expertise that is not universally available. So, effective pharmacological treatments for obstructive hypertrophic cardiomyopathy are urgently needed.

To this aim, the randomised, double-blind, placebo-controlled EXPLORER-HCM trial evaluated the efficacy and safety of mavacamten in patients with hypertrophic cardiomyopathy with an LVOT gradient of ≥50 mmHg and NYHA class II-III symptoms. Participants from 68 centres in 13 countries were randomly assigned to mavacamten (n=123) or placebo (n=128). The primary endpoint was a composite functional endpoint designed to specifically demonstrate benefit both in symptoms and function, namely a ≥1.5 mL/kg/min increase in peak oxygen consumption (pVO_2) and at least 1 NYHA class reduction or a ≥3.0 mL/kg/min pVO2 increase without NYHA class worsening.

Prof. Iacopo Olivotto (Azienda Ospedaliera Universitaria Careggi, Italy) presented the results, showing that 37% of patients in the mavacamten group versus 17% in the placebo group met the primary endpoint (difference +19.4; 95% CI 8.7-30.1; P=0.0005) after 30 weeks. Safety was similar between groups, and treatment-emergent adverse events were generally mild.

In this first randomised phase 3 trial with positive results in patients with obstructive hypertrophic cardiomyopathy, mavacamten not only improved functional capacity and LVOT gradient but also symptoms and key aspects of health status (secondary endpoints). These results highlight the benefits of diseasespecific treatment in hypertrophic cardiomyopathy.

1. Olivotto I. EXPLORER-HCM: Efficacy and safety of mavacamten in adults with symptomatic obstructive hypertrophic cardiomyopathy. Hot Line 1, ESC Congress 2020, 29 Aug.
2. Olivotto I, et al. Lancet 2020, August 29. Doi.org/10.1016/S0140-6736(20)31792-X.

Reduced cardiovascular outcomes with early rhythm control

Early initiation of rhythm control reduced cardiovascular outcomes in patients with early atrial fibrillation (AF) and comorbid cardiovascular conditions compared with contemporary, evidence-based usual care [1]. Although early rhythm control was associated with more adverse events, the overall safety of both strategies was comparable and did not affect the number of nights spent in hospital per year. These findings of the EAST-AFNET 4 trial were published simultaneously in the *New England Journal of Medicine* [2].

Even with current guideline-based management, approximately 5% of AF patients suffer acute coronary syndrome, heart failure, stroke, or cardiovascular death per year [2]. There is an increased risk of cardiovascular complications during the first year after AF is diagnosed. Researchers have hypothesised that rhythm-control therapy may be more effective when delivered early, but evidence supporting this notion was lacking in patients with confirmed AF.

The EAST-AFNET 4 trial, presented by Prof. Paulus Kirchhof (University Heart & Vascular Center Hamburg, Germany), attempted to address this unmet need. The EAST-AFNET 4 investigators enrolled 2,789 patients with early AF (median time since diagnosis 36 days) and cardiovascular conditions, who randomly received either early rhythm control or usual care. Early rhythm control included treatment with antiarrhythmic drugs or AF ablation after randomisation, while usual care limited rhythm control to the management of AF-related symptoms. The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalisation with worsening heart failure or acute coronary syndrome.

After a median follow-up of 5.1 years, the trial was stopped prematurely for efficacy at the third interim analysis because a first primary-outcome event occurred in 249 of the patients assigned to early rhythm control (3.9 per 100 person-years) and in 316 patients assigned to usual care (5.0 per 100 person-years) (HR 0.79; 95% CI 0.66-0.94; P=0.005; see Table).

Table: Efficacy Outcomes of the EAST-AFNET 4 trial [2]

Outcome	Early Rhythm Control	Usual Care	Treatment Effect
First primary outcome - events/person-yr (incidence/100 person-yr)	249/6399 (3.9)	316/6332 (5.0)	0.79 (0.66 to 0.94)
Components of first primary outcome - events/person-yr (incidence/100 person-yr)			
Death from cadiovascular causes	67/6915 (1.0)	94/6988 (1.3)	0.72 (0.52 to 0.98)
Stroke	40/6813 (0.6)	62/6856 (0.9)	0.65 (0.44 to 0.97)
Hospitalisation with worsening of heart failure	139/6620 (2.1)	169/6558 (2.6)	0.81 (0.65 to 1.02)
Hospitalisation with acute coronary syndrome	53/6762 (0.8)	65/6816 (1.0)	0.83 (0.58 to 1.19)

P=0.005 for the between group comparison

The EAST-AFNET 4 trial showed that early rhythm-control therapy was associated with a lower risk of cardiovascular outcomes than usual care among patients with early AF and cardiovascular conditions. These results have the potential to inform the future use of rhythm control therapy, further improving the care of patients with early AF.

1. Kirchhof P. EAST – AFNET 4: Effects of early rhythm control therapy in patients with atrial fibrillation. Hot Line 1, ESC Congress 2020, 29 Aug.
2. Kirchhof P, et al. New Engl J Med. 2020, August 29. DOI: 10.1056/NEJMoa2019422.

Trimetazidine after successful PCI not associated with fewer cardiac events

Patients undergoing a successful percutaneous coronary intervention (PCI) for angina and non-ST-segment elevation acute coronary syndromes (NSTE-ACS) have good long-term outcomes using optimal medical therapy. Routine use of trimetazidine did not reduce cardiac events in this patient population in the ATPCI trial [1]. These results, presented at the ESC Congress by Prof. Roberto Ferrari (University of Ferrara, Italy), were simultaneously published in *The Lancet* [2].

Little evidence is available regarding the prognostic benefits of antianginal drugs, such as trimetazidine, after PCI. Trimetazidine improves energy metabolism of the ischaemic myocardium and might improve outcomes and symptoms

of patients who recently had a PCI. The ATPCI study aimed to evaluate the long-term potential benefits and safety of trimetazidine added to standard guideline-recommended medical treatment in in a population of 6,007 patients who had had a recent PCI for stable angina, unstable angina, or non-ST-segment elevation myocardial infarction.

After a median follow-up of 47.5 months, trimetazidine did not improve the primary composite efficacy endpoint of cardiac death, hospital admission for cardiac event, or recurrence or persistence of angina incidence compared with placebo (23.3 vs 23.7%; HR 0.98; P=0.73). Also, no significant differences were observed in the incidence of the components of the primary endpoint between the treatment groups. Similar results were obtained in sub analyses by elective or urgent PCI. Long-term use of trimetazidine was not associated with any safety issues.

The routine use of oral trimetazidine 35 mg twice daily over several years in patients receiving optimal medical therapy after successful angioplasty does not influence the outcome or recurrence of angina. These findings should be taken into account when considering the place of trimetazidine in clinical practice.

1. Ferrari R. TPCI - Trimetazidine in angina patients with recent successful percutaneous coronary intervention: a randomized, double-blind, placebo-controlled trial. Hot Line 2 session, ESC Congress 2020, 30 Aug.
2. Ferrari R, et al. Lancet 2020, August 30. DOI: 10.1016/S0140-6736(20)31790-6.

POPular TAVI: Aspirin-only antiplatelet strategy?

The POPular TAVI trial continues to fuel debate and challenge current concepts of antiplatelet treatment after transcatheter aortic valve implantation (TAVI). Reported by Dr Jorn Brouwer (St Antonius Hospital, the Netherlands), the trial concluded that aspirin alone after TAVI reduces bleeding events significantly and does not increase the rate of thromboembolic events [1,2].

The ESC Guidelines recommend adding clopidogrel to aspirin therapy for 3-6 months after TAVI to mitigate thromboembolic risk. However, the POPular TAVI trial questioned the benefit of antiplatelet therapy with clopidogrel and hypothesised that patients taking aspirin alone compared with patients taking aspirin plus clopidogrel for 3 months would have a reduced bleeding rate at 1-year post-TAVI. To this end, 2 cohorts were investigated: patients not on oral anticoagulants (cohort A) and patients on chronic oral anticoagulation (cohort B). Dr Brouwer presented the results of cohort A.

A total of 665 patients without an indication for oral anticoagulation were randomised to aspirin alone (n=331) or aspirin plus 3 months of clopidogrel (n=334). The co-primary outcomes were all bleeding (i.e. procedural and non-procedural) together with non-procedural bleeding. In addition, POPular TAVI was designed to determine whether aspirin alone is non-inferior to aspirin plus clopidogrel with respect to 2 secondary outcomes at 1 year.

The co-primary outcomes were met; aspirin alone resulted in a significantly lower incidence of bleeding compared with aspirin plus clopidogrel at 1 year (15.1% vs 26.6%, respectively; RR 0.57; 95% CI 0.42-0.77; P=0.001) [1]. Non-procedural bleeding also favoured the aspirin only arm (15.1% vs 24.9%; RR 0.61; 95% CI 0.44-0.83; P=0.005). Likewise, the secondary outcome on bleeding and thromboembolic events indicated that aspirin alone was superior in this study (23.0% vs 31.1%; RR 0.74; 95% CI for non-inferiority 0.57- 0.95 P<0.001; 95% CI for superiority 0.57-0.95; P=0.04). The thromboembolic events secondary outcome was also significant for aspirin (9.7% vs9.9%; RR 0.98; 95% CI for non-inferiority 0.62-1.55; P=0.004).

Dr Brouwer concluded: "The trial showed that aspirin alone should be used in patients undergoing TAVI who are not on oral anticoagulation and have not recently undergone coronary stenting."

1. Brouwer J, et al. POPULAR TAVI- Aspirin with or without clopidogrel after transcatheter aortic valve implantation. Hot Line 2 session, ESC Congress 2020, 30 Aug.
2. Brouwer J, et al. N Engl J Med. 2020; Aug 30.DOI:10.1056/NEJMoa2017815.

Reduced NT-proBNP in HFpEF with sacubitril/valsartan

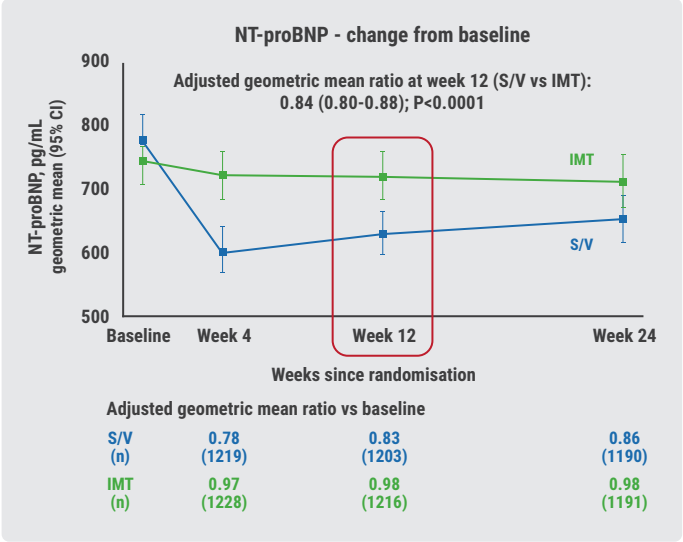
Although sacubitril/valsartan was associated with significant reductions in N-terminal pro-b-type natriuretic peptide (NT-proBNP) in patients with heart failure with preserved ejection fraction (HFpEF) compared with individual RAAS blockade at 12 weeks, no significant difference in 6-minute walk distance or secondary endpoints were found in the phase 3 PARALLAX study [1].

Previously, the PARAGON-HF trial showed that sacubitril/valsartan improves morbidity and mortality outcomes of patients with HFpEF [2]. The PARALLAX study aimed to build on these previous clinical data by assessing the effects of sacubitril/valsartan in heart failure patients (n=2,572) with an ejection fraction >40%, evidence of left ventricular

hypertrophy or left atrial enlargement, elevated NT-proBNP, and optimised treatment of comorbidities [1]. The PARALLAX study also compared sacubitril/valsartan to individualised therapy but with a different co-primary endpoint. While PARAGON-HF assessed a composite of hospitalisation for heart failure and cardiovascular death, PARALLAX assessed the biomarker NT-proBNP and 6-minute walk test, since loss of exercise capacity is a key indicator of heart failure.

Results of the PARALLAX study were presented by principal investigator Prof. Burkert Pieske (Charité University Medicine Berlin, Germany). At 12 weeks, sacubitril/valsartan was associated with a 16% greater reduction in NT-proBNP level compared with individualised medical therapy, including the angiotensin-converting enzyme (ACE) inhibitor enalapril, the angiotensin receptor blocker valsartan, or placebo (adjusted geometric mean ratio 0.84; P<0.0001; see Figure). At week 24, no significant difference was observed in the second co-primary endpoint, the 6-minute walk distance (adjusted mean difference -2.5 m; P=0.42). In accordance with this, there was also no significant difference in secondary endpoints, i.e. change of Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary scores (least square means difference 0.52; P=0.48) or NYHA class (OR 1.01; P=0.93), between the study arms at week 24.

Figure: Primary outcomes of PARALLAX [1]



IMT, individualised medical therapy; NT-proBNP, N-terminal pro-b-type natriuretic peptide; S/V, sacubitril/valsartan.

Post-hoc and exploratory analyses

A post-hoc analysis of the PARALLAX trial, comparing data from the study drug and placebo groups, showed that patients in the sacubitril/valsartan group had a 51% reduced risk of first hospitalisation due to heart failure at 24 weeks (HR 0.49; P=0.005). Also, the composite endpoint of time to death due to heart failure or heart failure hospitalisation in days was in favour of the study drug (HR 0.64; P=0.034).

However, a prespecified exploratory analysis of renal impact suggested sacubitril/valsartan was associated with a decline in estimated glomerular filtration rate (eGFR) compared with individualised medical therapy over 24 weeks (adjusted mean difference 1.10 mL/min/1.73 m2).

1. Pieske B. PARALLAX: Sacubitril/valsartan versus individualized RAAS blockade in patients with HFpEF. Hot Line 2 session, ESC Congress 2020, 30 Aug.
2. Solomon SD, et al. N Engl J Med 2019; 381:1609-1620.

DAPA-CKD: Dapagliflozin improves CKD survival ± diabetes

The DAPA-CKD trial found that the sodium glucose co-transporter 2 (SGLT2) inhibitor dapagliflozin reduced worsening kidney function or death from renal or cardiovascular disease by 39% [1]. DAPA-CKD assessed the effects of dapagliflozin on chronic kidney disease (CKD) in patients with and without type 2 diabetes mellitus (T2DM). The reductions of this primary endpoint were 36% and even 50% in patients with and without diabetes, respectively.

Previously, the CREDENCE study showed that the SGLT2 inhibitor canagliflozin was associated with a 30% risk reduction in renal decline and cardiovascular and renal death among patients with T2DM [2]. In the DAPA-CKD trial, a third of participants did not have diabetes. This raises the prospect of using dapagliflozin to prevent kidney failure in a new group of patients.

Prof. Hiddo Heerspink (University of Groningen, the Netherlands) presented the results of the randomised, double-blind, placebo-controlled DAPA-CKD trial, which enrolled 4,304 patients from 386 centres in 21 countries to assess the impact of dapagliflozin 10 mg versus placebo alongside standard of care (i.e. ACE inhibitor or ARB) [1]. Participants had a urinary albumin to creatinine ratio of ≥200 mg/g and an estimated glomerular filtration rate (eGFR) between 25-75 mL/min/1.73 m2. Average age was 61.8 years, 66.9% were male, and 67.5% had T2DM. The primary endpoint was a composite of sustained decline in eGFR of ≥50%, end-stage renal disease, and renal or cardiovascular mortality.

During a median follow-up of 2.4 years, 197 primary events occurred with dapagliflozin compared with 312 events with placebo (HR 0.61; 95% CI 0.51-0.72; P<0.0001). The primary endpoint was 36% lower with dapagliflozin versus placebo (HR 0.64) in patients with T2DM and 50% lower in patients without diabetes (HR 0.50). In addition, dapagliflozin was associated with a significant reduction in in the 3 secondary endpoints compared with placebo, namely:

- a 31% reduction in risk of all-cause mortality (HR 0.69; P=0.0035);
- a 29% reduction in hospitalisation for heart failure or cardiovascular death (HR 0.71; P=0.0089); and
- a 44% reduction in worsening function or death from kidney failure (HR 0.56; P<0.0001).

In the placebo group, slightly more patients had serious adverse events than in the dapagliflozin group (33.9% vs 29.5%). The rate of patients that discontinued the drug due to an adverse event was similar (5.7% vs 5.5%). No patients in the dapagliflozin group and 2 patients in the placebo arm experienced diabetic ketoacidosis. Additionally, no severe hypoglycaemia or diabetic ketoacidosis were reported in patients without T2DM.

Results from DAPA-CKD affirm the role of SGLT2 inhibition in the prevention of renal decline and kidney failure. These results show that SGLT2 inhibitors have clearly moved beyond their initial use as glucose-lowering therapies in T2DM.

1. Heerspink H. Dapagliflozin in patients with chronic kidney disease: DAPA-CKD. Hot Line 2 Session, ESC Congress 2020, 30 Aug.
2. Perkovic V, et al. N Engl J Med 2019; 380:2295-2306.

Low-dose colchicine reduces CV death and ischaemic events in coronary disease

Results from the LoDoCo2 trial have shown that low-dose colchicine reduces the risk of cardiovascular death, myocardial infarction, ischaemic stroke, or ischaemia-driven coronary revascularisation in patients with chronic coronary disease [1,2]. Together with findings from the COLCOT trial, these results confirm that colchicine on top of standard medical therapy can reduce cardiovascular events in patients with chronic and acute coronary syndromes.

Colchicine, primarily used in the treatment of gout, inhibits several inflammatory pathways in the pathogenesis of atherosclerosis. Earlier results from the open-label LoDoCo trial including 532 patients with chronic coronary disease suggested that low-dose colchicine (0.5 mg once daily) was safe and effective for preventing cardiovascular (CV) events [3]. The double-blind, randomised-controlled LoDoCo2 trial aimed to confirm these results in a larger cohort and assessed whether colchicine 0.5 mg prevents CV events in 6,528 patients with chronic coronary disease [2].

Participants were clinically stable for ≥6 months and had no advanced renal disease, heart failure, or severe heart disease. From the 6,528 participants who started the open-label run-in period, 5,522 patients were tolerant, clinically stable, and willing to proceed. They were randomised 1:1 to receive either placebo or colchicine 0.5 mg once daily on top of lipid lowering and antithrombotic therapy.

The primary endpoint was a composite of CV death, myocardial infarction, ischaemic stroke, or ischaemia-driven coronary revascularisation. After a median follow-up of 29 months, colchicine reduced the risk of this primary composite endpoint by 31% compared with placebo (HR 0.69; 95% CI 0.57-0.83; P<0.001). The effects of colchicine were seen to occur early and continued to accrue over time.

The effect of colchicine extended to the following secondary endpoints:

- CV death, myocardial infarction, or ischaemic stroke (HR 0.72; P=0.007);
- myocardial infarction or ischaemia-driven coronary revascularisation (HR 0.67; P<0.001);
- CV death or myocardial infarction (HR 0.71; P=0.010);
- ischaemia-driven coronary revascularisation (HR 0.75; P=0.012); and
- myocardial infarction (HR 0.70; P=0.014).

No significant effects with colchicine compared with placebo were found for the following individual secondary endpoints: ischaemic stroke, all-cause mortality, and CV death.

The effect of colchicine was consistent across several prespecified subgroups, including men and women, patients who were younger or older than 65 years, and those with and without a history of hypertension. Both treatment arms showed similar rates in serious adverse events.

The LoDoCo2 trial provides convincing evidence that colchicine, if tolerated, is effective and safe for secondary prevention in chronic coronary syndromes. It is important to use a low dose of colchicine because up to 10% of patients will not tolerate the drug, mainly due to gastrointestinal side

effects. Dr Stefan Nidorf (Heart Care Western Australia, Australia) warned that one should be aware of potential side effects and interactions.

1. Nidorf SM. LoDoCo2 low-dose colchicine in coronary disease. Hot Line 3 session, ESC Congress 2020, 31 Aug.
2. Nidorf SM, et al. New Engl J Med. 2020, August 31. DOI: 10.1056/NEJMoa2021372.
3. Nidorf SM, et al. J Am Coll Cardiol. 2013;61(4):404-410.

Similar outcomes sPESI and HESTIA for pulmonary embolism triage

The HOME-PE trial suggests that the simplified Pulmonary Embolism Severity Index (sPESI) score, recommended by European guidelines, and the HESTIA criteria, recommended by U.S. guidelines, performed equally well in selecting which haemodynamically stable patients with acute pulmonary embolism are eligible for home management [1].

Selected haemodynamically stable patients with acute pulmonary embolism could be treated at home. However, controversy persists about the optimal referral strategies and eligibility criteria for outpatient care. European guidelines recommend the PESI or sPESI score to assess the risk of all-cause mortality. If proper follow-up and anticoagulant therapy can be provided, patients with an sPESI score of 0 can be treated at home. The American guidelines do not require a predefined score and advise using pragmatic criteria, for example those formulated in the HESTIA Study.

Prof. Pierre-Marie Roy (University Hospital of Angers, France) presented the randomised, open-label, non-inferiority HOME-PE trial. The 1,974 normotensive participants, who presented to the emergency department with acute pulmonary embolism, were randomised to either the pragmatic HESTIA method or sPESI triage group:

- in the sPESI group, patients were eligible for outpatient care if the score was 0 (n=986); and
- in the HESTIA group, they were eligible for outpatient care if all 11 criteria were negative (n=984).

Patients who were not eligible for outpatient care were hospitalised. In both groups, the treating physician could overrule the decision on treatment location for medical or social reasons.

The primary endpoint, a composite of recurrent venous thromboembolism (VTE), major bleeding, and all-cause mortality within 30 days, occurred in 3.8% of patients in the HESTIA group and 3.6% in the sPESI group (P=0.005 for non-inferiority). Of note, a greater proportion of patients were eligible for home care using sPESI compared with HESTIA (48.4 vs 39.4%). However, the treating physician overruled sPESI more often than HESTIA. Consequently, a similar proportion of patients were discharged within 24 hours for home treatment (38.4 and 36.6%, respectively; P=0.42). In patients managed at home, the rate of complications was low.

The HOME-PE study showed that the HESTIA approach was non-inferior to the sPESI score as triaging strategy for outpatient care of patients with acute pulmonary embolism. Prof. Roy concluded, "These results support outpatient management of acute pulmonary embolism patients using either the HESTIA method or the sPESI score. In hospitals organised for outpatient management, both triaging strategies enable more than a third of pulmonary embolism patients to be managed at home with a low rate of complications."

1. Roy P-M. HOME-PE - Hospitalisation or Outpatient Management of PE Patients - HESTIA vs. Simplified PESI. Hot Line 3 session, ESC 2020 E-Congress, 31 Aug.

Antihypertensives also reduce CV risk in people with normal blood pressure

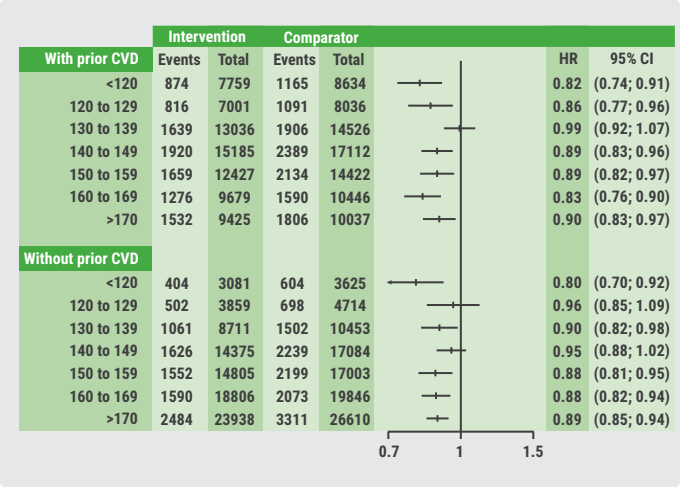
New research from the BPLTTC study supports the notion that people with normal blood pressure can prevent heart attacks and strokes by taking prophylactic blood pressure-lowering medication. These data will add fuel to the discussion of current and future blood pressure thresholds.

Prof. Kazem Rahimi (University of Oxford, UK) presented a meta-analysis of data from 348,854 participants from 48 clinical trials [1]. Participants were divided according to whether they had a prior diagnosis of cardiovascular disease, then further stratified according to 1 of 7 blood pressure groups ranging from systolic blood pressures of <120 mmHg up to ≥170 mmHg at study entry.

With an average follow-up of 4 years, the investigators noted a progressive reduction in relative risk of major cardiovascular events by roughly 10% for each 5 mmHg reduction in systolic blood pressure, including for the lowest systolic blood pressure category of <120 mmHg, in both primary and secondary prevention settings (see Figure). Risk for stroke, ischaemic heart disease, heart failure, and death from cardiovascular disease were reduced by 13%, 7%, 14%,

and 5%, respectively. The benefits were similar along the entire range of systolic blood pressures.

Figure: Effects on major cardiovascular events for each 5 mmHg SBP reduction, by CVD status at baseline [1]



	Intervention		Comparator			
With prior CVD	**Events**	**Total**	**Events**	**Total**	**HR**	**95% CI**
<120	874	7759	1165	8634	0.82	(0.74; 0.91)
120 to 129	816	7001	1091	8036	0.86	(0.77; 0.96)
130 to 139	1639	13036	1906	14526	0.99	(0.92; 1.07)
140 to 149	1920	15185	2389	17112	0.89	(0.83; 0.96)
150 to 159	1659	12427	2134	14422	0.89	(0.82; 0.97)
160 to 169	1276	9679	1590	10446	0.83	(0.76; 0.90)
>170	1532	9425	1806	10037	0.90	(0.83; 0.97)
Without prior CVD						
<120	404	3081	604	3625	0.80	(0.70; 0.92)
120 to 129	502	3859	698	4714	0.96	(0.85; 1.09)
130 to 139	1061	8711	1502	10453	0.90	(0.82; 0.98)
140 to 149	1626	14375	2239	17084	0.95	(0.88; 1.02)
150 to 159	1552	14805	2199	17003	0.88	(0.81; 0.95)
160 to 169	1590	18806	2073	19846	0.88	(0.82; 0.94)
>170	2484	23938	3311	26610	0.89	(0.85; 0.94)

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; SBP, systolic blood pressure.

In his interpretation of these results, Prof. Rahimi cautioned that "the fact that the relative effects are similar for everyone does not mean that everyone should be treated." He went on to suggest the decision to prescribe blood pressure-lowering medication should not be based simply on a prior diagnosis of cardiovascular disease or an individual's current blood pressure, but rather used as "risk-modifying treatments for prevention of incident or recurrent cardiovascular events, regardless of blood pressure values at baseline."

1. Rahimi K, et al. BPLTTC – Blood pressure lowering for prevention of cardiovascular events across different levels of blood pressure. Hot Line 3 session, ESC 2020 E-Congress, 31 Aug.

COVID-19: Continuing versus suspending ACE inhibitors and ARBs

Heart patients hospitalised with COVID-19 can safely continue ACE inhibitors and ARBs. The phase 4 BRACE CORONA trial showed that suspending these drugs for 30 days did not impact the number of days alive and out of hospital at 30 days compared with continuation of these drugs [1].

There is conflicting observational data available about the potential impact of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with COVID-19. On the one hand, preclinical research has raised concerns about their safety in patients with COVID-19, because ACE inhibitors and ARBs could increase ACE2 receptor expression and enhance viral entry, leading to worse outcomes. On the other hand, preliminary data has suggested that renin-angiotensin-aldosterone system (RAAS) inhibitors could benefit patients with COVID-19 by decreasing acute lung damage and preventing pulmonary inflammation. In addition, the expression of membrane-bound ACE2, the functional receptor for the SARS-CoV-2 virus, may increase due to upregulation in patients using ACE inhibitors and ARBs.

The phase 4, randomised BRACE CORONA trial enrolled 659 hospitalised adult patients who used ACE inhibitors or ARBs and had a confirmed diagnosis of COVID-19 and compared 2 strategies: suspending or continuing these drugs for 30 days. The results were presented by Prof. Renato Lopes (Duke University, USA).

The primary outcome, the number of days alive and out of hospital at 30 days, was 21.9 days in patients who suspended ACE inhibitors and ARBs and 22.9 days in patients who continued these drugs. The proportion of patients alive and out of hospital by the end of 30 days was 91.8% in the suspending group, and 95% in the continuing group. A similar 30-day mortality rate was seen (2.8% vs 2.7%, respectively; HR 0.97).

This is the first randomised trial comparing the impact of continuing and suspending ACE inhibitors and ARBs in patients hospitalised with COVID-19. In these patients, suspending these drugs for 30 days did not impact the number of days alive and out of hospital. Because these data indicate that there is no clinical benefit from routinely interrupting these medications in hospitalised patients with mild-to-moderate COVID-19, they should generally be continued for those with an indication.

1. Lopes R. BRACE CORONA: Continuing vs. Suspending ACE Inhibitors and ARBs in COVID-19. Hot Line 4 session, ESC Congress 2020, 31 Aug.

Drug initiation strategy not associated with increased use of oral anticoagulants

The IMPACT-AFib trial found that a single educational mailing to atrial fibrillation (AF) patients and their healthcare providers did not increase uptake of oral anticoagulant at 1 year compared with usual care [1].

Prof. Sean Pokorney (Duke University, USA) presented the IMPACT-AFib trial, a prospective, randomised, educational

intervention trial. The trial assessed whether early education on stroke prevention in AF for patients and their healthcare providers could increase the use of oral anticoagulants.

A total of 47,333 AF patients (average age of 78 years) who had an indication for oral anticoagulation, defined as a CHA_2DS_2-VASc score of ≥2, randomly received either an early educational intervention (i.e. one mailing at the start of the trial) or a delayed educational intervention (i.e. usual care). Participants had not been prescribed an anticoagulant in the prior 12 months and had not been admitted to hospital for bleeding in the prior 6 months.

The primary endpoint, the proportion of patients starting on oral anticoagulation during the 12-month follow-up period, occurred in 9.89% of patients in the intervention group and in 9.80% in the usual care group (adjusted odds ratio 1.01).

However, numerically more patients initiated oral anticoagulants early after the mailing. This raises the question whether multiple mailings or further contact could be beneficial. Additional trials are needed to assess feasibility of patient consent and repeat patient interactions.

1. Pokorney S. IMPACT-Afib Implementation of Stroke Prevention in Atrial Fibrillation. Hot Line 4 session, ESC Congress 2020, 31 Aug.

Restrictive blood transfusion non-inferior and cost-effective strategy

According to results of the REALITY trial, the largest randomised trial in this setting, restrictive blood transfusion has no negative impact on clinical outcomes compared with a more liberal strategy in anaemic patients with an acute myocardial infarction (AMI) [1]. Incidence rates of infections and acute lung injury were lower with the restrictive strategy.

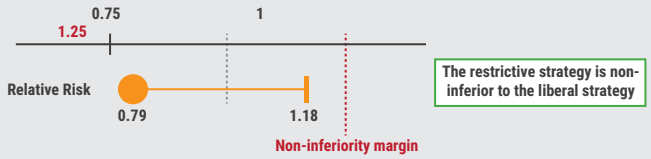
The optimal transfusion strategy in anaemic patients with AMI is unclear. Observational studies have reported that blood transfusion may be associated with a higher mortality rate in patients with AMI, and only 2 small randomised trials have been conducted, with conflicting results.

The REALITY trial enrolled 666 patients (mean age 77 years; 43% female) with AMI and haemoglobin (Hgb) 8-10 g/dL during admission, who were randomised to either a liberal or restrictive red blood cell (RBC) transfusion strategy. In the restrictive strategy, transfusion was withheld unless Hgb was ≤8 g/dL, with a target Hgb 8-10 g/dL (n=324); and in the liberal strategy, a transfusion was given as soon as Hgb was ≤10 g/dL, with a target Hgb >11 g/dL (n=342).

The primary outcome, a composite of all-cause mortality, reinfarction, stroke, and emergency percutaneous coronary intervention (PCI) prompted by ischaemia, occurred in 11.0% of patients who received the restrictive strategy, and in 14.0% of patients who received the liberal strategy (HR 0.77; P<0.05 for non-inferiority; P=0.22 for superiority; see Figure).

Figure: Restrictive strategy non-inferior to liberal strategy in the REALITY trial [1]

PP	Restrictive strategy n=327 n (%)	Liberal strategy n=321 n (%)	Diference (95%CI)	Relative Risk (Restrictive vs Liberal)	One sided 97.5%CI
Mace	36 11.0%	45 14.0%	-3.0% (-8.4%; 2.4%)	0.79	(-inf; 1.18)



IMace, all-cause death, reinfarction, stroke, and emergency revascularisation prompted by ischaemia.

The individual components of the primary outcome occurred in the following percentages of patients in the restrictive versus the liberal transfusion strategy groups:

- All-cause mortality: 5.6% vs 7.7% (P>0.05);
- Recurrent myocardial infarction: 2.1% vs 3.1%; and
- Emergency revascularisation: 1.5% vs 1.9%.

With respect to safety, patients allocated to the restrictive strategy were significantly less likely to develop an infection (0.0% vs 1.5%; P=0.03) or acute lung injury compared with the liberal strategy (0.3% vs 2.2%; P=0.03). Total 30-day hospital costs were €11,051 versus €12,572 (P=0.1).

The REALITY trial supports the use of a restrictive strategy for blood transfusion in AMI patients with anaemia. The restrictive strategy saves blood, is safe, and is at least as effective in preventing 30-day cardiac events compared with a liberal strategy, while saving money. Similar results in favour of a restrictive strategy have been noted for post-cardiac and non-cardiac surgery patients.

1. Steg PG. REALITY - A Trial of Transfusion Strategies for Myocardial Infarction and Anemia. Hot Line 4 session, ESC Congress 2020, 31 Aug.

Late-Breaking Science

Increased mortality with colchicine in patients with ACS

The Australian COPS trial demonstrated that addition of colchicine to standard medical therapy did not significantly affect cardiovascular outcomes at 12 months in patients with acute coronary syndromes (ACS). Colchicine may even be associated with a higher rate of mortality in this patient population [1,2].

Inflammation plays a crucial role in atherosclerosis and ultimately may contribute to the ongoing complications of ACS. The recently published CANTOS trial demonstrated that treatment with the interleukin (IL)-1β inhibitor canakinumab resulted in a reduction in cardiovascular events in ACS patients [3]. Because of its anti-inflammatory properties, colchicine, a commonly used treatment for gout, has recently emerged as a promising novel treatment option for cardiovascular disease. The proposed mechanisms of action of colchicine involve inhibition of innate immunity and modulation of downstream inflammatory cascades, which are pivotal processes involved in the pathogenesis of coronary artery disease (CAD) and thrombotic events of ACS. The previously published COLCOT and LoDoCo trials demonstrated a significant reduction in adverse cardiovascular events in patients with ACS and stable CAD who received colchicine in addition to standard secondary prevention therapies compared with standard medical therapy alone [4,5].

Prof. Jamie Layland (Monash University, Australia) presented the results of the COPS study, which evaluated the potential clinical utility of colchicine among a broad ACS population (n=795) [1]. The primary outcome was a composite of all-cause mortality, ACS, ischaemia-driven (i.e. unplanned) urgent revascularisation, and non-cardioembolic ischaemic stroke.

Over the 12-month follow-up period, there were 24 events in the colchicine group (n=396) compared with 38 events in the placebo group (n=399) (P=0.09). There was a higher rate of total death (8 vs 1; P=0.017) and particularly non-cardiovascular death in the colchicine group (5 vs 0; P=0.024). The rates of reported adverse events were not different (colchicine 23.0% vs placebo 24.3%) and predominantly gastrointestinal (colchicine 23.0% vs placebo 20.8%).

In conclusion, the addition of colchicine to standard medical therapy in the COPS trial did not significantly affect cardiovascular outcomes at 12 months in an ACS population and was associated with a higher rate of mortality. Despite these results, exploratory analysis suggested a potential role for colchicine to improve cardiovascular outcomes. Further clinical research is required before colchicine can be safely administered in ACS patients.

1. Layland J. COPS Trial - Colchicine to improve cardiovascular outcomes in ACS patients. Late-Breaking Science, ESC Congress 2020, 29 Aug.
2. Tong DC, et al. Circulation 2020, 29 Aug.
3. Ridker PM, et al. Am Heart J. 2011 Oct;162(4):597-605.
4. Tardif J-C, et al. N Engl J Med 2019; 381:2497-2505.
5. Nidorf SM, et al. J Am Coll Cardiol. 2013; 61(4):404-410.

Rivaroxaban protects limbs and ischaemic events in CAD-PAD patients

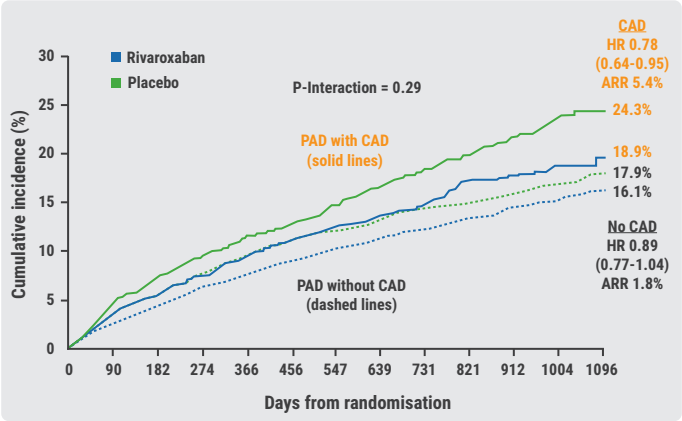
A new subanalysis from the VOYAGER PAD trial showed that rivaroxaban significantly reduced the risk of adverse limb ischaemia and cardiovascular events in patients with coronary artery disease (CAD) concomitant to symptomatic peripheral artery disease (PAD) after peripheral artery revascularisation [1]. Safety in the CAD subgroup of patients in this trial was also favourable.

Initial results from the multicentre, randomised, double-blind VOYAGER PAD trial (n=6,564) were recently published in the *New England Journal of Medicine* [2]. The subanalysis presented at the ESC Congress 2020 by Prof. William Hiatt (University of Colorado, USA) focused on the patients with concomitant CAD (n=2,067). Patient characteristic analysis revealed that the subgroup of patients who had CAD were more likely to have concomitant carotid disease and heart failure, were older, and were more burdened with cardiovascular risk factors, including hypertension, diabetes, and hyperlipidaemia. The primary endpoint of the subanalysis was a composite of acute limb ischaemia, major amputation of vascular aetiology, acute myocardial infarction, ischaemic stroke, and cardiovascular death.

At 3 years, the primary endpoint for CAD patients was met (see Figure). Among those with PAD and CAD, the endpoint occurred in 24.3% in the placebo arm versus 18.9% of those in the rivaroxaban arm (HR 0.78; 95% CI 0.64-0.95). In patients

with PAD only, the endpoint occurred in 17.9% in the placebo arm versus 16.1% in the rivaroxaban arm (HR 0.89; 95% CI 0.77-1.04).

Figure: Primary endpoint with rivaroxaban with and without CAD [1]



Regarding safety, the rate of TIMI major bleeding was increased in patients with and without CAD randomised to rivaroxaban versus placebo, but rates of intracranial haemorrhage or fatal bleeding occurred in less than 1% in each group.

In conclusion, Prof. Hiatt noted, "The efficacy and safety of rivaroxaban in PAD are consistent regardless of CAD, with no significant interactions. However, the absolute benefits of rivaroxaban appear greater in those with CAD, particularly for myocardial infarction and ischaemic stroke."

1. Hiatt W, et al. VOYAGER PAD and concomitant coronary artery disease. Hotline session. ESC Congress 2020, 30 Aug.
2. Bonaca MP, et al. N Engl J Med. 2020; DOI: 10.1056/NEJMoa2000052.

Antisense *APOC3* oligonucleotide lowers triglyceride and atherogenic lipoproteins

Targeting apolipoprotein C-III (apoC-III) mRNA may reduce the residual cardiovascular (CV) risk in patients with hypertriglyceridaemia and either established cardiovascular disease (CVD) or high CV risk. This was suggested by the findings of the phase 2 AKCEA-APOCIII-L_{Rx} study, which showed that treatment with this compound resulted in dose-dependent reductions of apoC-III, triglyceride levels, and other atherogenic lipoproteins compared with placebo [1].

Hypertriglyceridaemia is associated with severely increased CV risk in patients who, despite maximal treatment with lipid-lowering therapies, retain elevated lipid profiles. ApoC-III is a crucial regulator of the hepatic uptake of triglyceride-rich lipoproteins and plasma triglyceride levels. In addition, apoC-III may exert pro-atherogenic effects by enhancing vessel wall inflammation. As such, targeting apoC-III is an attractive approach to ameliorate excess triglyceride-rich lipoproteins, such as seen in patients with hypertriglyceridaemia. Indeed, loss-of-function germline mutation in the *APOC3* gene results in reduced levels of triglycerides and triglyceride-rich lipoproteins, increased HDL-cholesterol, and approximately 40% reduction of CVD compared with non-carriers. Epidemiologic studies have demonstrated that apoC-III levels predict CV risk.

Prof. Jean-Claude Tardif (University of Montréal, Canada) presented the placebo-controlled, dose-ranging, phase 2 AKCEA-APOCIII-L_{Rx} study. AKCEA-APOCIII-L_{Rx} is an antisense oligonucleotide targeting hepatic APOC3 mRNA. It is a second-generation GalNAc3-conjugated antisense oligonucleotide that enhances the intracellular hepatic uptake compared with unconjugated antisense oligonucleotides, allowing lower dosing. Eligible patients had fasting triglyceride levels of 200-500 mg/dL and either established CVD or high CV risk. Participants (n=114) were randomised into 4 parallel cohorts with AKCEA-APOCIII-L_{Rx} in different dosing strategies or placebo. The primary endpoint was the mean percentage change in fasting triglyceride levels from baseline to 6 months.

While there was no significant change in triglyceride levels in the placebo group (+6%), there were significant dose-related reductions in triglyceride levels in the AKCEA-APOCIII-L_{Rx} groups compared with the pooled placebo group, namely:

- -23% in 10 mg Q4W group (P=0.004);
- -56%, in 15 mg Q2W (P<0.0001);
- -60% in 10 mg QW (P<0.0001); and
- -60% in 50 mg Q4W (P<0.0001).

The percentage of patients who had triglyceride levels <150 mg/dL at 6 months were as follows:

- 4% in the placebo group;
- 14% in 10 mg Q4W group (P=0.2590);
- 65% in 15 mg Q2W (P<0.0001);
- 76% in 10 mg QW (P<0.0001); and
- 91% in 50 mg Q4W (P<0.0001).

The percentage change in secondary endpoints apoC-III, VLDL-c, and non-HDL-cholesterol showed significant dose-dependent reductions with AKCEA-APOCIII-L_{Rx} as well

as increases in HDL-cholesterol and ApoA1 with AKCEA-APOCIII-L_{Rx} compared with placebo.

The incidence of treatment-emergent adverse events (TEAE) was 83.3% in the pooled placebo group and ranged from 77.3% to 95.7% in the AKCEA-APOCIII-L_{Rx} treated groups. TEAEs leading to discontinuation did not change between placebo and AKCEA-APOCIII-L_{Rx} arms. There were no clinically significant effects on platelet counts, liver function, or kidney function by AKCEA-APOCIII-L_{Rx}.

Treatment with AKCEA-APOCIII-L_{Rx} resulted in dose-dependent reductions in apoC-III in up to 74% of patients and in dose-dependent reductions of triglyceride levels in up to 62% of patients compared with placebo. In addition, this compound showed favourable safety and tolerability profile. These results suggest that targeting *APOC3* mRNA may reduce the residual CV risk in patients with hypertriglyceridaemia.

1. Tardif J-C. Antisense oligonucleotide targeting apolipoprotein C-III (AKCEA-APOCIII-L_{Rx}) to lower triglycerides and atherogenic lipoproteins in patients with hypertriglyceridemia and cardiovascular disease. Lipids session, ESC Congress 2020, 29 Aug.

Antisense ANGPTL3 lowers triglycerides

Reduction of *ANGPTL3* mRNA levels with antisense oligonucleotide vupanorsen significantly lowered plasma triglyceride levels and other atherogenic lipoproteins in diabetic patients with hepatic steatosis and mild hypertriglyceridaemia. In addition, vupanorsen had a favourable safety and tolerability profile.

Prof. Daniel Gaudet (University of Montréal, Canada) presented the results of the multicentre, double-blind, placebo-controlled, dose-ranging phase 2 study [1]. Type 2 diabetes patients (n=105) with hepatic steatosis and fasting triglyceride levels >150 mg/dL were included in 3 dosing strategy cohorts (both dose and timing were variables). Within each cohort, participants were randomised 3:1 to vupanorsen or placebo. The primary endpoint was percentage change from baseline in fasting triglyceride levels at week 24.

The primary outcome was met. In the pooled placebo group, triglyceride change increased by a mean of 16%, whereas triglyceride dropped by 36% in the 40 mg vupanorsen every 4 weeks group (P=0.03), by 53% in the 80 mg every 4 weeks group (P<0.0001), and by 47% in the 20 mg once weekly group (P=0.0009). The secondary endpoints of percentage change in ANGPTL3, total cholesterol, VLDL-cholesterol, non-HDL-cholesterol, and ApoC-III were significantly affected in all groups receiving vupanorsen compared with placebo. However, glycaemic control or hepatic steatosis markers were not affected by vupanorsen.

Regarding safety, injection site reactions were the most frequent treatment-emergent adverse events (TEAEs). Any TEAE occurred in 59.3% in the pooled placebo group and in 73.1% to 88.5% of the patients in the 3 vupanorsen groups. TEAEs leading to discontinuation occurred in 3.8% to 11.5% of patients in the vupanorsen groups compared with none in the placebo group. There were no effects of vupanorsen on platelet count, liver function markers, and renal function markers compared with placebo.

In conclusion, vupanorsen lowered triglycerides and atherogenic lipoproteins in patients with diabetes, hepatic steatosis, and hypertriglyceridaemia. Vupanorsen may provide a new strategy for reduction of residual CV risk.

1. Gaudet D, et al. ANGPTL3 antisense oligonucleotide to lower triglycerides. Lipids session, ESC Congress 2020, 29 Aug.

Reduced progression of coronary atherosclerosis with icosapent ethyl

The EVAPORATE trial showed that icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, significantly reduced multiple plaque components over 18 months, including a significant regression of low-attenuation plaque volume on multidetector computed tomography (MDCT) [1,2].

Although statins reduce cardiovascular (CV) events and slow progression of coronary atherosclerosis, significant CV risk remains. The REDUCE-IT trial previously showed that the addition of icosapent ethyl to statin therapy reduced initial CV events by 25% and total CV events by 32% [3]. However, the mechanisms of this benefit are not yet fully explained. The EVAPORATE trial set out to further assess the effects of icosapent ethyl plaque volume, measured by serial MDCT, compared with placebo [2].

Icosapent ethyl versus placebo

The randomised, double-blind, placebo-controlled EVAPORATE trial, presented by Prof. Matthew Budoff (Harbor-UCLA Medical Center, USA), enrolled 80 patients with manifest coronary atherosclerosis, as documented by

MDCT (≥1 angiographic stenoses with ≥20% narrowing). Participants had to be on statin therapy and have persistently elevated triglyceride levels. The median triglyceride level was 259.1 mg/dL.

In the placebo group, low-attenuation plaque volume more than doubled from baseline to 18 months follow-up (increase in plaque quantity: 109%) and decreased in the icosapent ethyl group (reduction in plaque quantity: 17%). Change in plaque quantity was statistically significant between treatment groups (P=0.0061).

Plaque progression versus regression

While patients in the placebo group had a progression of plaque quantity, patients in the icosapent ethyl group showed reduced plaque at 18 months follow-up compared with baseline. In addition, significant differences were observed in rates of progression between icosapent ethyl and placebo at follow-up of 18 months, including:

- fibrofatty plaque: +32% versus -34% (P=0.0002);
- fibrous plaque: +1% versus -20% (P=0.0028);
- total non-calcified plaque: +9% versus -19% (P=0.0005);
- total plaque volume: +11% versus -9% (P=0.0019), respectively.

Only dense calcium did not show a significant difference between groups after multivariate adjustment (15% vs -1%; P=0.053).

1. Budoff M. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy. ESC 2020 E-Congress, Lipids session 29 Aug.
2. Budoff MJ, et al. Eur Heart J. 2020, 29 August.
3. Bhatt DL, et al. N Engl J Med 2019; 380:11-22.

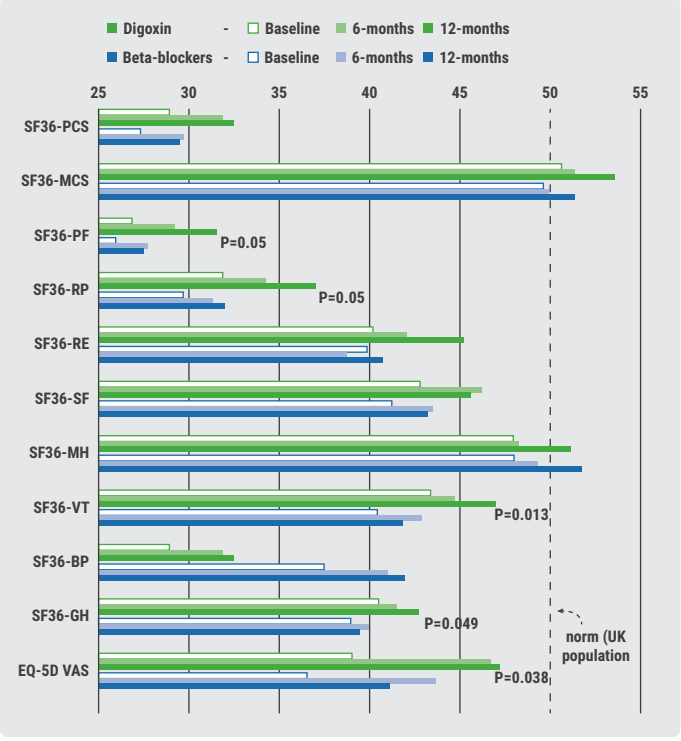
Digoxin improves symptoms in stable patients with permanent AF

The RATE-AF trial showed a similar effect of low-dose digoxin on both heart rate and the physical component of quality of life compared with beta-blockers [1]. Yet, digoxin-treated patients showed significantly better symptom improvement, a reduction in natriuretic peptides, and substantially less adverse events without compromising left ventricular function. These results suggest that digoxin could be considered as a first-line approach for rate control in stable patients with permanent atrial fibrillation (AF).

Beta-blockers are commonly used for rate control due to their beneficial effects in heart failure with reduced ejection fraction. However, the observed mortality benefit does not appear to extend to those with AF in double-blind, randomised trials. Data on digoxin suffers from prescription bias, as doctors typically preserve digoxin for sicker, older patients with more comorbidities. Although digoxin has been in use since 1785, no longer-term trials with digoxin in patients with AF or AF with heart failure have been performed.

This was the motivation for the randomised, phase 4 RATE-AF trial to evaluate beta-blockers and digoxin for long-term heart rate control in patients with permanent AF and symptoms of heart failure. The trial, presented by Prof. Dipak Kotecha (University of Birmingham, UK), included 160 patients in need of rate control for AF, aged ≥60 years (mean age 76 years), and with permanent AF and breathlessness (NYHA class II or above). Most AF symptoms at baseline were moderate or severe: modified EHRA 2b was present in 47% of patients and mEHRA 3 in 40%. Over half (52%) had signs of heart failure at baseline (median NTproBNP 1,057 pg/mL; 19% had a LVEF <50%).

Figure: Patient-reported quality of life in the RATE-AF trial [1]



The results showed that heart rate reduced at a similar extent in patients who received a beta-blocker or digoxin. The primary outcome, SF36 quality of life using the Physical Component Summary score at 6 months, increased in both groups with no significant difference (adjusted mean difference 1.33; 95% CI -1.22-3.89; P=0.30; see Figure). Notably, the participants

showed a substantial lower quality of life across all domains compared with the norm for these patients. Over time, quality of life across these domains continued to improve with digoxin.

1. Kotecha D. RAte control Therapy Evaluation in permanent Atrial Fibrillation. Atrial Fibrillation session, ESC Congress 2020, 29 Aug.

SGLT2 inhibitor ertugliflozin shows similar mortality but fewer HF hospitalisations

In the VERTIS CV trial, SGLT2 inhibitor ertugliflozin did not meet the primary endpoint but did reduce the risk for first heart failure (HF) hospitalisations compared with placebo in patients with type 2 diabetes mellitus (T2DM) and established atherosclerotic cardiovascular disease (ASCVD) with or without a history of HF [1]. These findings are consistent with results for other SGLT2 inhibitors.

No fewer than 6 recent cardiovascular outcomes trials in patients with T2DM have consistently found a significant reduction in risk of HF hospitalisations with SGLT2 inhibitors [1]. Recent guidelines from the ESC and other scientific societies recommend the use of SGLT2 inhibitors in patients with T2DM to reduce the risk of HF hospitalisations events.

VERTIS CV was a multicentre, randomised, placebo-controlled, event-driven trial including 8,246 patients with T2DM and established ASCVD. Of the participants, 24% had a history of HF, which is consistent with the 20-30% of patients with HF present in the general T2DM population. The primary endpoint was a composite of CV death, non-fatal myocardial infarction, and non-fatal stroke.

The event rate of the primary endpoint was 3.9 events per 100 patient-years in the ertugliflozin versus 4.0 events in the placebo group (HR 0.97; 95% CI 0.85-1.11; P<0.001 for non-inferiority). In accordance with this, some other endpoints were also not significantly different between the 2 arms, namely:

- CV death or HF hospitalisations: 2.3 versus 2.7 events per 100 patient-years (HR 0.88; P=0.11);
- CV death: 1.8 versus 1.9 events per 100 patient-years (HR 0.92; P=0.39); and
- renal composite: 0.9 versus 1.2 events per 100 patient-years (HR 0.81; P=0.08);

In contrast, the event rate of HF hospitalisation was significantly different: 0.7 versus 1.1 events per 100 patient-years (HR 0.70; P=0.006).

The prespecified endpoint of time to first HF hospitalisation was 30% lower in the ertugliflozin versus the placebo group (HR 0.70). Prior history of HF did not influence this effect of ertugliflozin (P for interaction 0.40), neither was this affected by pre-trial ejection fraction (P for interaction 0.15 in case of a cut-off of 45% for ejection fraction). Interestingly, the effect of ertugliflozin was significantly greater in patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m2 and in patients with albuminuria (both P=0.04), and in those taking diuretics (P=0.02). A prespecified analysis of total events showed that also the number of first and recurrent HF hospitalisation (rate ratio 0.70; P=0.001) and the composite of HF hospitalisation and CV death (RR 0.83; P=0.011) were significantly different between the 2 arms.

These results provide additional evidence in support of current guidance from cardiology and diabetes societies that recommend the use of SGLT2 inhibitors in patients with T2DM to reduce the risk of HF hospitalisations events.

1. Cosentino F. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: results of the VERTIS trial. Chronic HF session, ESC Congress 2020, 31 Aug.

COVID and Cardiovascular Disease

Risk factors for thromboembolism and bleeding in COVID-19: lessons from Wuhan

An evaluation of patients with COVID-19 who were admitted to the hospital in Wuhan, China, showed that they were at high risk for thromboembolic and bleeding events, as well as mortality [1]. Anticoagulant use, especially use of parenteral anticoagulants, significantly reduced the risk of the composite outcome of thromboembolism, bleeding events, and death. The presence of atrial fibrillation (AF) was a contributor to systemic thromboembolism in COVID-19 patients.

COVID-19 is associated with a high risk of thrombotic complications, which contribute to the high mortality rate. Limited data is yet available on systemic thromboembolism and the value of anticoagulation regimens. Prof. Yutao Guo (Chinese PLA General Hospital, China) presented the study that investigated the prevalence of systemic and venous thromboembolism, as well as major bleeding and mortality, in relation to underlying risk factors and the impact of anticoagulation use in hospitalised patients with COVID-19.

The study enrolled 1,125 patients with COVID-19 admitted to Union Hospital, Wuhan, China. Half of the participants (49.9%) were male and mean age was 58 years (36.3% were >65 years). They were followed for a mean of 21 days. Of the participants, 33 (2.9%) underwent surgery, and 249 patients (22.1%) received anticoagulants, of whom 7.7% received oral anticoagulants, 18.6% parenteral anticoagulants, and 4.2% oral plus parenteral anticoagulants.

Thromboembolic and bleeding events

There were 82 thromboembolism events (7.3%; 37 systemic and 45 venous events), 128 major bleeding events (11.4%), and 91 deaths (8.1%). About 25 patients (30%) with thromboembolism also suffered bleeding events. Age was an independent risk factor for thromboembolism, bleeding events, and death (all P<0.05).

After adjusting for the severity of COVID-19 infection, comorbidities, surgery, and use of antiviral drugs, immunomodulators, Chinese herbs, and antithrombotic drugs:

- low lymphocyte counts (HR 1.03; P=0.01) and surgery (HR 2.80; P=0.03) independently predicted the risk for major bleeding;
- liver dysfunction (HR 4.13; P=0.02) was an independent risk factor for patients with both thromboembolism and bleeding events; and
- AF or irregular rhythm increased the risk for systemic thromboembolism (HR 3.16; P=0.04).

Anticoagulant use

Both oral anticoagulant (HR 0.32) and parenteral anticoagulant (HR 0.39) use reduced the risk for thromboembolism (all P<0.001). After adjustment, parenteral anticoagulant use had a borderline significant effect on both thromboembolism and bleeding events (HR 0.36; P=0.053), but significantly reduced the risk for the composite outcome of thromboembolism, bleeding events, and mortality (HR 0.70; P=0.02).

1. Guo Y. Risk factors for systemic and venous thromboembolism, mortality and bleeding risk in 1125 patients with COVID-19: relationship to anticoagulation status. COVID and Cardiovascular Disease session, ESC Congress 2020, 30 Aug.

The Yale COVID-19 Cardiovascular Registry

Preliminary prospective cohort data from the Yale COVID-19 Cardiovascular Registry showed that at least 40% of patients hospitalised with verified COVID-19 had a high cardiovascular (CV) risk at baseline, including a high prevalence of diabetes and hypertension. Patients with CV risk in the Yale registry cohort had high mortality rates and CV complications; about 1 in 5 patients died, 2 in 5 experienced a CV event, and 1 in 5 required mechanical ventilation [1].

Dr Manan Pareek (Yale University School of Medicine, USA) presented the data, which was intended to supplement the sparse body of evidence suggesting that patients with a high CV risk or disease burden tend to be more vulnerable during SARS-CoV-2 infection. The aim of the analysis was to determine the prevalence of CV risk factors, established CV disease, and associated medications. Additionally, they sought to identify risk factors for incident CV events and mortality. Using the Yale New Haven Hospital COVID-19 Cardiovascular Registry, Dr Pareek and colleagues performed

a prospective cohort study including 1,200 hospitalised patients positive for COVID-19 (median age 68 years; 54% male). Dr Pareek presented the analysis of the first 495 patients.

The primary endpoint was in-hospital death from any cause. Secondary endpoints were CV outcomes, such as major adverse CV event (MACE), and non-CV outcomes, such as intensive care admission, mechanical ventilation, and renal replacement therapy. Within the first 495 patients, more than 40% presented with CV risk factors, among which diabetes, hypertension, and hyperlipidaemia were the most common. In addition, 46% of the cohort had a history of any CV disease, the most prevalent being coronary artery disease (CAD), heart failure, and atrial fibrillation; accordingly, medication use by this cohort was frequent, including antihypertensives, aspirin, and statins.

In-hospital CV events included atrial fibrillation (19%), myocardial infarction (17%), and acute decompensated heart failure (14%). Non-CV related events were intensive care admission (35%), mechanical ventilation (21%), and dialysis (4%). Furthermore, 18% of patients died in hospital, and 39% experienced a MACE after admission. Applying logistic regression to determine potential predictors of MACE, independent variables were male gender, history of atrial fibrillation, use of a diuretic, oxygen therapy at admission, low albumin, and high troponin T levels. Similarly, in-hospital mortality was characterised by independent variables of age, a history of ventricular tachycardia, use of P2Y12 inhibitors, lower platelet count, higher aspartate aminotransferase, lower albumin, and high troponin T levels.

Limitations of the study included the observational nature of the study as well as the limited event rate and short follow-up. Because all participants were hospital patients, the population was generally older with more comorbidities than the non-hospitalised COVID-19 patients.

1. Pareek M, et al. YNHHS-COVID-19 - Cardiac Complications Registry. COVID and Cardiovascular Disease session, ESC Congress 2020, 30 Aug.

COVID-19 treatments and the importance of randomised trials

Currently, just two COVID-19 treatments have shown benefit in randomised trials: remdesivir and dexamethasone. No benefit was found for hydroxychloroquine, lopinavir-ritonavir, and tocilizumab.

Prof. Martin Landray (University of Oxford, United Kingdom) gave an overview of randomised trials of COVID-19 treatments with a focus on hospitalised patients [1].

For most people, an infection with SARS-CoV-2 is self-limiting, but for hospitalised patients, mortality is high (10-20%) and for ventilated patients even higher (40-50%). The pathophysiology of COVID-19 is characterised by 2 components: a viral response in the first week to 10 days, and an increasing inflammatory response, where the immune system is initially combating the virus but can also drive lung damage and need for ventilation.

Current treatment falls into 3 categories: repurposed anti-virals, immunomodulatory drugs, and some drugs targeted specifically at SARS-CoV-2. In addition, there are some treatments targeted at complications, such as antithrombotics. Currently, hundreds of candidate drugs exist but very little reliable data is available (only uncontrolled case series and inconclusive randomised trials). According to Prof. Landray, it is worth remembering that it is unlikely to have a single "big win," but that moderate benefits will be important.

RECOVERY trial

The controlled, open-label RECOVERY trial evaluated hospitalised patients with SARS-CoV-2 in 176 hospitals in the United Kingdom and Northern Ireland [2]. The most important outcome was 28-day mortality, but it also evaluated use of ventilation and duration of hospitalisation. Patients were randomised between a range of suitable and available treatments:

- repurposed antivirals, i.e. hydroxychloroquine and lopinavir-ritonavir;
- immunomodulatory drugs, i.e. dexamethasone, azithromycin, and tocilizumab; and
- targeted anti-SARS-CoV-2, i.e. convalescent plasma.

Both hydroxychloroquine and lopinavir-ritonavir had no effect on all-cause mortality among these hospitalised patients. In contrast, dexamethasone reduced mortality with about a third in patients requiring oxygen or ventilation.

Remdesivir and tocilizumab

In a similar patient population, a double-blind, randomised, placebo-controlled trial found that remdesivir reduced time to recovery with approximately 4 days (11 vs 15 days; RR

1.32; P<0.001) [3]. However, no impact on mortality was found (RR 0.70).

There is one reported trial evaluating the anti-IL-6 monoclonal antibody tocilizumab. This relatively small study showed no impact on either clinical status (OR 1.19; P=0.36) or mortality (19.7 vs 19.4%; P=0.94) at day 28, but did observe a shorter hospitalisation duration (20 vs 28 days; P=0.04). Additional studies are ongoing, including the evaluation of >800 patients in the RECOVERY study.

1. Landray M. Randomized trials of COVID-19 treatments. COVID and Cardiovascular Disease session, ESC Congress 2020, 30 Aug.
2. The RECOVERY Collaborative Group. N Engl J Med 2020; 17 July. DOI: 10.1056/NEJMoa2021436.
3. Beigel JH, et al. N Engl J Med 2020; 22 May. DOI: 10.1056/NEJMoa2007764.

Figure: Incidence of in-hospital events in COVID-19 patients [1]