ESC Congress 2019 In Review

Official peer-reviewed highlights

Main Edition

In This Issue

Highlights of the 2019 ESC Clinical Practice Guidelines

The European Society of Cardiology has released 5 new guideline updates developed by expert Task Forces for the management and prevention of cardiovascular disease in patients with diabetes, acute pulmonary embolism, supraventricular tachycardia, chronic coronary syndromes, and well as management of dyslipidaemia. The evidence base supporting the guidelines are summarised, and valuable clinical decision-making tools are provided.

Also

- Results from ISAR-REACT 5
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ESC
European Society of Cardiology

Dear Colleagues,

In this issue of *ESC Congress 2019 in Review,* we are pleased to share with you the peer-reviewed highlights from the European Society of Cardiology (ESC) Congress 2019, held in the heart of Paris, France, at the Paris Expo Porte de Versailles. Over the 5 days of the congress, with over 33,500 healthcare professionals attending from 146 different countries, over 4,500 abstracts were presented and 6 centre-stage Hot Line sessions featured many practice-changing trials presented at ESC Congress 2019.

Also new this year, the ESC sessions were joined by the World Congress of Cardiology (WCC) 2019, which is departing from its every-2-years solo meeting format to be held annually in conjunction with other major cardiology meetings. Accordingly, the combined congress has taken on "global cardiovascular health" as its theme, with recognition that the majority of cardiovascular death today occurs in low- and middle-income countries, as underscored by the PURE and HOPE 4 trials. In addition, many other large trials reported their results at the congress, such as the DAPA HF, COMPLETE, and ISAR-REACT 5 trials, which will likely change aspects of daily practice.

Five new ESC Clinical Practice Guidelines updates were released during the congress, namely diabetes, pre-diabetes and cardiovascular diseases; acute pulmonary embolism; supraventricular tachycardia; chronic coronary syndromes; and dyslipidaemias. In-depth sessions with Guideline Task Force members presented the underlying science behind the Guideline changes and are covered here as well.

We hope that you find the articles and practical perspectives that are contained in the pages of this issue of *ESC Congress 2019 in Review* helpful in integrating this new information and providing fresh perspectives on your cardiology practice. Please be reminded that ESC 365, presenting all the congress resources in one online library, provides access to all abstracts, slides and videos. To access this unique source of up-to-date information, visit www.escardio.org/365.

We hope you will enjoy this issue of *ESC Congress 2019 in Review* and look forward to seeing you next year in Amsterdam, the Netherlands, for ESC Congress 2020.

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Dear Practitioner,

We are pleased to share with you highlights from the European Society of Cardiology (ESC) Congress 2019 which was held this year together with the World Congress of Cardiology in Paris, France. More than 33,500 healthcare professionals gathered over 5 days to attend more than 600 expert sessions covering the entire spectrum of cardiovascular medicine. The 14 covered trials presented in 6 Hot Line sessions attracted large crowds, as did the 3 Late Breaking Science studies in acute coronary syndromes, cardiovascular pharmacology, and atrial fibrillation reported on in this report.

The featured article provides a topline summary of the 5 new ESC Clinical Practice Guidelines released during the congress, covering diabetes and cardiovascular diseases, acute pulmonary embolism, supraventricular tachycardia, chronic coronary syndromes, and dyslipidaemia.

Several highly anticipated clinical trials were presented at ESC Congress 2019, such as DAPA-HF, COMPLETE, or ISAR-REACT 5, which will no doubt influence practice. Other landmark studies presented addressed important unmet needs, such as THEMIS and PARAGON- HF.

In addition to the 2019 Guideline updates and results presented in the Hot Line sessions, you will find additional treatment updates in cardiovascular medicine including trial outcomes on the regulation of inflammation and how to achieve effective decongestion without increasing the risk of worsening renal function in patients with type 2 diabetes.

We hope that you find the articles and practical perspectives that are contained in the pages of this edition of *ESC Congress 2019 in Review* helpful in integrating this new information into your clinical practice.

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ESC Clinical Practice Guidelines

Late-Breaking Science

New Treatment Updates

Highlights of the 2019 ESC Clinical Practice Guidelines

Written by **Lisa Buttle**

The European Society of Cardiology (ESC) released 5 guideline updates developed by expert Task Forces covering the topics of acute pulmonary embolism; dyslipidaemias; chronic coronary syndromes; diabetes, pre-diabetes, and cardiovascular diseases; and supraventricular tachycardias. The guidelines summarise the evidence base on these topics and provide a valuable clinical decision-making tool for practicing clinicians. All guidelines can be accessed from the ESC website (www.escardio.org/guidelines) and the ESC Pocket Guidelines App.

Acute Pulmonary Embolism

The 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism (PE) [Konstantinides S et al. *Eur Heart J*. 2019] were developed in collaboration with the European Respiratory Society (ERS) by a joint Task Force led by Stavros Konstantinides, MD, PhD, Johannes Gutenberg University, Mainz, Germany, and Guy Meyer (ERS Co-Chairperson), MD, PhD, Georges Pompidou European Hospital, Paris, France.

Updates in the 2019 guidelines include new:

- definitions of haemodynamic instability and high-risk PE (Table 1);
- risk-adapted diagnostic algorithms;
- recommendations for diagnosis;
- reinforcement of the prognostic importance of right ventricular dysfunction;
- integrated management plan;
- indications for extended treatment after acute PE;
- recommendations for cancer-associated PE;
- recommendations on the diagnosis and management of PE in pregnancy; and
- algorithm for long-term follow up.

The guidelines clarify how to diagnose acute PE step by step, based on symptoms and blood tests (D-dimers), with computed tomography (CT) or ultrasound scan if needed (Table 2).

The guidelines recommend to assess severity of PE based on a combination of clinical, imaging, and laboratory results, which will dictate appropriate treatment. Anticoagulants treat the acute episode and prevent recurrence but also raise bleeding risk, and advice on duration of anticoagulant treatment is provided. Lastly, the 2019 guidelines support a multidisciplinary approach to patient management after acute PE and discharge.

Table 2. Main New Recommendations in the 2019 ESC Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism*

Recommendations	Class[a]
Diagnosis	
A D-dimer test, using an age-adjusted cut-off or adapted to clinical probability, should be considered as an alternative to the fixed cut-off level.	IIa
If a possible proximal CUS is used to confirm PE, risk assessment should be considered to guide management.	IIa
V/Q SPECT may be considered for PE diagnosis.	IIb
Risk assessment	
Assessment of the RV by imaging or laboratory biomarkers should be considered, even in the presence of a low PESI or a sPESI of 0.	IIa
Validated scores combining clinical, imaging, and laboratory prognostic factors may be considered to further stratify PE severity.	IIb
Treatment in the acute phase	
When oral anticoagulation is initiated in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is the recommended form of anticoagulant treatment.	I
Set-up of multidisciplinary teams for management of high risk and selected cases of intermediate-risk PE should be considered, depending on the resources and expertise available in each hospital.	IIa
ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in refractory circulatory collapse or cardiac arrest.	IIb
Chronic treatment and prevention of recurrence	
Indefinite treatment with a VKA is recommended for patients with antiphospholipid antibody syndrome.	I
Extended anticoagulation should be considered for patients with no identifiable risk factor for the index PE event.	IIa

* Table continued on next page.

Table 1. Definition of Haemodynamic Instability and High-Risk Pulmonary Embolism

1. Cardiac Arrest	2. Obstructive Shock	3. Persistent Hypotension
Need for cardiopulmonary resuscitation	Systolic BP < 90 mmHg, or vasopressors required to achieve a BP ≥ 90 mmHg despite adequate filling status **And** End-organ hypoperfusion (altered mental state; cold, clammy skin; oliguria/anuria; increased serum lactate)	Systolic BP < 90 mmHg, or systolic BP drop ≥ 40 mmHg, either lasting longer than 15 minutes and not caused by new-onset arrhythmia, hypovolaemia, or sepsis

BP, blood pressure.

Reproduced and modified from Konstantinides S et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the ERS. *Eur Heart J*. 2019. Doi:10.1093/eurheartj/ehz405. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Extended anticoagulation should be considered for patients with a persistent risk factor other than antiphospholipid antibody syndrome.	IIa
Extended anticoagulation should be considered for patients with a minor transient/reversible risk factor for the index PE event.	IIa
A reduced dose of apixaban or rivaroxaban should be considered after the first 6 months.	IIa
PE in cancer	
Edoxaban or rivaroxaban should be considered as an alternative to LMWH, with the exception of patients with gastrointestinal cancer.	IIa
PE in pregnancy	
Amniotic fluid embolism should be considered in a pregnant or post-partum woman, with unexplained haemodynamic instability or respiratory deterioration, and disseminated intravascular coagulation.	IIa
Thrombolysis or surgical embolectomy should be considered for pregnant women with high-risk PE.	IIa
NOACs are not recommended during pregnancy or lactation.	III
Post-PE care and long-term sequelae	
Routine clinical evaluation is recommended 3-6 months after acute PE.	I
An integrated model of care is recommended after acute PE to ensure optimal transition from hospital to ambulatory care.	I
It is recommended that symptomatic patients with mismatched perfusion defects on a V/Q scan > 3 months after acute PE are referred to a pulmonary hypertension/CTEPH expert centre, taking into account the results of echocardiography, natriuretic peptide, and/or cardiopulmonary exercise testing.	I

[a]Class of recommendation I to III. Colours denote whether to recommend: green, yes; yellow, should be considered; orange, may be considered; red, no.

CPET, cardiopulmonary exercise testing; CTEPH, chronic thrombo–embolic pulmonary hypertension; CUS, compression ultrasonography; ECMO, extracorporeal membrane oxygenation; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; PE, pulmonary embolism; (s)PESI, (simplified) Pulmonary Embolism Severity Index; RV, right ventricular; SPECT, single-photon emission computed tomography; VKA, vitamin K antagonist; V/Q, ventilation/perfusion (lung scintigraphy).

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Guidelines on Dyslipidaemias

The 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk [Mach F et al. *Eur Heart J*. 2019] were developed in collaboration with the European Atherosclerosis Society (EAS) by a joint Task Force led by François Mach (ESC), MD, Geneva University Hospital, Switzerland, and Colin Baigent (ESC), FRCP, University of Oxford, United Kingdom, and Alberico L. Catapano (EAS), MD, PhD, University of Milan, Italy.

The 2019 guidelines incorporate these fundamental principles for lowering low-density lipoprotein cholesterol (LDL-C):

- relative risk reduction is proportional to the absolute reduction in LDL-C;
- lower is better – lowering LDL-C with statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is safe and effective to < 1.4 mmol/L (55 mg/dL), with an alternative goal of < 1.0 mmol/L (40 mg/dL) in patients with recurrent events on maximal therapy;
- the intensity of LDL-C lowering therapy should be based upon:
  A. risk, irrespective of cause of the risk (e.g., primary or secondary prevention, diabetes, or chronic kidney disease); and
  B. baseline LDL-C, which determines how much reduction in risk can be achieved.

The guidelines recommend to first determine level of risk (with revised risk stratification categories provided; Table 3) and to apply the appropriate goal for LDL-C reduction (Table 4). Patients at very high risk should be offered intensive LDL-lowering therapy to achieve both a target LDL-C level and a minimum 50% relative reduction. The revised guidelines aim to ensure that available drugs (i.e., statins, ezetimibe, PCSK9 inhibitors) are used effectively to lower LDL-C levels in those most at risk, for which a new treatment algorithm is provided (Figure 1, on page 6).

Table 3. Cardiovascular Risk Categories

Very high risk	People with any of the following: • Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG, and other arterial revascularisation procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with 2 major epicardial arteries having > 50% stenosis), or on carotid ultrasound. • DM with target organ damage,[a] or at least 3 major risk factors, or early onset of T1DM of long duration (> 20 years). • Severe CKD (eGFR < 30 mL/min/1.73 m^2). • A calculated SCORE ≥ 10% for 10-year risk of fatal CVD. • FH with ASCVD or with another major risk factor.
High risk	People with: • Markedly elevated single risk factors, in particular TC > 8 mmol/L (> 310 mg/dL), LDL-C > 4.9 mmol/L (> 190 mg/dL), or BP ≥ 180/110 mmHg. • Patients with FH without other major risk factors. • Patients with DM without target organ damage,[a] with DM duration ≥ 10 years or another additional risk factor. • Moderate CKD (eGFR 30-59 mL/min/1.73 m^2). • A calculated SCORE ≥ 5% and < 10-year risk of fatal CVD.
Moderate risk	Young patients (T1DM < 35 years; T2DM < 50 years) with DM duration < 10 years, without other risk factors. Calculated SCORE ≥ 1% and < 5% for 10-year risk of fatal CVD.
Low risk	Calculated SCORE < 1% for 10-year risk of fatal CVD.

[a]Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; BP, blood pressure; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; LDL-C low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCORE, Systematic Coronary Risk Estimation; T1DM, type 1 DM; T2DM, type 2 DM; TC, total cholesterol; TIA, transient ischaemic attack.

Reproduced from Mach F et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*. *Eur Heart J*. 2019. Doi:10.1093/eurheartj/ehz455. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Table 4. Recommended Treatment Goals for LDL-C Lowering Therapy: Main Changes from 2016 to 2019

	LDL goals (starting with untreated LDL-C)	
Risk category	**2016**	**2019**
Low risk	< 3.0 mmol/L (115 mg/dL)	< 3.0 mmol/L (115 mg/dL)
Moderate risk	< 3.0 mmol/L (115 mg/dL)	< 2.6 mmol/L (100 mg/dL)
High risk	< 2.6 mmol/L (100 mg/dL) or > 50% ↓ if LDL-C 2.6-5.2 (100 - 200 mg/dL)	< 1.8 mmol/L (70 mg/dL) and > 50% ↓
Very high risk	< 1.8 mmol/L (70mg/dL) or > 50% ↓ if LDL-C 1.8-3.5 (70 - 135mg/dL)	< 1.4 mmol/L (55mg/dL) and > 50% ↓

LDL-C, low-density lipoprotein cholesterol.

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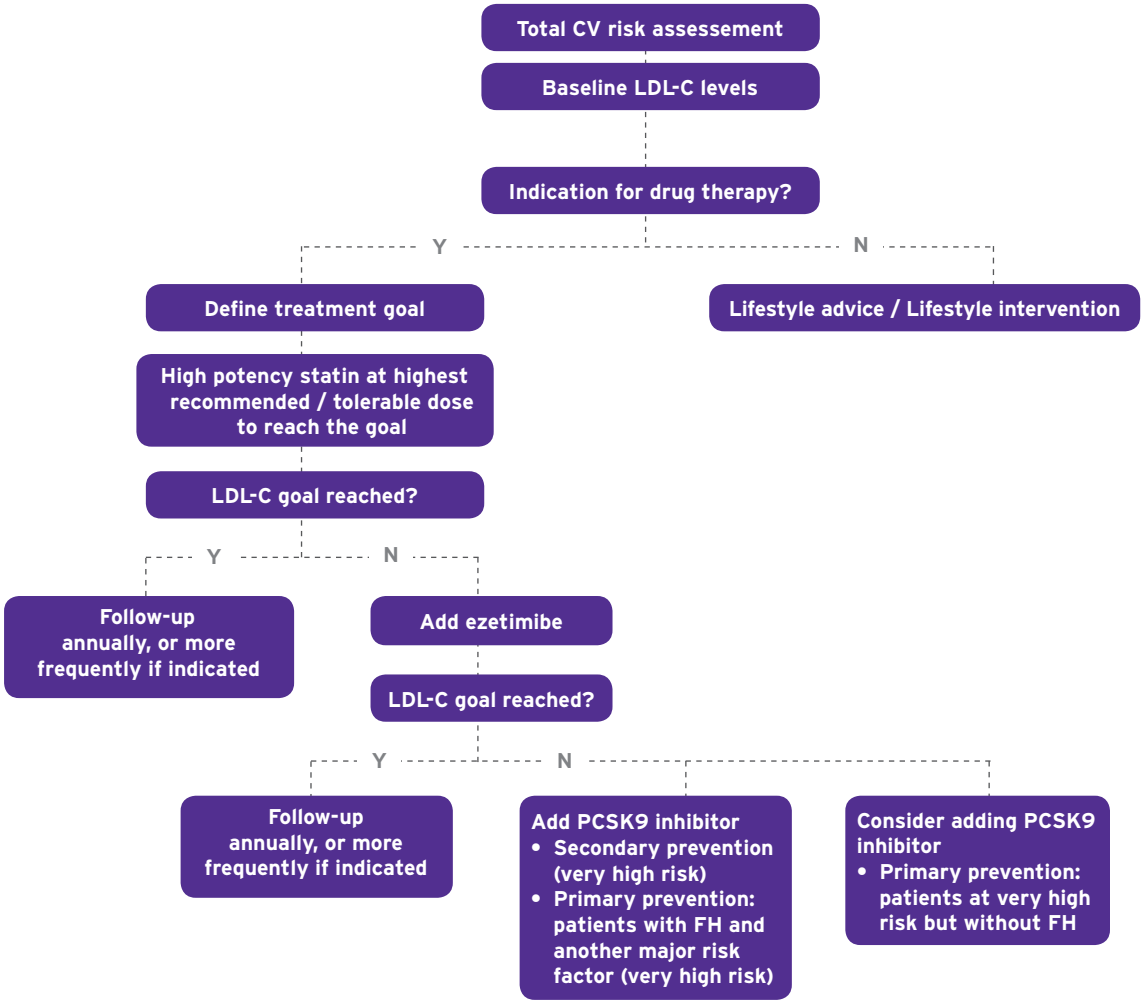
Chronic Coronary Syndromes

The 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [Knuuti J et al. *Eur Heart J*. 2019] were developed by a Task Force led by Juhani M. Knuuti, MD, PhD, Turku University Hospital, Turku, Finland, and William Wijns, MD, PhD, National University of Ireland, Galway, Ireland. The guidelines were revised to focus on chronic coronary syndromes (CCS) instead of stable coronary artery disease (CAD), which reflects the fact that CAD can be acute (covered in separate guidelines) or chronic, and both are dynamic conditions.

The 2019 guidelines incorporate significant new evidence on:

- the prevalence of CAD, in the symptomatic population, which has decreased, leading to lower pre-test probability of disease. This has a major impact on the use of diagnostic testing;

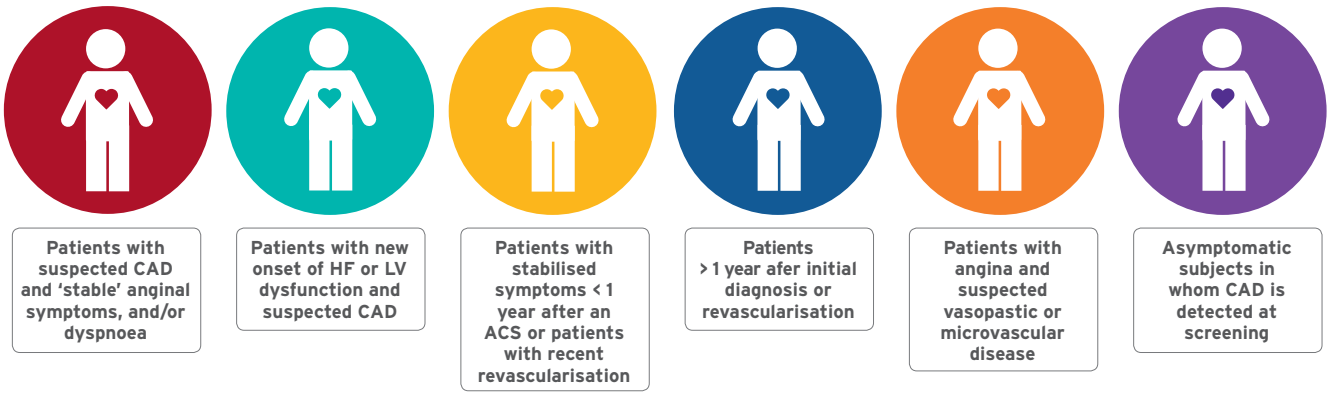
Figure 1. Treatment Algorithm for Pharmacological LDL-C Reduction



CV, cardiovascular; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

Reproduced from Mach F et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*. *Eur Heart J*. 2019. Doi:10.1093/eurheartj/ehz455. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Figure 2. Chronic Coronary Syndromes: 6 Common Scenarios at Outpatient Clinics



ACS, acute coronary syndrome; CAD, coronary artery disease; HF, heart failure; LV, left ventricular.

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- advances in imaging; both anatomy and function are available invasively and non-invasively, and the role of CT is increasing;
- intensified antithrombotic therapy; and
- revascularisation using PCI has prognostic impact on the prevention of myocardial infarction.

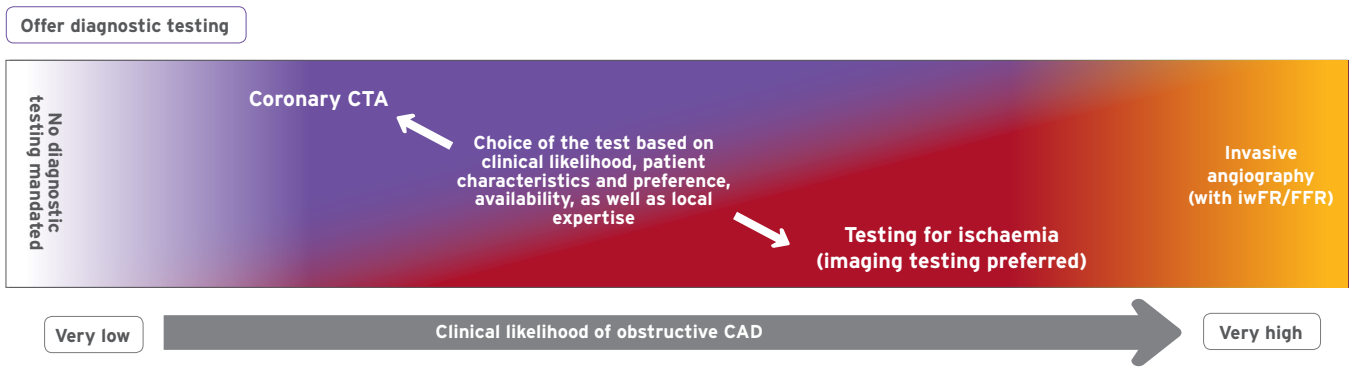
The diagnosis of CCS has evolved significantly since the 2013 guidelines. The 6 most frequently encountered clinical scenarios are outlined in Figure 2; each of which requires different diagnostic and therapeutic approaches. A stepwise approach to diagnosis and treatment of a symptomatic patient with suspected CAD is recommended (Figure 3).

Treatment of CCS demands long-lasting healthy lifestyle behaviours, medication adherence, and interventions in selected patients. Statins are recommended in all patients and antithrombotic drugs in most patients. Revascularisation is important for patients at high risk, and for those whose symptoms are not controlled through lifestyle and medication. Finally, the guidelines recommend a schematic follow-up protocol that could be implemented in clinical practice.

Diabetes and Cardiovascular Diseases

The 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases (CVD) [Cosentino F et al. *Eur Heart J.* 2019] were developed in collaboration with the European Association for the Study of Diabetes (EASD) by a joint Task Force led by Francesco Cosentino, MD, PhD, Karolinska Institute, Stockholm, Sweden, and Peter J Grant (EASD Co-Chairperson), MD, University of Leeds, Leeds, United Kingdom. The 2019 guidelines provide information on how to prevent and manage the effects of diabetes on the heart and vasculature.

Figure 3. Algorithm for Diagnostic Testing



CAD, coronary artery disease; CTA, computed tomography angiography; FFR, fractional flow reserve; iwFR, instantaneous wave-free ratio.

Reproduced and modified from Knuuti J et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2019. Doi:10.1093/eurheartj/ehz425. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Changes in the 2019 guidelines include:

- reclassification of cardiovascular (CV) risk into 3 categories (Table 5);
- new treatment algorithms with glucose-lowering agents for the prevention and management of CVD (Figure 4);
- rew recommendations regarding the role of aspirin and of non-vitamin K antagonist oral anticoagulants (NOACs) in diabetes;
- recommendations on the duration of dual antiplatelet therapy (DAPT) post-acute coronary syndromes in diabetes;
- new lipid targets relating to severity of CV risk and new recommendations for the use of PCSK9 inhibitors [see also: Mach F et al. *Eur Heart J*. 2019]; and
- introduction of individualised blood pressure targets.

Recent evidence showing the CV safety and benefit of antidiabetic agents has led to a paradigm shift. The main recommendation resulting from CV outcomes trials is that glucagon-like peptide-1 (GLP-1) receptor agonists and sodium glucose co-transporter 2 (SGLT2) inhibitors should be used first-line in type 2 diabetes mellitus patients with established CVD or at high/very high CV risk (Table 6).

Aspirin (75-100 mg/day) for primary prevention is no longer recommended in patients with diabetes at moderate CV risk, but rather only for patients identified at very high/high risk, with concomitant use of a proton pump inhibitor in patients receiving aspirin or oral anticoagulant monotherapy, or DAPT, at high risk of gastrointestinal bleeding. Extension of DAPT beyond 12 months should be considered for ≤ 3 years in patients with diabetes at very high risk who have tolerated DAPT without major bleeding complications. NOACs are now recommended in preference to vitamin K antagonists for the management of arrhythmias in people with diabetes aged > 65 years (and a CHA_2DS_2-VASc score ≥ 2), if not contraindicated.

The key recommendations on 'what to do' and 'what not to do' in the management of CVD in diabetes patients are summarised in Table 10 on page 12.

Table 5. Cardiovascular Risk Categories in Patients with Diabetes

Moderate risk	Young patients (T1DM < 35 years; T2DM < 50 years) with DM duration < 10 years, without other risk factors.
High risk	Patients with DM duration ≥ 10 years without target organ damage[a] plus any other additional risk factor[b]
Very high risk	Patients with DM **and** established CVD **or** other target organ damage[a] **or** three or more major risk factors **or** early onset T1DM of long duration (> 20 years)

[a]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy. [b]Age, hypertension, dyslipidaemia, smoking, obesity.

CVD, cardiovascular disease; DM, diabetes mellitus; T1DM, type 1 DM; T2DM, type 2 DM. Reproduced and modified from Cosentino F et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2019. Doi:10.1093/eurheartj/ehz486. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Table 6. Recommendations for Glucose-Lowering Treatment for Patients with Diabetes

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events.	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.	I	B
GLP1-RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events.	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce the risk of death.	I	B
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.	IIa	C

[a]Class of recommendation; [b]Level of evidence.

CV, cardiovascular; CVD, cardiovascular disease; GLP1-RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium glucose co-transporter 2; T2DM, type 2 diabetes mellitus.

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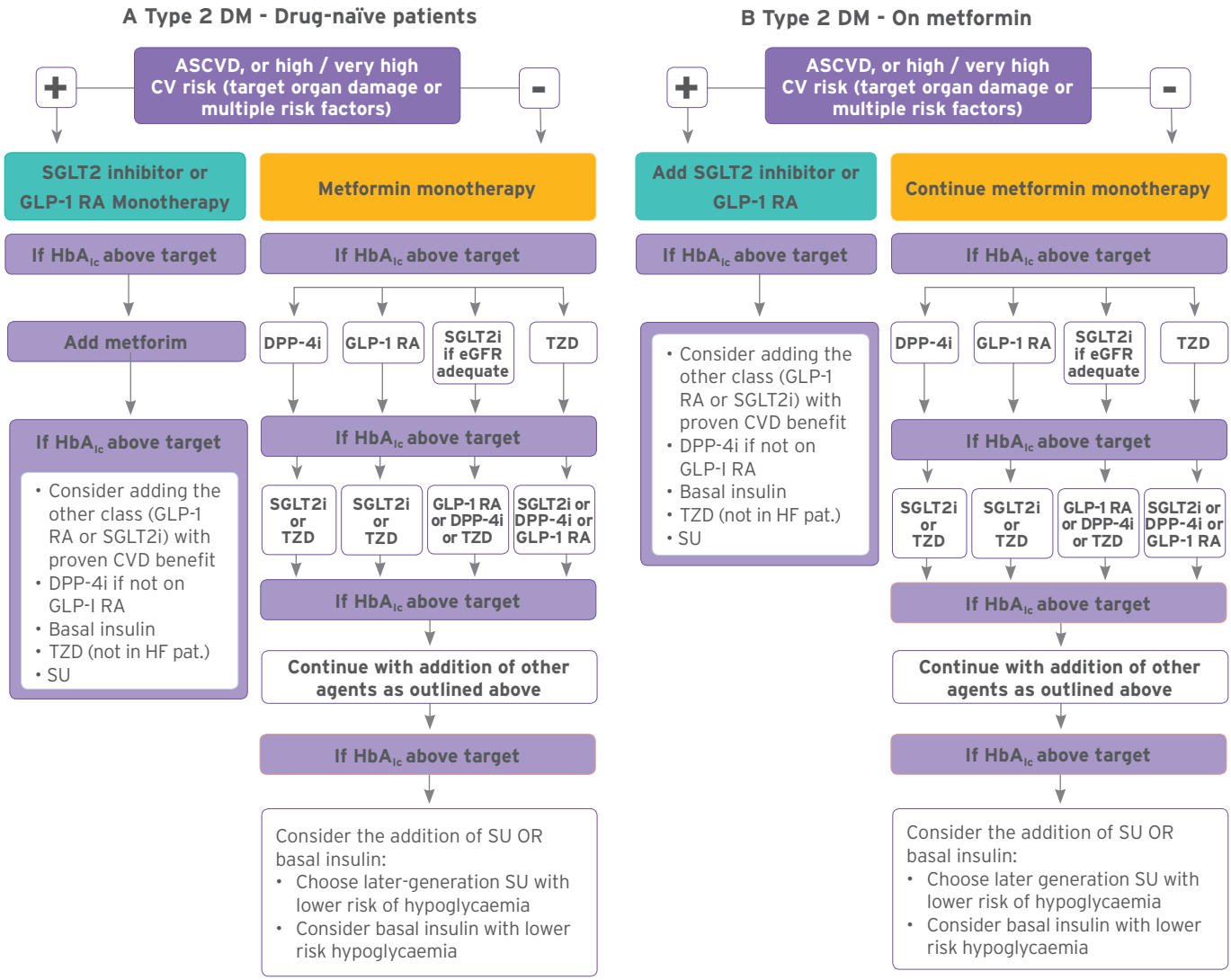
Figure 4. Treatment Algorithm in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease, or High/Very High Cardiovascular Risk for A) Drug-Naïve Patients and B) Metformin-Treated Patients



ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, CV disease; DM, diabetes mellitus; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA glucagon-like peptide-1 receptor agonist; HbA1c, haemoglobin A1c; HF, heart failure; SGLT2i, sodium glucose co-transporter 2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

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Supraventricular Tachycardia

The 2019 ESC Guidelines for the management of patients with supraventricular tachycardia [Brugada J et al. *Eur Heart J*. 2019] were developed by a Task Force led by Josep Brugada, MD, PhD, Hospital Sant Joan de Déu, University of Barcelona, Spain, and Demosthenes G. Katritsis, MD, PhD, Hygeia Hospital, Athens, Greece, in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC).

The 2019 guidelines provide treatment recommendations for all types of supraventricular tachycardias (SVTs).

Newly revised concepts include:

- drug therapy for inappropriate sinus tachycardia and focal atrial tachycardia;
- therapeutic options for acute conversion and anticoagulation of atrial flutter;
- therapy of atrioventricular nodal re-entrant tachycardia;
- therapy of antidromic atrioventricular re-entrant tachycardia and pre-excited atrial fibrillation;
- management of patients with asymptomatic pre-excitation; and
- diagnosis and therapy of tachycardiomyopathy.

Drug therapies for SVT have not fundamentally changed since 2003; however, data has amassed on the potential benefits and risks associated with several drugs and some new antiarrhythmic drugs are available leading to revised guidance (Table 7, on page 10).

Table 7. Guideline Changes for the Management of Supraventricular Tachycardia: 2003 to 2019

	Class of recommendation	
Recommendations	**2003**	**2019**
Acute management of narrow QRS tachycardias		
Verapamil and diltiazem	I	IIa
Beta-blockers	IIb	IIa
Amiodarone and digoxin are not mentioned in the 2019 Guidelines		
Acute management of wide QRS tachycardias		
Procainamide	I	IIa
Adenosine	IIb	IIa
Amiodarone	I	IIb
Sotalol and lidocaine are not mentioned in the 2019 Guidelines		
Therapy of inappropriate sinus tachycardia		
Beta-blockers	I	IIa
Verapamil/diltiazem and catheter ablation are not mentioned in the 2019 Guidelines		
Therapy of postural orthostatic tachycardia syndrome		
Salt and fluid intake	IIa	IIb
Head-up tilt sleep, compression stockings, selective beta-blockers, fludrocortisone, clonidine, methylphenidate, fluoxetine, erythropoietin, ergotamine/octreotide, and phenobarbitone are not mentioned in the 2019 Guidelines		
Therapy of focal AT		
Acute		
Flecainide/propafenone	IIa	IIb
Beta-blockers	I	IIa
Amiodarone	IIa	IIb
Procainamide, sotalol, and digoxin are not mentioned in the 2019 Guidelines		
Chronic		
Beta-blockers	I	IIa
Verapamil and diltiazem	I	IIa
Amiodarone, sotalol, and disopyramide are not mentioned in the 2019 Guidelines		
Therapy of atrial flutter		
Acute		
Atrial or transoesophageal pacing	I	IIb
Ibutilide	IIa	I
Flecainide/propafenone	IIb	III
Verapamil and diltiazem	I	IIa
Beta-blockers	I	IIa
Digitalis is not mentioned in the 2019 Guidelines		
Chronic		
Dofetilide, sotalol, flecainide, propafenone, procainamide, quinidine, and disopyramide are not mentioned in the 2019 Guidelines		
Therapy of AVNRT		
Acute		
Amiodarone, sotalol, flecainide, and propafenone are not mentioned in the 2019 guidelines		
Chronic		
Verapamil and diltiazem	I	IIa
Beta-blockers	I	IIa
Amiodarone, sotalol, flecainide, propafenone, and the 'pill-in-the-pocket' approach are not mentioned in the 2019 Guidelines		
Therapy of AVRT		
Flecainide/propafenone	IIa	IIb
Beta-blockers	IIb	IIa
Amiodarone, sotalol, and the 'pill-in-the-pocket' approach are not mentioned in the 2019 Guidelines		
SVT in pregnancy		
Verapamil	IIb	IIa
Catheter ablation	IIb	IIa*
Sotalol, propranolol, quinidine, and procainamide are not mentioned in the 2019 Guidelines.		

*When fluoroless ablation is available.

AT, atrial tachycardia; ACNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; SVT, supraventricular tachycardia.
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The main change in clinical practice over the past 16 years is the availability of more efficient and safe invasive methods for eradication of arrythmia through catheter ablation, which may now be offered to most patients with SVT (Table 8). Finally, the guidelines list key messages of 'what to do' and 'what not to do' for SVTs (Table 9).

Table 8. New Recommendations for Management of Supraventricular Tachycardias in 2019

Recommendations	Class[a]
Ivabradine alone or in combination with a beta-blocker should be considered in symptomatic patients with inappropriate sinus tachycardia.	IIa
Ibutilide (i.v.) ibulitide may be considered for acute therapy of focal atrial tachycardia.	IIb
Ivabradine for postural orthostatic tachycardia syndrome, and ivabradine with a beta-blocker for chronic therapy of focal atrial tachycardia, may be considered.	IIb
Patients with atrial flutter without AF should be considered for anticoagulation, but the threshold for initiation is not established.	IIa
Ibulitide (i.v.) or i.v. or oral (in-hospital) dofetilide are recommended for conversion of atrial flutter.	I
High-rate atrial pacing is recommended for termination of atrial flutter in the presence of an implanted pacemaker or defibrillator.	I
I.v. amiodarone is not recommended for pre-excited AF.	III
Performance of an EPS to risk-stratify individuals with asymptomatic pre-excitation should be considered.	IIa
Catheter ablation is recommended in asymptomatic patients in whom electrophysiology testing with the use of isoprenaline identifies high-risk properties, such as SPERRI ≤ 250 ms, APERP ≤ 250 ms, multiple APs, and an inducible AP-mediated tachycardia.	I
Non-invasive evaluation of the conducting properties of the AP in individuals with asymptomatic pre-examination may be considered.	IIb
Catheter ablation may be considered in a patient with asymptomatic pre-excitation and low-risk AP at invasive or non-invasive risk stratification.	IIb
Catheter ablations should be considered in patients with asymptomatic pre-excitation and LV dysfunction due to electrical dyssynchrony.	IIa
AV nodal ablation with subsequent pacing ('ablate and pace'), either biventricular or His-bundle pacing, is recommended if a tachycardia responsible for TCM cannot be ablated or controlled by drugs.	I

During the first trimester of pregnancy, it is recommended that all antiarrhythmic drugs are avoided, if possible.	I
In pregnant women, beta-1 selective blockers (except atenolol) or verapamil, in order of preference, should be considered for prevention of SVT in patients without WPW syndrome.	IIa
In pregnant women, flecainide or propafenone should be considered for prevention of SVT in patients with WPW syndrome and without ischaemic or structural heart disease.	IIa

[a]Class of recommendation

AF, atrial fibrillation; AP, accessory pathway; AT, atrial tachycardia; AV, atrioventricular; EPS, electrophysiology study; ERP, effective refractory period; HF, heart failure; i.v., intravenous; LV, left ventricular; POTS, postural orthostatic tachycardia syndrome; SPERRI, shortest pre-excited RR interval during AF; SVT, supraventricular tachycardia; TCM, tachycardiomyopathy; WPW, Wolff-Parkinson-White.

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Table 9. Key Messages from the 2019 Guidelines on Supraventricular Tachycardia: 'What to Do' and 'What not to Do'

'What to do' messages	Class[a]	Level[b]
Recommendations for acute management of narrow QRS tachycardia in the absence of an estabished diagnosis		
Haemodynamically stable patients		
A 12 lead ECG during tachycardia is recommended.	I	C
Vagal manoeuvres, preferably in the supine position with leg elevation, are recommended.	I	B
Adenosine (6-8 mg i.v. bolus) is recommended if vagal manoeuvres fail.	I	B
Recommendations for acute management of wide QRS tachycardia in the absence of an estabished diagnosis		
Haemodynamically stable patients		
A 12 lead ECG during tachycardia is recommended.	I	C
Vagal manoeuvres are recommended.	I	C
Recommendations for the therapy of focal AT		
Chronic therapy		
Catheter ablation is recommended for recurrent focal AT, especially if incessant or causing TCM.	I	B
Recommendations for the therapy of focal MRATs		
Anticoagulation as in AF is recommended for patients with atrial flutter and concomitant AF.	I	B
Chronic therapy		
Catheter ablation is recommended for symptomatic, recurrent episodes of CTI-dependent flutter.	I	A
Catheter ablation is recommended in patients with persistent atrial flutter or in the presence of depressed LV systolic function due to TCM.	I	B
Recommendations for the management of focal AVNRT		
Chronic therapy		
Catheter ablation is recommended in symptomatic, recurrent AVNRT.	I	B
Recommendations for the therapy of AVRT due to manifest or concealed APs		
Catheter ablation of AP(s) is recommended in patients with symptomatic, recurrent AVRT.	I	B
Recommendations for the acute therapy of pre-excited AF		
Haemodynamically stable patients		
Synchronised DC cardioversion is recommended if drug therapy fails to convert or control the tachycardia.	I	B
Recommendations for the management of patients with asymptomatic pre-excitation		
Performance of an EPS, with the use of isoprenaline, is recommended to risk stratify individuals with asymptomatic pre-excitation who have high-risk occupations/hobbies and those who participate in competitive athletics. Catheter ablation is recommended in asymptomatic patients in whom electrophysiology testing with use of isoprenaline identifies high-risk properties, such as SPERRI ≤250 ms, AP ERP ≤250 ms, multiple APs, and an inducible AP-mediated tachycardia.	I	B
Recommendations for the therapy SVT in pregnancy		
Catheter ablation is recommended in symptomatic women with recurrent SVT who plan to become pregnant.	I	C
Chronic therapy		
During the first tremester of pregnancy, it is recommended that all antiarrhythmic drugs are avoided, if possible.	I	C
Recommendations for the therapy of SVT in patients with suspected or established HF due to TCM		
Catheter ablation is recommended for TCM due to SVT.	I	B
AV nodal ablation with subsequent pacing ('ablate and pace'), either biventricular or His-bundle pacing, is recommended if the tachycardia responsible for the TCM cannot be ablated or controlled by drugs.	I	C

'What not to do' messages		
Recommendations for the acute management of wide QRS tachycardia in the absence of an established diagnoses		
Verapamil is not recommended in wide QRS-complex tachycardia of unknown aetiology.	III	B
Recommendations for the therapy of MRATs		
Acute therapy		
Propafenone and flecainide are not recommended for conversion to sinus rhythm.	III	B
Recommendations for the therapy of AVRT due to manifest or concealed APs		
Chronic therapy		
Digoxin, beta-blockers, diltiazem, verapamil, and amiodarone are not recommended and are potentially harmful in patients with pre-excited AF.	III	B
Recommendations for the acute therapy of pre-excited AF		
Haemodynamiccally stable patients		
Amiodarone (i.v.) is not recommended.	III	B
Recommendations for the therapy of SVTs in congenital heart disease in adults		
Chronic therapy		
Sotalol is not recommended as a first-line antiarrhythmic drug as it is related to an increased risk of pro-arrhythmias and mortality.	III	C
Flecainide and propafenone are not recommended as first-line antiarrhythmic drugs in patients with ventricular dysfunction and severe fibrosis.	III	C

Recommendations for the therapy of SVT in pregnancy		
Chronic therapy		
Amiodarone is not recommended in pregnant woman.	III	C

[a]Class of recommendation; [b]Level of evidence.

AF, atrial fibrillation; AP, accessory pathway; AT, atrial tachycardia; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; CTI, cavotricuspid isthmus; DC, direct current; ECG, electrocardiogram; EPS, electrophysiology study; ERP, effective refractory period; HF, heart failure; i.v., intravenous; MRAT, macro-re-entrant atrial tachycardia; SPERRI, shortest pre-excited RR interval during AF; SVT, supraventricular tachycardia; TCM, tachycardiomyopathy.

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Table 10. 'What to do' and 'What not to do' in the Management of CVD in Diabetes Patients

Diagnosis of disorders of glucose metabolism		
Recommendations	**Class[a]**	**Level[b]**
It is recommended that screening for potential T2DM in patients with CVD is initiated with HbA1c and FPG, and that an OGTT is added if HbA1c and FPG are inconclusive.	I	A
It is recommended that an OGTT is used to diagnose IGT.	I	A
It is recommended that the diagnosis of DM is based on HbA1c and/or FPG, or on an OGTT if still in doubt.	I	B
Use laboratory, ECG, and imaging testing for CV risk assessement in asymptomatic patients with DM		
Routine assessement of microalbuminuria is indicated to identify patients at risk of developing renal dysfunction or at high risk of future CVD.	I	B
A resting ECG is indicated in patients with DM diagnosed with hypertension or with suspected CVD.	I	C
Carotid ultrasound intima–media thickness screening for CV risk assessment is not recommended.	III	A
Routine assessment of circulating biomarkers is not recommended for CV risk stratification.	III	B
Risk scores developed for the general population are not recommended for CV risk assessement in patients with DM.	III	C
Lifestyle modifications in DM and pre-DM		
Smoking cessation guided by structured advice is recommended in all individuals with DM and pre-DM.	I	A
Lifestyle intervention is recommended to delay or prevent the conversion of pre-DM states, such as IGT, to T2DM.	I	A
Reduced calorie intake is recommended for lowering excessive body weight in individuals with pre-DM and DM.[c]	I	A
Moderate-to-vigorous physical activity, notably a combination of aerobic and resistance exercise for ≥150 min/week, is recommended for the prevention and control of DM, unless contraindicated, such as when there are servere comorbidities or a limited life expactancy.[d]	I	A
Vitamin or micronutrient supplementation to reduce the risk of DM or CVD in patients with DM is not recommended.	III	B
Glycaemic control in DM		
It is recommended to apply tight glucose control, targeting a near-normal HbA1c (< 7.0% or < 53 mmol/mol), to decrease microvascular complications in patients with DM.	I	A
It is recommended that HbA1c targets are invidualised according to the duration of DM, comorbidities, and age.	I	C
Avoidance of hypoglycaemia is recommended.	I	C
Management of blood pressure in patients with DM and pre-DM		
Treatment targets		
Antihypertensive drug treatment is recommended for people with DM when office BP is > 140/90 mmHg.	I	A
It is recommended that a patient with hypertension and DM is treated in an individualised manner. The BP goal is to target SBP to 130 mmHg and < 130 mmHg if tolerated, but not < 120 mmHg. In older people (aged > 65 years), the SBP goal is to a range of 130-139 mmHg.	I	A
It is recommended to target DBP to < 80 mmHg but not < 70 mmHg.	I	C
Treatment and evaluation		
Lifestyle changes [weight loss if overweight, physcal activity, alcohol restriction, sodium restriction, and increased consumption of fruits (e.g. 2-3 servings), vegetables (e.g. 2-3 servings), and low-fat dairy products] are recommended in patients with DM and pre-DM with hypertension.	I	A
A RAAS blocker (ACEIor ARB) is recommended in the treatment of hypertension in patients with DM, particularly in the presence of microalbumimuria, albumimuria, proteinuria, or LV hypertrophy.	I	A
It is recommended that treatment is initiated with a combination of a RAAS blocker with calcium channel blocker or a thiazide/thiazide-like diuretic.	I	A
Management of dyslipidaemia with lipid-lowering agents		
Targets		
In patients with T2DM at moderate CV risk,[e] an LDL-C target of < 2.6 mmol/L (< 100mg/dL) is reommended.	I	A
In patients with T2DM at high CV risk,[e] an LDL-C target of < 1.8 mmol/L (< 70 mg/dL) and LDL-C reduction of at least 50% is reommended.[f]	I	A
In patients with T2DM at very high CV risk,[e] an LDL-C target of < 1.4 mmol/l (<55 mg/dL) and LDL-C reduction of at least 50% is recommended.[f]	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of < 2.2 mmol/L (< 85 mg/dL) in very high-CV risk patients and < 2.6 mmol/L (< 100 mg/dL) in high-CV risk patients is recommended.	I	B
Treatments		
Statins are recommended as the first-choice lipid-lowering treatment in patients with DM and high LDL-C levels: administration of statins is defined based on the CV risk profile of the patient[e] and the recommended LDL-C (or non-HDL-C) target levels.	I	A
If the target LDL-C is not reached, combination therapy with ezetimibe is recommended.	I	B
In patients at very high CV risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance, a PCSK9 inhibitor is recommended.	I	A
Statins are not recommended in women of childbearing potential.	III	A
Antiplatelet therapy in primary prevention in DM		
In patients with DM at moderate CV risk,[e] aspirin for primary prevention is not recommended.	III	B
Glucose-lowering treatment in DM		
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[e] to reduce CV events.	I	A

Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.	I	B
GLP-1 RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[e] to reduce CV events.	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[e] to reduce the risk of death.	I	B
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF.	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and high risk of HF.	III	B
Management of patients with DM, and ACS or CCS		
ACEIs or ARBs are indicated in patients with DM and CAD to reduce the risk of CV events.	I	A
Statin therapy is recommended in patients with DM and CAD to reduce the risk of CV events.	I	A
Aspirin at a dose of 75-160 mg/day is recommended as secondary prevention in patients with DM.	I	A
Treatment with a $P2Y_{12}$ receptor blocker, ticagrelor or prasugrel, is recommended in patients with DM and ACS for 1 year with aspirin, and in those who undergo PCI or CABG.	I	A
Concomitant use of a proton pump inhibitor is recommended in patients receiving DAPT or oral anticoagulant monotherapy who are at high risk of gastrointestinal bleeding.	I	A
Clopidogrel is recommended as an alternative antiplatelet therapy in case of aspirin intolerance.	I	B
Cononary revascularisation in patients with DM		
It is recommended that the same revascularisation techniques are implemented (e.g. the use of DES and the radial approach for PCI, and the use of the left internal mammary artery as the graft for CABG) in patients with and without DM.	I	A
It is recommended to check renal function if patients have taken metformin immediately before angiography and withhold metformin if renal function deteriorates.	I	C
Treatment of HF in patients with DM		
ACEIs and beta-blockers are indicated in symptomatic patients with HFrEF and DM, to reduce the risk of HF hospitalisation and death.	I	A
MRAs are indicated in patients with HFrEF and DM who remain symptomatic despite treatment with ACEIs and beta-blockers, to reduce the risk of HF hospitalisation and death.	I	A
Device therapy with an ICD, CRT, or CRT-D is recommended in patients with DM, as in the general population with HF.	I	A
ARBs are indicated in symptomatic patients with HFrEF and DM who do not tolerate ACEIs, to reduce the risk of HF hospitalisation and death.	I	B
Sacubitril/valsartan is indicated instead of ACEIs to reduce the risk of HF hospitalisation and death in patients with HFrEF and DM who remain symptomatic, despite treatment with ACEIs, beta-blockers, and MRAs.	I	B
Diuretics are recommended in patients with HFpEF, HFmrEF, or HFrEF with signs and/or symptoms of fluid congestion, to improve symptoms.	I	B
Cardiac revascularisation with CABG surgery has shown similar benefits for the reduction of long-term risk of death in patients with HFrEF with and without DM, and is recommended for patients with two- or three-vessel CAD, including a significant LAD stenosis.	I	B
Aliskiren (a direct renin inhibitor) is not recommended for patients with HFrEF and DM because of a higher risk of hypotension, worsening renal function, hyperkalaemia, and stroke.	III	B
T2DM treatment to reduce HF risk		
Recommendations	**Class[a]**	**Level[b]**
SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are recommended to lower risk of HF hospitalisation in patients with DM.	I	A
Thiazolidinediones (pioglitazone and rosiglitazone) are associated with an increased risk of incident HF in patients with DM, and are not recommended for DM treatment in patients at risk of HF (or with previous HF).	III	A
The DPP4 inhibitor saxagliptin is associated with an increased risk of HF hospitalisation, and is not recommended for DM treatment in patients at risk of HF (or with previous HF).	III	B
Management of arrhythmias in patients with DM		
Oral anticoagulation with a NOAC, which is preferred over VKAs, is recommended in DM patients aged > 65 years with AF and a CHA_2DS_2-VASc score ≥ 2, if not contraindicated.	I	A
a) ICD therapy is recommended in DM patients with symptomatic HF (New York Heart Association class II or III) and LVEF ≤ 35% after 3 months of optimal medical therapy, who are expected to survive for at least 1 year with good functional status. b) ICS therapy is recommended in DM patients with documented ventricular fibrillation or haemodynamically unstable VT in the absence of reversible causes, or within 48 hours of MI.	I	A
Beta-blockers are recommended for patients with DM with HF after acute MI with LVEF < 40%, to prevent sudden cardiac death.	I	A
Diagnosis and management of PAD in patients with DM		
Carotid artery disease		
In patients with DM and carotid artery disease it is recommended to implement the same diagnostic workup and therapeutic options (conservative, surgical, or endovascular) as in patients without DM.	I	C
LEAD diagnosis		
Screening for LEAD is indicated on a yearly basis, with clinical assessment and/or ABI measurement.	I	C
Patient education about foot care is recommended in patients with DM, and especially those with LEAD, even if asymptomatic. Early recognition of tissue loss and/or infection, and referral to a multidisciplinary team,[g] is mandatory to improve limb salvage.	I	C
An ABI < 0.90 is diagnostic for LEAD, irrespective of symptoms. In case of symptoms, further assessment, including duplex ultrasound, is indicated.	I	C
In case of elevated ABI (> 1.40), other non-invasive tests, including TBI or duplex ultrasound, are indicated.	I	C
Duplex ultrasound is indicated as the fist-line imaging method to assess the anatomy and haemodynamic status of lower extremity arteries.	I	C
CT angiography or magnetic resonance angiography is indicated in case of LEAD when revascularisation is considered.	I	C
LEAD management		
In patients with DM and symptomatic LEAD, antiplatelet therapy is recommended.	I	A
As patients with DM and LEAD are at very high CV risk,[d] an LDL-C target of <1.4 mmol/L (< 55 mg/dL) or an LDL-C reduction of at least 50% is recommended.	I	B

In patients with DM with CLTI, the assessment of the risk of amputation is recommended; the WIfI score[h] is useful for this purpose.	I	B
In case of CLTI, revascularisation is indicated whenever feasible for limb salvage.	I	C
Prevention and management of CKD in patients with DM		
It is recommended that patients with DM are screened annually for kidney disease by assessment of eGFR and urinary albumincreatinine ratio.	I	A
Tight glucose control, targeting HbA1c < 7.0% (or < 53 mmol/mol), is recommended to decrease microvascular complications in patients with DM.	I	A
It is recommended that patients with hypertension and DM are treated in an individualised manner, SBP to 130 mmHG and < 130 mmHG if tolerated, but not < 120 mmHg. In older people (aged > 65 years) the SBP goal is to a range of 130-139 mmHg.	I	A
A RAAS blocker (ACEI or ARB) is recommended for the treatment of hypertension in patients with DM, particularly in the presence of proteinuria, microalbuminuria, or LVH.	I	A
Treatment with an SGLT2 inhibitor (empagliflozin, canagliflozin, or dapagliflozin) is associated with a lower risk of renal endpoints and is recommended if eGFR is 30 to < 90 mL/min/1.73m²).	I	B
Patient-centred care in DM		
Group-based structured education programmes are recommended in patients with DM, to improve DM knowledge, glycaemic control, disease management, and patient empowerment.	I	A
Patient-centred care is recommended to facilitate shared control and decision-making within the context of patient priorities and goals.	I	C

ABI, ankle–brachial index; ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndromes; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, chronic coronary syndromes; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years (Doubled), Diabetes mellitus, Stroke or transient ischaemic attack (Doubled), Vascular disease, Age 65–74 years, Sex category; CKD, chronic kidney disease; CLTI, chronic limb-threatening ischaemia; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with implantable defibrillator; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; DBP, diastolic blood pressure; DES, drug-eluting stent; DM, diabetes mellitus; DPP4, dipeptidyl peptidase-4; EAS, European Atherosclerosis Society; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FPG, fasting plasma glucose; GLP1-RA, glucagon-like peptide-1 receptor agonist; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HR, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; IGT, impaired glucose tolerance; LAD, left anterior descending coronary artery; LDL-C, low-density lipoprotein cholesterol; LEAD, lower extremity artery disease; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI,myocardial infarction; MRAs, mineralocorticoid receptor antagonists; NOAC, non-vitamin K antagonist oral anticoagulant; OGTT, oral glucose tolerance test; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter 2; T2DM, type 2 diabetes mellitus; TBI, toe-brachial index; VKA, vitamin K antagonist; VT, ventricular tachycardia; WIfI, Wound, Ischaemia, and foot Infection.

[a]Class of recommendation. [b]Level of evidence. [c]A commonly stated goal for obese patients with DM is to lose around 5% of baseline weight. [d]It is recommended that all individuals reduce the amount of sedentary time by breaking up periods of sedentary activity with moderate-to-vigorous physical activity in bouts of ≥10 min (broadly equivalent to 1000 steps). [e]See Table 7 of Cosentino F et al. *Eur Heart J*. 2019. doi:10.1093/eurheartj/ehz486. [f]See the 2019 ESC/EAS Guidelines for the management of dyslipidaemias for non-HDL-C and apolipoprotein B targets. [g]Including a diabetologist and a vascular specialist. [h]See Table 12 of Cosentino F et al. *Eur Heart J*. 2019. doi:10.1093/eurheartj/ehz486

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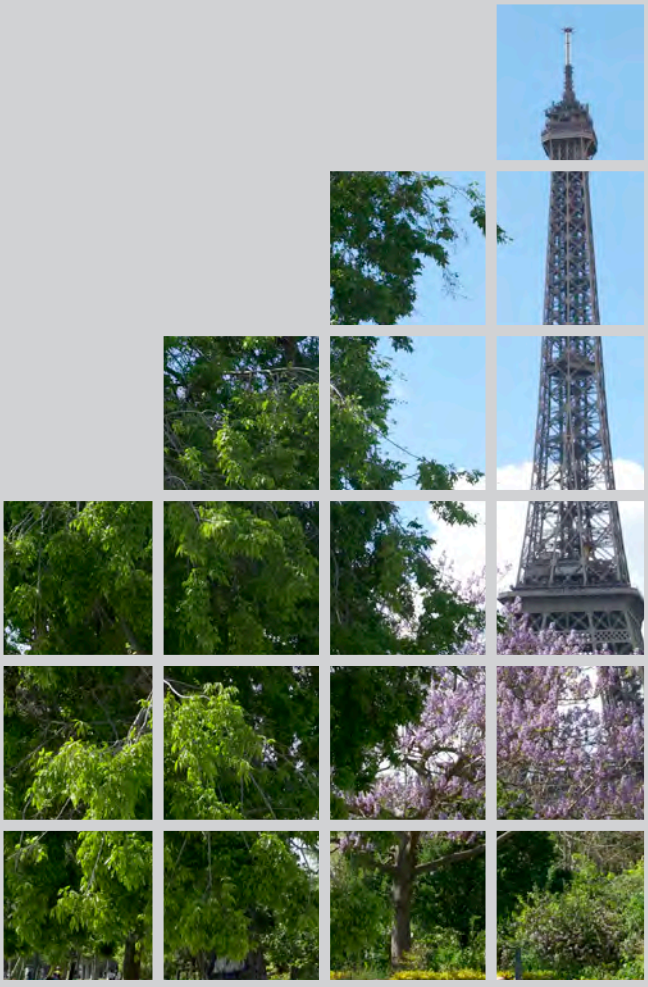
The editors would like to thank the many members of the ESC Congress 2019 presenting faculty who generously gave their time to ensure the accuracy and quality of the articles in this publication



Late-Breaking Science

Ticagrelor versus Prasugrel in Patients with Acute Coronary Syndrome

Written by **Michiel Tent**

Among patients with acute coronary syndrome (ACS) with or without ST-segment elevation, prasugrel was associated with a significantly lower incidence of death, myocardial infarction, or stroke at 1 year than was ticagrelor in the ISAR-REACT 5 study [Schüpke S et al. *N Engl J Med* 2019]. The incidence of major bleeding was not significantly different.

Both prasugrel and ticagrelor have a class I recommendation for 1-year use in ACS patients with and without ST-segment elevation. Thus far, a head-to-head comparison of these 2 agents had not yet been performed in ACS patients with planned invasive strategy. ISAR-REACT 5 was an investigator-initiated, multicentre, randomised, open-label trial testing the hypothesis that ticagrelor is superior to prasugrel in these patients. Lead author Stefanie Schüpke, MD, Deutsches Herzzentrum München, Munich, Germany, said 4,018 patients admitted for ACS and planned invasive strategy were enrolled in 23 German and Italian centres. She stressed that not only were 2 $P2Y_{12}$ receptor antagonists compared, but in fact 2 different antiplatelet treatment strategies in non-ST-segment elevation ACS, i.e., pre-treatment versus no pre-treatment. The timing of ticagrelor administration was the same irrespective of clinical presentation and knowledge on coronary anatomy; it was given as soon as possible after randomisation and before percutaneous coronary intervention (PCI). In ST-elevation myocardial infarction (STEMI) patients, prasugrel was also given as soon as possible. However, in patients with non-ST-segment elevation ACS, administration of prasugrel was postponed until coronary anatomy was known and before proceeding to PCI. An exception was made for patients with known coronary anatomy in whom pre-treatment was allowed.

A total of 4,018 patients were randomised; mean age was 64 years, 23.8% were women. At baseline, 46% had non-STEMI, 41% had STEMI, and 13% had unstable angina. In 84% of patients, PCI was performed, the others underwent coronary artery bypass grafting (2%) or received conservative therapy (14%). After 12 months, 15.2% and 12.5% of patients in the ticagrelor and prasugrel group permanently discontinued the drug at a median timing of 2.5 months and 3.5 months from randomisation, respectively.

At 1 year, the primary composite endpoint of death, myocardial infarction, or stroke occurred in 184 of 2,012 patients (9.3%) in the ticagrelor group and in 137 of 2,006 patients (6.9%) in the prasugrel group (HR, 1.36; 95% CI, 1.09 to 1.70; *P* = .006). The lower incidence of the composite endpoint was primarily driven by fewer myocardial infarctions in the prasugrel group than in the ticagrelor group. The respective incidences of the individual components in the ticagrelor and prasugrel group were:

- death 4.5% and 3.7%;
- myocardial infarction 4.8% and 3.0%; and
- stroke 1.1% and 1.0%.

Treatment effects were consistent irrespective of clinical presentation. Dr Schüpke noted that these results came not at the expense of a higher bleeding risk in the prasugrel group. Major bleeding (BARC type 3 to 5) was observed in 5.4% of patients in the ticagrelor group and in 4.8% of patients in the prasugrel group (HR, 1.12; 95% CI, 0.83 to 1.51; *P* = .46). Definite or probable stent thrombosis occurred in 1.3% and 1.0% of patients in the ticagrelor and prasugrel group, respectively; definite stent thrombosis occurred in 1.1% and 0.6%.

The scheduled discussant of the ISAR-REACT 5 study was Gilles Montalescot, MD, PhD, Pitié-Salpêtrière Hospital, Paris, France. He noted a few weaknesses, notably the randomisation by envelopes and the open-label design. Nevertheless, he considered ISAR-REACT 5 a landmark study, which will impact the 2020 guidelines for the treatment of ACS.

Supplemental Oxygen Does Not Lower Mortality in ACS Patients

Written by **Michiel Tent**

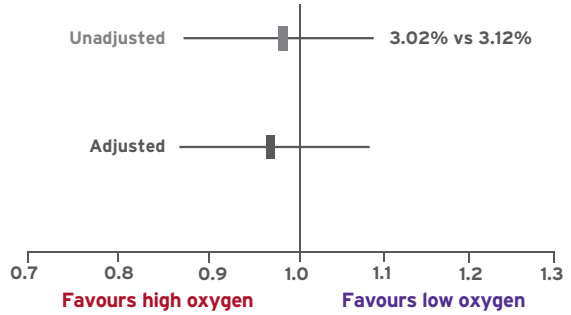
In a New Zealand-wide study of non-hypoxaemic or mildly hypoxaemic patients presenting with suspected acute coronary syndrome (ACS), a liberal oxygen strategy was neither beneficial nor harmful and did not significantly alter 30-day all-cause mortality.

Supplemental oxygen has been part of the treatment of non-hypoxaemic patients presenting with ST-elevation myocardial infarction (STEMI) for over 50 years, but no large clinical trial has yet shown that it improves outcomes. However, a modest favourable or harmful effect could not be excluded. The New Zealand Oxygen Therapy in Acute Coronary Syndrome [NZOTACS; Stewart R et al. *Heart Lung Circ*. 2019] study was a pragmatic, randomised, cross-over trial, explained Ralph Stewart, MD, University of Auckland, New Zealand, who presented its results. The trial compared high flow versus no oxygen (a liberal and a conservative protocol, respectively) in

ambulances, emergency departments, coronary care units, and cardiac catheter laboratories for all patients with suspected or diagnosed ACS throughout New Zealand. The liberal oxygen protocol recommended high-flow oxygen (6 to 8 L/min by face mask) irrespective of oxygen saturation (SpO_2). The conservative protocol recommended oxygen only if SpO_2 was < 90%, with the target being an SpO_2 of 90 to 94%. The study population included all patients participating in 2 national registries: the All New Zealand Acute Coronary Syndromes Quality Improvement Registry (ANZACS-QI; n = 19,566) and the St John Ambulance ACS pathway (n = 29,401). The primary outcome was 30-day mortality for all patients with suspected ACS. The liberal and the conservative protocol were evaluated in 20,304 and 20,568 patients, respectively. Baseline characteristics were well matched for the 2 protocols.

All-cause mortality at 30 days for all patients with suspected ACS was 613 (3.02%) in the liberal protocol group and 642 (3.12%) in the conservative protocol group (OR, 0.97; 95% CI, 0.86 to 1.08; *P* = .55; Figure 5). There was a trend towards benefit in the 11% of patients with SpO_2 < 95% on ambulance arrival. Mortality after 30 days was 168 (10.1%) in the liberal oxygen group and 179 (11.1%) in the conservative protocol group (OR, 0.88; 95% CI, 0.70 to 1.11); this 12% reduction in mortality was not significant but may suggest a trend to benefit, the authors concluded. In the 4,159 patients with STEMI, 30-day mortality was 178 (8.8%) in the liberal protocol group and 225 (10.6%) in the conservative protocol group (OR, 0.81; 95% CI, 0.66 to 1.00). Prof. Stewart noted that the STEMI subgroup findings should be considered hypothesis-generating. Because the study design allowed for clinician and patient choice and use of oxygen was not blinded, protocol non-adherence was higher than in blinded trials where therapies are mandated. Furthermore, the 2 registry populations used for oxygen-protocol evaluation included some patients who did not present with ischaemic symptoms, therefore lacking indication for oxygen administration. These factors reduced the power of the study to detect modest differences between protocols.

Figure 5. Primary Endpoint: Death at 30 days



Reproduced with kind permission from Prof. R. Stewart

Patients with suspected ACS with a normal oxygen saturation level are unlikely to benefit from high-flow oxygen, Prof. Stewart concluded. High-flow oxygen may improve outcomes for patients with SpO_2 < 95% and for those with STEMI, but this should be confirmed in another study. Robin Hofmann, MD, PhD, Karolinska Institute, Stockholm, Sweden, who was the scheduled discussant of the results at the presentation, said this study provided level A evidence that routine oxygen should not be given in patients with SpO_2 ≥ 90%. To identify subgroups who may benefit from oxygen therapy and its ideal cut-off value, more data from existing or new trials are warranted.

PARAGON-HF Misses Endpoint in Preserved Heart Failure, but Sacubitril/Valsartan Benefits Some Patients

Written by **Rachel Giles**

The full results of the PARAGON-HF trial [NCT01920711; Solomon SD et al. *N Engl J Med* 2019] provided some evidence that sacubitril/valsartan treatment might improve outcomes in certain patient subsets; although it failed to significantly reduce the risk of hospitalisation for heart failure or cardiovascular death in patients with heart failure with preserved ejection fraction (HFpEF).

Sacubitril/valsartan is currently approved to improve outcomes in patients with chronic heart failure with reduced ejection fraction (HFrEF; 40% or lower) based on previous results, which showed that the angiotensin receptor/neprilysin inhibitor significantly reduced a composite of cardiovascular death or hospitalisation for heart failure [McMurray J et al. *N Engl J Med* 2014]. However, there is no evidence of therapies improving outcomes in patients with preserved ejection fraction. PARAGON-HF attempted to fill that evidence gap.

The trial enrolled 4,822 patients (mean age 73 years; 52% women) who had NYHA class II to IV heart failure, an ejection fraction of 45% or higher, elevated natriuretic peptides, and evidence of structural heart disease. They were randomised to sacubitril/valsartan (with target doses of 97 mg for sacubitril and 103 mg for valsartan) or valsartan alone (with a target dose of 160 mg) taken twice daily. All background medications were continued, except for renin/angiotensin system inhibitors other than mineralocorticoid receptor antagonists.

With a median follow-up of nearly 3 years, the rate of the composite primary endpoint per 100 patient years was 12.8 with sacubitril/valsartan and 14.6 with valsartan alone (HR, 0.87; 95% CI, 0.75 to 1.01; *P* = .06) (Table 11). Scott Solomon, MD, Brigham and Women's Hospital,

Table 11. Primary and Secondary Outcomes of PARAGON-HF

Outcome	Sacubitril-Valsartan (n = 2,407)	Valsartan (n = 2,389)	Ratio Difference (95% CI)
Primary composite outcome and components			
Total hospitalisations for heart failure and death from cardiovascular causes[a]			RR, 0.87 (0.75 - 1.01)
Total no. of events	894	1,009	
Rate per 100 patient-years	12.8	14.6	
Total no. hospitalisations for heart failure	690	797	RR, 0,85 (0.72 - 1.00)
Death from cardiovascular causes – no. (%)	204 (8.5)	212 (8.9)	HR, 0,95 (0.79 - 1.16)
Secondary outcomes			
Change in NYHA class from baseline to 8 months – no./total no. (%)			OR, 1.45 (1.13 - 1.86)
Improved	347/2,316 (15.0)	289/2,305 (12.6)	
Unchanged	1,767/2,316 (76.3)	1,792/2,302 (77.8)	
Worsened	202/2,316 (8.7)	221/2,302 (9.6)	
Change in KCCQ clinical summary score at 8 months[b]	-1.6±0.4	-2.6±0.4	Difference, 1.0 (0.0 - 2.1)
Renal composite outcome – no. (%)[c]	33 (1.4)	64 (2.7)	HR, 0.50 (0.33 - 0.77)
Death from any cause – no. (%)	342 (14.2)	349 (14.6)	HR, 0.97 (0.84 - 1.13)

CI, confidence interval; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy; OR; odds ratio; RR, rate ration.
Plus-minus values are means ±SD. CI for secondary and exploratory efficacy outcomes have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible.
[a] Total hospitalisations for heart failure included first and recurrent events. The primary analysis was based on the model of Lin DW et al. J R Stat Soc B 2000;62:711-30 and the composite outcome was adjudicated. [b] KCCQ scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations. [c] The renal composite outcome was defined as death from renal failure, end-stage renal disease, or a decrease in the estimated glomerular filtration rate of 50% or more from baseline.

Boston, MA, USA, commented during his presentation that the study "just missed statistical significance".

Several secondary outcomes indicated an advantage for sacubitril/valsartan, such as improvement of New York Heart Association (NYHA) Classification for 15.0% of patients treated with sacubitril/valsartan (vs 12.6% on valsartan alone; OR, 1.45; 95% CI, 1.13 to 1.86; *P* = .004). Furthermore, patients in the sacubitril/valsartan arm were more likely to have at least a 5-point improvement on the Kansas City Cardiomyopathy Questionnaire clinical summary score (33.0% vs 29.6%; OR, 1.30; 95% CI, 1.04 to 1.61; *P* = .02), and they were less likely to have worsening renal function (1.4% vs 2.7%; HR, 0.50; 95% CI, 0.33 to 0.77; *P* = .002). The PARAGON investigators observed evidence of significant heterogeneity with greater benefit observed in patients with ejection fraction at or below the median of 57% and in women. In the context of the benefit observed in patients with HFrEF in PARADIGM-HF, these findings suggest that patients with heart failure and ejection fraction that is below normal but not frankly reduced may also benefit from sacubitril/valsartan.

Safety and tolerability of sacubitril/valsartan were similar to what was seen in patients with HFrEF, with a higher rate of hypotension and lower rates of elevated potassium and creatinine compared with valsartan alone. Angio-oedema was more frequent in the sacubitril/valsartan arm (0.6% vs 0.2%), although none of the cases were associated with airway compromise.

In conclusion, sacubitril/valsartan did not result in a significantly lower rate of total hospitalisations for heart failure and death from cardiovascular causes among patients with heart failure and an ejection fraction of 45% or higher, although further analyses may indicate clinical benefit for particular subgroups of patients. Future research should focus on the potential role of angiotensin receptor/neprilysin inhibition in patients with a mildly reduced ejection fraction.

Rivaroxaban Alone versus Combination Therapy in Patients with AF and CAD

Written by **Michiel Tent**

As anticoagulant regimen, rivaroxaban monotherapy was non-inferior to combination therapy with rivaroxaban plus an antiplatelet agent with respect to cardiovascular (CV) events and death from any cause, and superior in

terms of major bleeding in patients with atrial fibrillation (AF) and stable coronary artery disease (CAD). This was the main conclusion from the primary results of the Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease Study [AFIRE; Yasuda S et al. *N Engl J Med* 2019].

Current European and US guidelines recommend monotherapy with an oral anticoagulant after 12 months of combination therapy with an anticoagulant and a $P2Y_{12}$ inhibitor in patients with AF and stable CAD. However, evidence from randomised controlled trials for this approach is lacking, particularly for direct oral anticoagulants. This is why the multicentre, open-label AFIRE trial was performed in Japan. It aimed to investigate whether rivaroxaban monotherapy is non-inferior to combination therapy in patients with AF ($CHADS_2$ score ≥ 1) and stable CAD more than 1 year after revascularisation, or in those with angiographically confirmed CAD not requiring revascularisation. The 2,236 participants were randomised to rivaroxaban 15 mg daily (or 10 mg when creatinine clearance < 50 mL; i.e., the approved dosing regimen in Japan) monotherapy, or to rivaroxaban at these doses plus a single antiplatelet agent: aspirin, clopidogrel, or prasugrel. The primary efficacy endpoint was a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularisation, or death from any cause. This endpoint was analysed for non-inferiority with a margin of 1.46 (power 80%). The primary safety endpoint was major bleeding.

The trial was terminated prematurely due to a higher risk of death from any cause in the combination-therapy group. As the trial's first author, Satoshi Yasuda, MD, PhD, National Cerebral and Cardiovascular Center, Suita, Japan, pointed out, not only was the efficacy of the monotherapy non-inferior to the combination therapy, it was in fact better. The cumulative incidence of the primary efficacy endpoint was 4.14% per patient year in the monotherapy group and 5.75% in the combination group (HR, 0.72; 95% CI, 0.55 to 0.95; *P* < .001 for non-inferiority; *P* = .02 for superiority). Safety of the monotherapy was superior with cumulative incidence rates of the primary safety event of 1.62% and 2.76% per patient year in the monotherapy and combination-therapy group, respectively (HR, 0.59; 95% CI, 0.39 to 0.89; *P* = .01 for superiority). In both groups, 2 fatal bleeding events occurred. Incidence rates of secondary efficacy and safety endpoints can be found in Table 12.

The main limitations of the study were the open-label design, potentially introducing bias; the relatively high rates of withdrawal of consent and loss of patients to follow-up; and the trial population receiving 15 mg / 10 mg of rivaroxaban daily rather than the globally approved once-daily dosage of 20 mg / 15 mg, which may have led to an underestimation of the bleeding risk. Also, the early termination of the trial may have caused an overestimation of the efficacy data. To confirm and extend the outcomes of the AFIRE study in a European cohort, the French AQUATIC study will start in 2020, recruiting 2,000 subjects. The present results support the general concept that rivaroxaban monotherapy without antiplatelet therapy is the better approach for patients with AF and stable CAD.

Table 12. Incidence Rates of All Secondary Endpoints

Endpoint – no. of patients (% per patient year)	Rivaroxaban monotherapy (n = 1,107)	Combination therapy (n = 1,108)	HR (95% CI)
All-cause death #	41 (1.85)	73 (3.37)	0.55 (0.38 - 0.81)
Cardiovascular	26 (1.17)	43 (1.99)	0.59 (0.36 - 0.96)
Non-cardiovascular	15 (0.68)	30 (1.39)	0.49 (0.27 - 0.92)
Cardiovascular events			
Ischaemic stroke #	21 (0.96)	28 (1.31)	0.73 (0.42 - 1.29)
Haemorrhagic stroke #	4 (0.18)	13 (0.60)	0.30 (0.10 - 0.92)
Myocardial infarction #	13 (0.59)	8 (0.37)	1.60 (0.67 - 3.87)
Unstable angina requiring revascularisation	13 (0.59)	18 (0.84)	0.71 (0.35 - 1.44)
Systemic embolism	2 (0.09)	1 (0.05)	1.97 (0.18 - 21.73)
Bleeding events			
Major bleeding #	35 (1.62)	58 (2.76)	0.59 (0.39 - 0.89)*
Non-major bleeding	121 (5.89)	198 10.31)	0.58 (0.46 - 0.72)
All bleeding	146 (7.22)	238 (12.72)	0.58 (0.47 - 0.71)
Net adverse clinical events	84 (3.90)	131 (6.28)	0.62 (0.47 - 0.82)

*P = .01

CI, confidence interval; HZ, hazard ratio. The 95% CIs presented in this table have not been adjusted for multiplicity; # components of net adverse clinical events.

Modified from Yasuda S et al. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. *N Engl J Med* 2019. DOI: 10.1056/NEJMoa1904143

EVOPACS: Substantial Cholesterol-Lowering Achieved with Early Evolocumab for High-Risk ACS

Written by **Lisa Buttle**

Adding evolocumab to high-intensity statin therapy in the acute phase of acute coronary syndrome (ACS) significantly reduces low-density lipoprotein cholesterol (LDL-C), allowing > 90% of very high-risk patients to achieve currently recommended targets. This was the finding of the EVOlocumab for early reduction of LDL-cholesterol levels in Patients with Acute Coronary Syndromes [EVOPACS; Koskinas et al. *J Am Coll Cardiol*. 2019] trial presented by Konstantinos C Koskinas, MD, MSc, Bern University Hospital, Switzerland.

EVOPACS was the first randomised, double-blind trial to test LDL-C reduction with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor in the acute phase of ACS, a clinical setting with the highest risk of early event recurrence. Although previous trials have included patients with a history of ACS, the time between the index event and enrolment was much longer, with a mean 2.6 months

in ODYSSEY and more than 3 years in the FOURIER trial, compared with 1 to 3 days in the EVOPACS trial.

In EVOPACS, patients hospitalised for ACS with elevated LDL-C levels were randomised to receive either evolocumab (420 mg subcutaneously/every 4 weeks; n = 155) or matching placebo (n = 153), alongside atorvastatin (40 mg) daily therapy. Most patients (78%) were statin-naïve at baseline.

At 8 weeks, the primary endpoint of percentage change in LDL-C from baseline was -77.1% (mean 3.61 mmol/L to 0.79 mmol/L [139 mg/dL to 31 mg/dL]) in the evolocumab group and -35.4% (mean 3.42 mmol/L to 2.06 mmol/L [132 mg/dL to 80 mg/dL]) in the placebo group (difference in mean percentage change from baseline, -40.7%; 95% CI, -45.2 to -36.2; $P < .001$; Figure 6).

Overall, 95.7% of patients in the evolocumab group and 37.6% in the placebo group reached an LDL-C target of < 1.8 mmol/L (< 70 mg/dL). Moreover, an LDL-C level of <1.4 mmol/L (< 55 mg/dL) –a more stringent target for very high-risk patients set out in the 2019 ESC dyslipidaemia guidelines [Mach F et a l. *Eur Heart J*. 2019]– was achieved by 90.1% with evolocumab versus 10.7% with placebo.

Rates of adverse events, serious adverse events, and events leading to drug discontinuation were similar between groups. Adjudicated cardiovascular events also did not differ in the evolocumab and placebo groups, although the trial was not powered to assess clinical outcomes.

EVOPACS shows that evolocumab can safely and rapidly lower LDL-C in very high-risk ACS patients. These findings warrant further investigation in a dedicated cardiovascular outcomes trial.

Multi-Faceted Intervention in Colombia and Malaysia Lowers CVD Risk

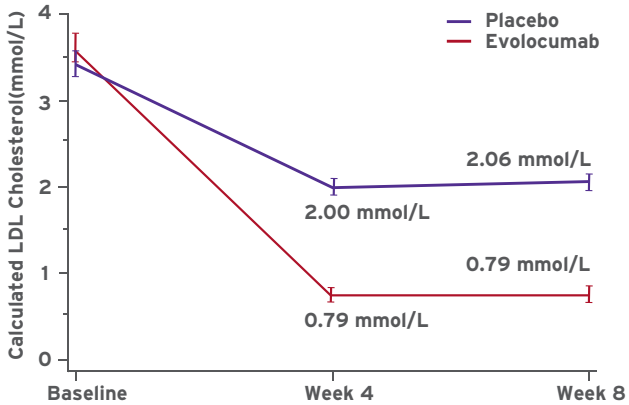
Written by **Michiel Tent**

A comprehensive model of care led by non-physician health workers (NPHWs) resulted in a 49% relative reduction in cardiovascular disease (CVD) risk defined as improvements in systolic blood pressure, LDL cholesterol, medication adherence, and health behaviour in 2 middle-income countries: Colombia and Malaysia. This strategy is widely applicable and scalable.

Hypertension is the leading cause of CVD globally, but hypertension control remains poor [Schwalm JD et al. *Lancet*. 2019]. Of all CVD deaths, 80% occur in low- and middle-income countries. The Heart Outcomes Prevention and Evaluation [HOPE 4; NCT01826019] trial evaluated a community-based intervention focusing on a collaborative approach between NPHWs and primary-care physicians, along with strategies to overcome health system barriers, to substantially reduce CVD risk. It was designed as a community-based cluster randomised controlled trial involving 30 urban and rural communities in Colombia and Malaysia. Participants (n = 1,371) were ≥50 years old with new or poorly controlled hypertension. Communities were randomised to control (usual care; n = 727) or to a multifaceted intervention (n = 644) consisting of:

1. community screening, treatment, and control of CVD risk factors by NPHWs (in conjunction with local physicians) using tablet-based, simplified management algorithms and counselling programmes;

Figure 6. Primary Endpoint: Percentage Change in Low-Density Lipoprotein Cholesterol (LDL-C) at 8 Weeks



No. of patients			
Placebo	148	144	149
Evolocumab	146	136	141
Absolute difference (mmol/L)		1.34	1.43
Percentage difference		38.4%	40.7%
P-value		< .001	< .001

Reprinted from Koskinas KC et al. Evolocumab for Early Reduction of LDL-cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS). *J Am Coll Cardiol*. 2019. DOI: https://doi.org/10.1016/j.jacc.2019.08.010. Copyright 2019 by the American College of Cardiology Foundation. Reprinted with permission from Elsevier.

2. free antihypertensive and cholesterol lowering medication recommended by NPHWs and supervised by physicians; and
3. a treatment supporter (i.e., friend or family) to improve adherence to medication and healthy behaviour.

The primary outcome was change in Framingham Risk Score (FRS) at 12 months. All communities completed 12-month follow-up and provided data on 97% of living participants (n = 1,299).

The results were presented by Jon-David Schwalm, MD, Msc, Population Health Research Institute, McMaster University, and Hamilton Health Sciences, Hamilton, Canada. The reduction in FRS for 10-year CVD risk estimate was 49% larger in the intervention versus control group: -11.17 (95% CI, -12.88 to -9.47) versus -6.40 (95% CI, 8.00 to -4.80). The difference of change is -4.78% (95% CI, 7.11 to -2.44; *P* < .0001; Table 13).

The intervention group saw an absolute greater reduction in systolic blood pressure of 11.45 mmHg (95% CI, -14.94 to -7.97; *P* < .0001), and an LDL reduction of 0.41 mmol/L (95% CI, -0.60 to -0.23; *P* < .0001). Change in blood pressure control status (< 140 mmHg) was 69% in the intervention group versus 30% in the control group (*P* < .0001). The intervention also resulted in substantially higher rates of combination antihypertensive medications (84% vs 65%; *P* < .001), statins (84% vs 38%; P < .001), and medication adherence (61% vs 40%; *P* < .0001) at 12 months. There were no safety concerns described with the intervention.

Dr Schwalm concluded that adaptation of the HOPE 4 strategy to specific contexts and its widespread implementation, including community screening, can help achieve the United Nations General Assembly Action Plan's one-third reduction of premature mortality from CVD.

High-Sensitivity 1-Hour Troponin Assay Facilitates Quicker Discharge in Potential ACS Cases

Written by **Rachel Giles**

A 1-hour protocol including a high-sensitivity troponin T assay compared to standard practice (3-hour protocol) was non-inferior for subsequent death and MI and was associated with faster discharge of patients with suspected acute coronary syndrome (ACS).

In his late-breaking abstract, Derek P. Chew, MBBS, MPH, PhD, Flinders University, Adelaide, Australia, presented the results of the Rapid Assessment of Possible ACS In the emergency Department with high-sensitivity Troponin T [RAPID-TnT; ACTRN12615001379505], which were simultaneously published online [Chew DP et al. *Circulation* 2019].

The researchers randomly allocated 3,288 participants (median age 59 years; 47% women) presenting to the emergency department (ED) between August 2015 and April 2019 to care guided by a 1-hour protocol with a high-sensitivity troponin T assay or to standard care guided by a 3-hour protocol. The 1-hour protocol was based on 2 blood draws, with the relative levels of troponin between the 2 draws stratifying the participants. Patients with substantial elevations in troponin were recommended for admission, those with intermediate levels were recommended for close observation for ACS, and those with very low-level troponin concentrations were considered at low risk for ACS. The primary endpoint was death or myocardial infarction (MI) within 30 days, powered for non-inferiority.

At 30 days, the primary endpoint was met; death or MI occurred in 1% of both groups (incidence rate ratio = 1.06;

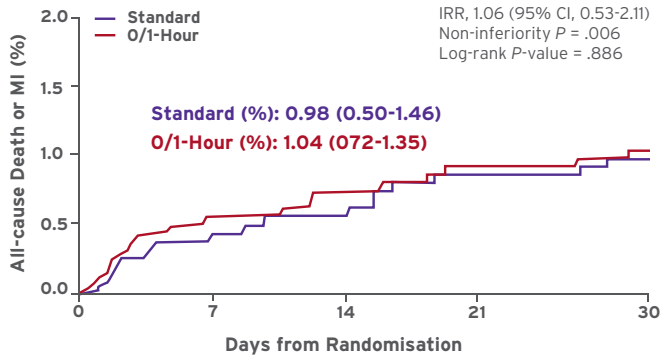
Table 13. Incidence Rates of All Secondary Endpoints

Outcome	Baseline mean (SD) or n (%)		Change at 12 months from baseline* (95% CI)		Test between intervention and control
	Control (n = 727)	Intervention (n = 644)	Control (n = 692)	Intervention (n = 607)	*P*-value
FRS 10-year risk estimate	35.5%	32.6%	-6.4% (-8 to -4.8)	-11.2% (-12.9 to -9.5)	< .0001
SBP (mmHg)	151.8 (15.6)	152.1 (15.4)	-9.7 (-12.1 to -7.3)	-21.1 (-23.7 to -18.6)	< .0001
Controlled SBP < 140 mmHg	125 (17.2%)	74 (11.5%)	30.4 (25.8 to 34.9)	68.9 (64.9 to 72.9)	< .0001
LDL (mmol/L)	3.4 (1.1)	3.3 (1.1)	-0.2 (-0.3 to -0.06)	-0.6 (-0.7 to -0.5)	< .0001

*Mean for within-person differences.

FRS, Framingham Risk Score; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

Figure 7. RAPID-TnT Results: Primary Endpoint (30-day Death or MI)



CI, confidence interval; IRR, incidence rate ratio; MI, myocardial infarction.

Modified from Chew DP et al. A Randomized Trial of a 1-Hour Troponin T Protocol in Suspected Acute Coronary Syndromes: The Rapid Assessment of Possible ACS In the Emergency Department with High Sensitivity Troponin T (RAPID-TnT) Study. *Circulation* 2019. DOI.org/10.1161/CIRCULATIONAHA.119.042891.

95% CI, 0.53 to 2.11; *P* for non-inferiority = .006, *P* for superiority = .867; Figure 7). Among the 1-hour protocol cohort, those discharged from the ED had a 99.6% negative predictive value (95% CI, 99.0 to 99.9) for 30-day MI or death. Individuals treated with the 1-hour protocol were also more likely to be discharged without being admitted than those being treated with the 3-hour protocol (45.1% vs 32.3%; OR, 1.68; 95% CI, 1.45 to 1.93; *P* < .001) and had a shorter median length of stay in the ED (4.6 hours vs 5.6 hours, *P* < .001). In the 3-hour protocol, 33.4% of patients were admitted and the rest were recommended for discharge, whereas in the 1-hour protocol, 8.3% were admitted, 18.7% were admitted for further observation, and 72.1% were ruled out for MI and recommended for discharge.

However, CV rehospitalisation, defined as rehospitalisation for nonelective coronary revascularisation, heart failure, cerebrovascular accident, or arrhythmias at 30 days was somewhat higher in the 1-hour group (1.4% vs 0.9%; incidence rate ratio = 1.53; 95% CI, 1.12 to 2.10; *P* = .008), and the 1-hour group had more cases of MI or myocardial injury (1.6% vs 1.0%; incidence rate ratio, 1.53; 95% CI, 1.14 to 2.04; *P* = .004).

In conclusion, embedding this 1-hour high-sensitivity troponin protocol (Figure 8) into ED care enabled more rapid discharge of suspected ACS patients. Improving short-term outcomes among patients with newly recognised troponin T elevation will require new management strategies for these patients.

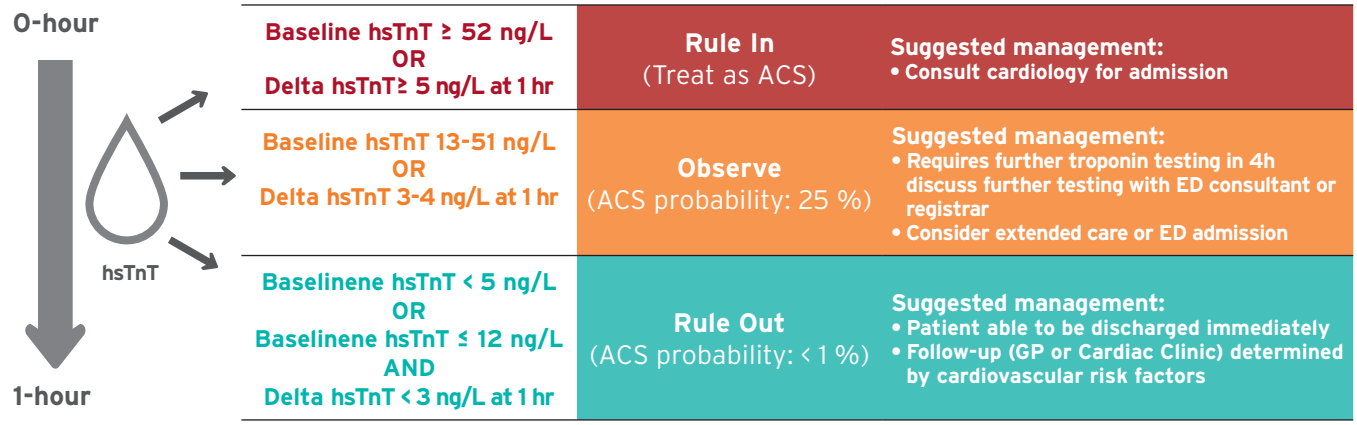
Better Outcomes After PCI of Non-Culprit and Culprit Lesions After STEMI

Written by **Rachel Giles**

The results of the late-breaking clinical trial Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI [COMPLETE; NCT01740479] demonstrated that patients who have ST-segment elevation myocardial infarction (STEMI) with multivessel disease benefit from complete revascularisation of any angiographically significant lesion, rather than percutaneous coronary intervention (PCI) only on the culprit lesion.

Presented in the first Hot Lines session and simultaneously published [Mehta SR et al. *N Engl J Med* 2019], Shamir R. Mehta, McMaster University, Hamilton, Canada, revealed the outcomes of this landmark, international randomised trial. Prior randomised trials that found some evidence of better outcomes in patients treated with non-culprit lesion PCI but these trials were not powered to detect improvements in hard outcomes

Figure 8. One-hour Protocol High-Sensitive Troponin T to Stratify Risk in Patients with Suspected ACS



ACS, acute coronary syndrome; ED, emergency department; hsTnT, high-sensitivity troponin T.

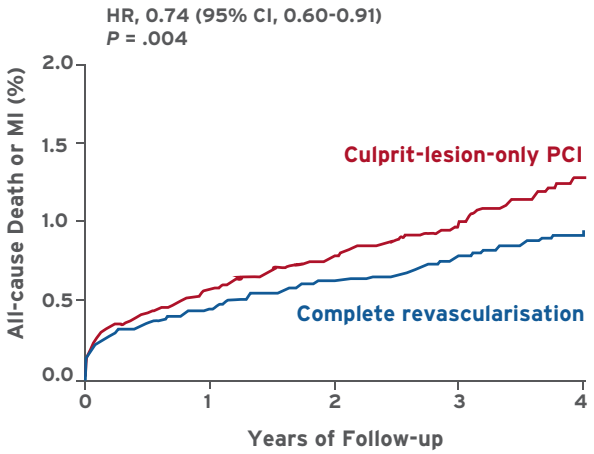
Reproduced with kind permission from Prof. D Chew.

such as cardiovascular death or recurrent myocardial infarction. Observational studies on this question were limited by selection bias and confounders. While meta-analyses suggest a possible reduction in cardiovascular death or myocardial infarction with non-culprit lesion PCI, there has been no single, large trial showing benefit on this clinically important outcome. Thus, it has been unclear whether PCI of non-culprit lesions reduces future cardiovascular events. The COMPLETE trial was designed to address this evidence gap.

A total of 4,041 patients were randomised with STEMI and multivessel coronary artery disease from 140 centres in 31 countries. Patients were randomly allocated to complete revascularisation with additional PCI of angiographically significant non-culprit lesions (n = 2,016), or to no further revascularisation (i.e., culprit-lesion PCI only; n = 2,025).

After a median follow-up of > 3 years, the first coprimary outcome of cardiovascular death or myocardial infarction occurred in 158 patients (7.8%) in the complete-revascularisation group compared with 213 (10.5%) in the culprit-lesion-only group (HR, 0.74; 95% CI, 0.60 to 0.91, *P* = .004; Figure 9). The second coprimary outcome of cardiovascular death, myocardial infarction, or ischaemia-driven revascularisation occurred in 179 patients (8.9%) in the complete-revascularisation group compared with 399 (16.7%) in the culprit-lesion-only group (HR, 0.51; 95% CI, 0.43 to 0.61, *P* < .001). There were no significant differences between groups in the occurrence of stroke (*P* = .27) or major bleeding (*P* = .15).

Figure 9. Cumulative Incidence of the first Coprimary Outcome (i.e., Death from CardiovascularC or new Myocardial Infarction)



HR, hazard ratio; PCI, percutaneous coronary intervention.

Modified from Mehta SR et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med* 2019. DOI: 10.1056/NEJMoa1907775.

Regarding the timing of non-culprit lesion PCI, complete revascularisation consistently reduced the first coprimary outcome in those stratified to receive non-culprit lesion PCI during index hospitalisation (HR, 0.77; 95% CI, 0.59 to 1.00) and after hospital discharge (HR, 0.69; 95% CI, 0.49 to 0.97) (*P* for interaction= .62).

In conclusion, the COMPLETE study conclusively demonstrated that among patients with STEMI and multivessel coronary artery disease, complete revascularisation was superior to culprit-lesion-only PCI in reducing the risk of cardiovascular death or myocardial infarction, as well as the risk of cardiovascular death, myocardial infarction, or ischaemia-driven revascularisation. COMPLETE is the first adequately powered randomised trial that has demonstrated the benefit of complete revascularisation on hard cardiovascular outcomes.

PCI versus CABG: Overall No Difference in Mortality, Yet Subgroups Make the Difference

Written by **Michiel Tent**

10-Year Follow-Up of the SYNTAX Trial

In the SYNTAX Extended Survival study [SYNTAXES; Thuijs DJFM et al. *Lancet*. 2019], no significant difference was found in all-cause death between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in the overall cohort of 1,800 patients with de *novo* 3-vessel disease (3VD) and left main coronary artery disease (LMCAD) after 10 years. However, in the subgroup of patients with 3VD (n = 1,095), CABG provided a significant survival benefit. These results may aid in determining the optimal revascularisation strategy in coronary artery disease patients.

The randomised Synergy between PCI with TAXUS and Cardiac Surgery [SYNTAX; Serruys PW et al. *New Engl J Med* 2009] trial reported comparable survival rates in patients with de *novo* 3VD and LMCAD between PCI with paclitaxel-eluting stents and CABG at 5 years, yet the survival curves appeared to be diverging during the relatively short follow-up. SYNTAXES is the first large-scale randomised trial of PCI versus CABG to determine 10-year survival (n = 1,800; CABG = 897, PCI = 903). The results were assessed according to the intention-to-treat principle. Prespecified subgroup analyses of PCI versus CABG were performed in patients with 3VD, LMCAD, with and without medically treated diabetes, and according to coronary complexity defined by SYNTAX scores.

Daniel Thuijs, MD, MSc, Erasmus University Medical Center, Rotterdam, the Netherlands, pointed out that the 10-year follow-up data had a "remarkably high" rate of completeness of follow-up. Vital status information at 10 years was complete for 841 (93%) patients in the PCI group and 848 (95%) patients in the CABG group. At 10 years, 244 (27%) patients had died after

PCI and 211 (24%) after CABG. The corresponding HR of 1.17 (95% CI, 0.97 to 1.41, *P* = .092) was not significant. In the 3VD subgroup, more patients died after PCI compared with CABG (28% vs 21%, HR, 1.41; 95% CI, 1.10 to 1.80; *P* = .006). In patients with LMCAD, there were no significant differences in death between PCI and CABG (26% vs 28%, HR, 0.90; 95% CI, 0.68 to 1.20; *P* = .47). This treatment-by-subgroup interaction was statistically significant, indicating a potential benefit for CABG in more complex coronary disease (*P* interaction = .019). There was no difference in outcomes based on the presence or absence of diabetes (HR, 1.10; 95% CI, 0.80 to 1.52 vs HR, 1.20; 95% CI, 0.96 to 1.51; *P* interaction = .66). In addition, there was no relationship between SYNTAX score tertiles and outcomes (*P* trend = .30).

Gregg Stone, MD, PhD, Columbia University Medical Center/NewYork-Presbyterian and the Cardiovascular Research Foundation, New York, USA, commented on the SYNTAXES results during the same session. He argued that a multidisciplinary heart team has numerous factors to weigh, in concert with patient preferences, when choosing between PCI and CABG in complex coronary artery disease. Short-term advantages of PCI include the less invasive nature of this procedure, which also has fewer peri-procedural complications and is followed by a more rapid recovery with a better early quality of life and earlier angina relief. CABG has more long-term advantages, notably fewer late myocardial infarcts and fewer repeat revascularisation procedures. Long-term survival depends, among others, on clinical and anatomic factors, operator expertise, and completeness of revascularisation.

2-Year Outcome MITRA-FR shows no Benefit Percutaneous Mitral Valve Repair

Written by **Michiel Tent**

After 2 years of follow-up, percutaneous repair with the MitraClip still did not improve the prognosis of patients with secondary mitral regurgitation in the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation [MITRA-FR; Obadia JF et al. *N Engl J Med* 2018] trial. These results are in contrast to findings of the COAPT study [Stone GW et al. *N Engl J Med* 2018] in which percutaneous mitral valve repair significantly reduced heart failure (HF) rehospitalisation and death after 2 years.

MITRA-FR was an academically-led, prospective, multicentre, randomised controlled, open-label trial performed in France. Participants had chronic HF, severe secondary mitral regurgitation (i.e., regurgitation volume > 30 mL/beat and/or a regurgitant orifice area > 20 mm^2), and reduced left ventricular function ejection fraction (LVEF; 15 to 40%), who were symptomatic (NYHA class ≥ II) despite guideline-directed medical treatment and had been hospitalised for an HF event within the previous 12 months. A total of 304 eligible patients (70 ± 10 years, 74% males) were randomised from 37 centres. Patients underwent either percutaneous valve repair plus medical treatment (intervention group, n = 152) or medical treatment alone (control group, n = 152). The primary efficacy outcome was the composite of all-cause death and unplanned hospitalisation for HF at 12 months.

Principal investigator Jean-François Obadia, MD, PhD, Hospices Civils de Lyon, France, presented the 2-year results [Iung B et al. *Eur J Heart Fail.* 2019]. At baseline, most patients were severely symptomatic (67% in NYHA class ≥ III), STS score for mortality was 5.7 ± 6.7%, LVEF was 33 ± 7%, regurgitant volume was 45 ± 14 ml, and regurgitant orifice area was 31 ± 11 mm^2 at baseline. At 24 months, the primary efficacy outcome of all-cause death and unplanned hospitalisations for HF occurred in 63.8% (97/152) and 67.1% (102/152) of the intervention and control group, respectively (HR, 1.01; 95% CI, 0.77 to 1.34). There were no significant differences between groups, whether the outcomes were analysed together or separately. Rates of all-cause mortality were 34.9% (53/152) and 34.2% (52/152) in the intervention and control groups, respectively (HR, 1.02; 95% CI, 0.70 to 1.50). Unplanned hospitalisation for heart failure occurred in 55.9% (85/152) and 61.8% (94/152) of patients, respectively (HR, 0.97; 95% CI, 0.72 to 1.30). Prof. Obadia also observed that percutaneous repair remained safe, with only a small number of prespecified serious adverse events related to it. Between 12 months and 24 months, 4 serious adverse events occurred in the intervention group and 7 in the control group.

An exploratory post-hoc analysis of events occurring between 12 and 24 months suggested a lower rate of first hospitalisation for HF in the intervention group (HR, 0.47; 95% CI, 0.22 to 0.98), Prof. Obadia added. This trend was consistent with a divergence in the curves of recurrent hospitalisations for HF for each group. This is the rationale for 2 complementary studies that will be performed: a 5-year follow-up of the MITRA-FR cohort, and a meta-analysis on individual data of the MITRA-FR and COAPT studies.

Discussant Rebecca Hahn, MD, Columbia University Medical Center/New York-Presbyterian, New York City, USA, discussed the differences in MITRA-FR and COAPT trial outcomes. She noted that the 2 trials are in fact concordant. She hypothesised that patients might be more likely to benefit from the MitraClip if they have truly severe secondary mitral regurgitation without excessive left ventricular dilatation, while receiving optimal guideline-directed medical treatment.

Modifiable Risks Account for Majority of Cardiovascular Disease

Written by **Rachel Giles**

Cardiovascular disease (CVD) remains the leading cause of mortality among middle-aged adults globally, accounting for 40% of all deaths, but this is no longer the case in some high-income countries, where cancer causes twice as many deaths as CVD (Figure 10). Furthermore, modifiable metabolic factors, behavioural factors, socioeconomic factors, psychosocial factors, strength, and environmental factors (specifically air pollution) accounted for approximately 70% of all CVD cases globally.

Two presentations from the Prospective Urban and Rural Epidemiologic [PURE; NCT03225586] study refreshed the statistics and provided unique information on common disease incidence, hospitalisation, and death, as well as modifiable cardiovascular risk factors in middle-aged adults across 21 high-income, middle-income, and low-income countries (HIC, MIC, LIC, respectively). Both papers were published simultaneously [Dagenais GR et al. *Lancet*. 2019; Yusuf S et al. *Lancet*. 2019]. The PURE study is the only large, prospective, international cohort study that involves substantial data from a large number of HIC, MIC, and LIC during the same period, and employs standardised methods of sampling, measurement, and follow-up.

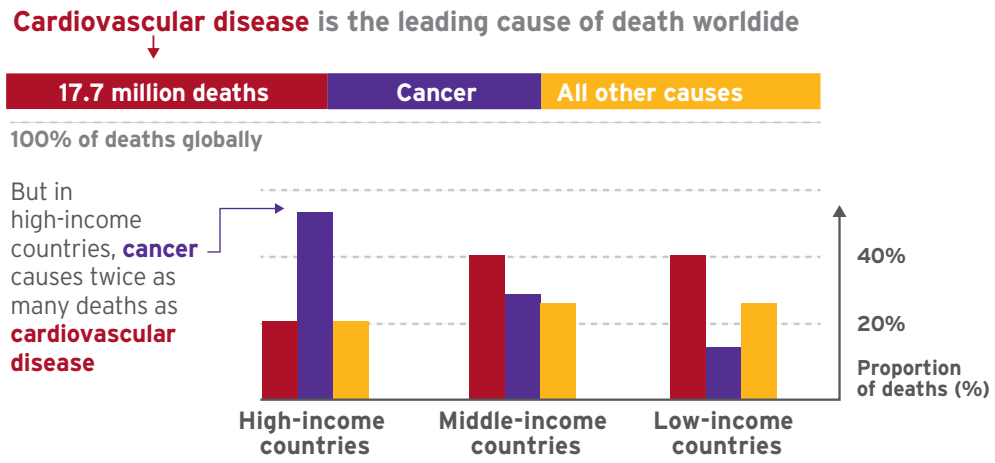
Salim Yusuf, MD, PhD, and Darryl Leong, MBBS, PhD, McMaster University, Hamilton, Ontario, Canada, presented the reports, which followed approximately 160,000 middle-aged adults (aged 35 to 70; 58% women) between 2005 and 2019 in 4 HIC, 12 MIC, and 5 LIC over a median of 9.5 years. They found that CVD-related deaths were 2.5 times more common in middle-aged adults in the LIC compared with in HIC, despite populations from the LIC having a substantially lower burden of CVD risk factors compared with wealthier countries. Prof. Yusuf suggested that higher CVD-related mortality in LIC may be mainly due to lower quality of healthcare, given that the report found first hospitalisation rates and CVD medication use to be both substantially lower in LIC and in MIC, compared with in HIC. The differences may also be due to factors that are not generally considered, such as higher indoor and outdoor air pollution, lower physical strength, lower education, and poor-quality diets.

Remarkably, the study by Dagenais et al. [*Lancet*. 2019] found that the incidence of CVD per 1,000 person years was 7.1, 6.8, and 4.3 in LIC, MIC, and HIC, respectively. In contrast, the investigators found cancer, pneumonia, COPD, and injuries to be less common in LIC and MIC than in HIC. Despite lower incidences of many of these conditions, overall mortality rates were twice as high in LICs compared with MIC, and 4 times higher in LICs compared with HIC, though rates of deaths from cancer were similar across all country income levels.

A further report from the PURE study [Yusuf S et al. *Lancet*. 2019] explored the relative contribution (population attributable factor; PAF) of 14 modifiable risk factors to CVD, among 155,722 community-dwelling, middle-aged people without a prior history of CVD, within the same 21 HIC, MIC, and LIC. Overall, modifiable risk factors, including metabolic, behavioural, socioeconomic and psychosocial factors, strength, and environment, accounted for approximately 70% of all CVD cases globally. Metabolic risk factors were the largest contributory risk factor globally (41.2%), with hypertension (22.3%) the leading factor within this group.

However, the relative importance of risk factors for CVD cases and death varied widely between countries at different stages of economic development. For deaths, the largest group of PAFs overall were for behavioural risk factors (26.3%), but in MIC and LIC, the importance of household air pollution, poor diet, low education, and low grip

Figure 10. Cardiovascular Disease is the Leading Cause of Death Worldwide



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strength were substantially larger compared with their impact in HIC. In line with the findings of the first report, metabolic risk factors, including hypertension, high cholesterol, abdominal obesity, and diabetes, played a larger role in causing deaths in HIC, compared with in LIC.

Authors of both studies acknowledged some limitations. Despite being the only study involving as many as 21 countries in a single cohort study, caution should be exercised in generalising results to all countries. In particular, PURE does not include data from northwest Africa or Australia; the number of participants from Europe and the Middle East is modest; and data from LICs are predominantly from south Asia with a few African countries.

In conclusion, the major findings of the study were that as country income increases, a higher proportion of deaths and hospitalisations comes from non-communicable diseases compared with infectious diseases. Also, among non-communicable diseases, the proportion of deaths from cancer as compared with CVD increases. Secondly, the higher rates of CVD and related deaths in poorer countries compared with richer countries occurs despite fewer traditional CVD risk factors in poor countries. Thirdly, there is an inverse association between use of hospital care and effective medication versus deaths, suggesting that lower quality healthcare may be responsible, at least in part, for the higher mortality in poorer countries. Lastly, this data can form the basis of informed policy decisions at the governmental level.

Stable Coronary Patients with Diabetes Benefit from Aspirin/Ticagrelor Despite Increased Bleeding Risk

Written by **Rachel Giles**

The THEMIS trial, as well as the pre-specified THEMIS-PCI subanalysis, reported that diabetic patients with stable coronary artery disease benefited from dual aspirin/ticagrelor therapy, whether or not they had had previous percutaneous coronary intervention (PCI). However, patients experienced a greater risk of major bleeding when ticagrelor was added to aspirin.

Presented during the first Hot Line session in 2 consecutive talks, and published simultaneously in the *New England Journal of Medicine* and *The Lancet*, investigators Deepak L. Bhatt, MD, MPH, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, and Philippe Gabriel Steg, MD, Hospital Bichat-Claude Bernard, Paris, France, reported the late-breaking clinical trial results from The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study [THEMIS; Bhatt DL et al. *Lancet*. 2019; Steg PG et al. *N Engl J Med* 2019].

THEMIS enrolled over 19,000 patients with stable coronary artery disease and type 2 diabetes, but without a history of heart attack or stroke and randomised them to receive either ticagrelor plus aspirin or a placebo plus aspirin. The primary efficacy outcome was the composite of cardiovascular death, heart attack, or stroke. The primary safety outcome was Thrombolysis in Myocardial Infarction (TIMI) major bleeding. The median follow-up was 39.9 months.

During that time, 736 of 9,619 patients (7.7%) taking ticagrelor plus aspirin experienced cardiovascular death, myocardial infarction, or stroke versus 818 of 9,601 patients (8.5%) taking placebo plus aspirin –a significant 10% reduction (P = .04; Table 14). However, patients on this dual-antiplatelet therapy also experienced greater risk of major bleeding (206 patients vs 100 patients) and intracranial haemorrhage (70 patients vs 46 patients) compared with placebo. The difference in intracranial haemorrhages was driven by an increased number of traumatic bleeds, most of them subdural, and not by spontaneous or procedural bleeding.

In THEMIS-PCI, a pre-specified analysis that specifically looked at THEMIS patients with a history of previous PCI that included stenting, compared with the overall THEMIS population, investigators found even more favourable benefits for patients taking ticagrelor plus aspirin.

Table 14. Full Data from the THEMIS Trial

Endpoint	Ticagrelor (n = 9,619)	Control (n = 9,601)	Statistics
Cardiovascular death, myocardial infarction, or stroke	736 (7.7%)	818 (8.5%)	HR, 0.90; 95% CI, 0.81 to 0.99; P = .04
Cardiovascular death	364 (3.8%)	357 (3.7%)	HR, 1.02; 95% CI, 0.88 to 1.18; P = .79
Myocardial infarction	274 (2.8%)	328 (3.4%)	HR, 0.84; 95% CI, 0.71 to 0.98; P = .029
Stroke	152 (1.6%)	192 (2.0%)	HR, 0.80; 95% CI, 0.64 to 0.99; P = .038
Major bleeding	206 (2.2%)	100 (1%)	HR, 2.32; 95% CI, 1.82 to 2.94; P < .001
Intracranial haemorrhage	70 (0.7%)	46 (0.5%)	HR, 1.71; 95% CI, 1.18 to 2.48; P = .005

CI, confidence interval; HR, hazard ratio.

Patients who had received PCI accounted for 58% of the total THEMIS population. Among these patients in THEMIS-PCI, the prespecified subgroup analysis, 404 of 5,558 (7.3%) participants taking ticagrelor plus aspirin experienced cardiovascular death, myocardial infarction, or stroke versus 480 of 5,596 (8.6%) participants taking placebo plus aspirin -the relative reduction was 15% in patients with prior PCI (HR, 0.85; 95% CI, 0.74 to 0.97; *P* = .013). Major bleeding occurred in 111 of 5,536 (2.0%) patients receiving ticagrelor and in 62 of 5,564 (1.1%) patients receiving placebo (HR, 2.03; 95% CI, 1.48 to 2.76; *P* < .0001]. The risk for intracranial bleeding was similar between ticagrelor and placebo (33 patients vs 31 patients, respectively). For patients without prior PCI, there was no significant between-group difference in the predefined exploratory outcome of irreversible harm (death from any cause, myocardial infarction, stroke, fatal bleeding, or intracranial haemorrhage). Prof. Steg concluded: "The results suggest that long-term therapy with ticagrelor in addition to aspirin may be considered in patients with diabetes and a history of PCI who have tolerated antiplatelet therapy and have high ischaemic risk and low bleeding risk. This is a novel therapeutic option for a large and easy to identify patient population."

Increased Oral Anticoagulation Use Associated with Less Ischaemic Stroke in AF Patients

Written by **Lisa Buttle**

A rise in use of oral anticoagulation among patients with atrial fibrillation (AF), largely driven by growing prescription of non-vitamin K oral anticoagulants (NOACs), is associated with a decline in hospital admissions for ischaemic stroke. This was a key finding of a 4-year database study involving over 13 million Italian inhabitants presented by Aldo Pietro Maggioni, MD, Research Centre of the Italian Association of Hospital Cardiologists, Florence, Italy.

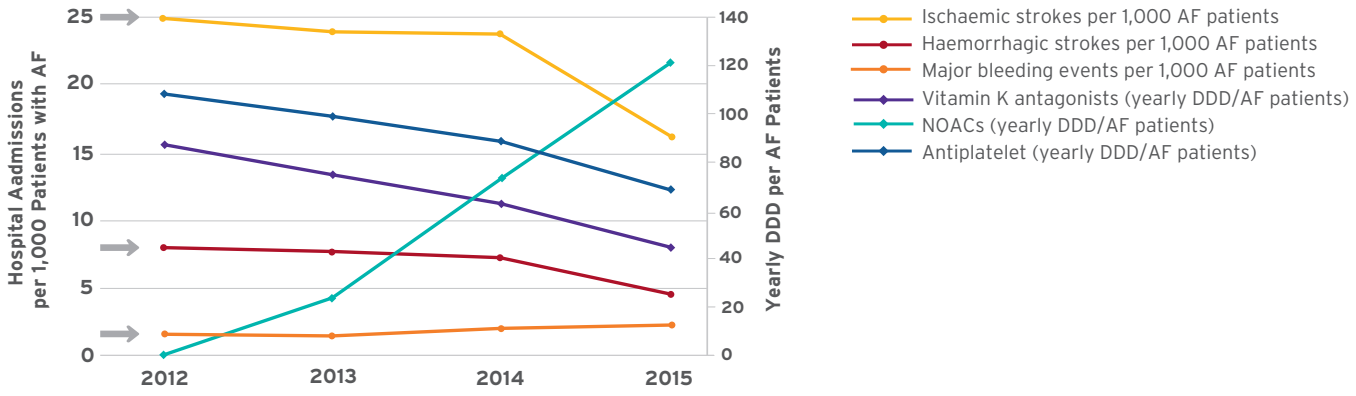
The aim of this 4-year analysis (2012 to 2015) of the Ricerca e Salute (ReS) database was to assess rates of hospitalisations for AF, ischaemic stroke, and major haemorrhage, prescription of oral anticoagulants and antiplatelet agents, and to evaluate annual costs per patient with AF. Patients discharged alive after an admission for AF (primary or secondary; n = 194,030) were followed for 1 year to measure medication use and further hospitalisations.

The study found that ~4 in every 1,000 people in Italy are admitted each year with AF, a number that remained stable from 2012 to 2015. The proportion of patients treated with a vitamin K antagonist (VKA) dropped during this time (from 55.9% to 36.7%) while the proportion taking a NOAC increased from < 1% in 2012 to 27.7% in 2015. Overall the use of any oral anticoagulant increased from 56.7% to 64.4%. At the same time, antiplatelet therapy use -which is not recommended in the guidelines for stroke prevention in AF patients – fell from 42.6% to 28.1%.

The 1-year rate of hospitalisation for ischaemic stroke declined by around one-third from 21.3% in 2012 to 14.7% in 2015. The rate of haemorrhagic stroke fell from 6.5% to 4.1% during the study period, and major bleeding increased from 1.5% to 2.3% (Figure 11).

The study also investigated the annual total cost of treating patients with AF (including drug prescriptions, outpatient services, and hospitalisations), which declined from €5,927 in 2012 to €5,239 in 2015. While

Figure 11. Yearly Trends in Antithrombotic Drug Use and in Admissions for Ischaemic or Haemorrhagic Stroke and Major Bleeds



AF, atrial fibrillation; DDD, defined daily dose; NOAC, non-vitamin K oral anticoagulants.

Reproduced with kind permission from Maggioni AP, Dondi L, Andreotti F et al.

more money was spent on NOACs, the costs associated with hospitalisations decreased, and the cost of other medications that became generic in 2015 was lower.

Prof. Maggioni concluded that, while there have been promising trends in guideline-recommended drug prescription and a reduced number of hospitalisations due to ischaemic stroke, this analysis represents only a descriptive association between these findings and cannot demonstrate causality. However, the findings are consistent with a recent 10-year study from England that showed an association between increased uptake of oral anticoagulation and a reduction in hospitalisations for strokes related to AF [Cowan JC et al. *Eur Heart J.* 2018].

Dapagliflozin Decreases Cardiovascular Death and Worsening Heart Failure

Written by **Rachel Giles**

The Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure [DAPA-HF; McMurray et al. *N Engl J Med* 2019] met its primary endpoint, demonstrating that dapagliflozin in addition to standard of care reduced the incidence of cardiovascular (CV) death or worsening heart failure (HF) in patients with chronic heart failure.

DAPA-HF is the first randomised, cardiovascular outcomes trial investigating a sodium glucose cotransporter 2 (SGLT2) inhibitor in a broad population of patients with heart failure and reduced ejection fraction (HFrEF), which included patients with and without diabetes. Dapagliflozin is currently approved to improve glycaemic control in patients with T2DM.

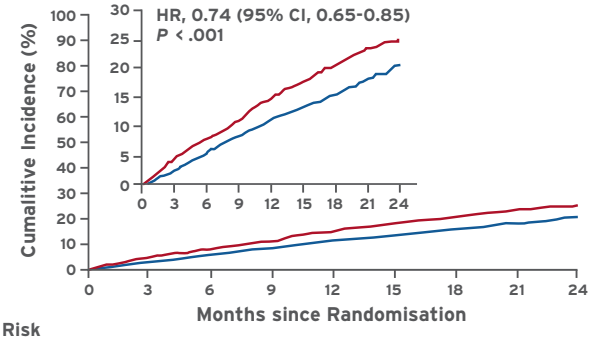
DAPA-HF enrolled 4,744 patients with HFrEF. Typical for a population in a heart failure trial, just under half of these patients had diabetes. At randomisation, the majority of patients were already being treated with an angiotensin-converting enzyme (ACE) inhibitor (56%), angiotensin receptor blocker (27%), or angiotensin receptor-neprilysin inhibitor (ARNI) (11%). Nearly all patients (96%) were taking a beta-blocker, and 71% were taking a mineralocorticoid receptor antagonist.

John McMurray, MD, University of Glasgow, Scotland, presented the results of the DAPA-HF trial. The trial met its primary endpoint and found that dapagliflozin reduced the composite endpoint of CV death or worsening of heart failure after a median follow-up of 18.2 months (16.3% vs 21.2%; HR, 0.74; 95% CI, 0.65 to 0.85; $P < .0001$; see Figure 12). In analysing each of the components of the primary composite endpoint, there was a 30% decrease in the risk of experiencing a first episode of worsening heart failure (i.e., hospitalisation or an urgent visit resulting in intravenous therapy for heart failure) (HR, 0.70; 95% CI, 0.59 to 0.83; $P < .0001$) and an 18% decrease in the risk of CV death (HR, 0.82; 95% CI, 0.69 to 0.98; $P = .0294$). The effect of dapagliflozin on the primary composite endpoint was consistent across the key subgroups examined, including those with and without diabetes at baseline.

Symptoms were similar at baseline and symptoms improved with dapagliflozin, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score. The safety profile of dapagliflozin in the DAPA-HF trial was consistent with the previously reported safety profile of the medicine. The proportion of patients with volume depletion (7.5% vs 6.8%) and renal adverse events (6.5% vs 7.2%) were comparable with placebo. Major hypoglycaemic events were rare in both treatment groups (0.2% for both).

Discussant Marco Metra, MD, University of Brescia, Italy, said that DAPA-HF is a "landmark trial" and that the hazard ratios for the primary as well as the secondary endpoints are similar to, if not larger than, those in recent major successful trials, such as Effects of Ivabradine on Cardiovascular Events in Patients With Moderate to Severe Chronic Heart Failure and Left Ventricular Systolic Dysfunction. A Three-year International Multicentre Study [SHIFT; NCT02441218], Effect Of Eplerenone Versus Placebo On Cardiovascular Mortality And Heart Failure Hospitalization In Subjects With NYHA Class II Chronic Systolic Heart Failure [EMPHASIS-HF; NCT00232180], and the Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure [PARADIGM-HF; NCT01035255].

Figure 12. Primary Composite Outcome of Cardiovascular Death or Worsening Heart Failure



No. at Risk									
Placebo	2,371	2,258	2,163	2,075	1,917	1,478	1,096	593	210
Dapaglizoflin	2,373	2,305	2,221	2,147	2,002	1,560	1,146	612	210

From McMurray JJV et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019. DOI: 10.1056/NEJMoa1911303.

Edoxaban Dual Therapy is Non-Inferior to Triple Therapy in AF, Post-PCI

Written by **Rachel Giles**

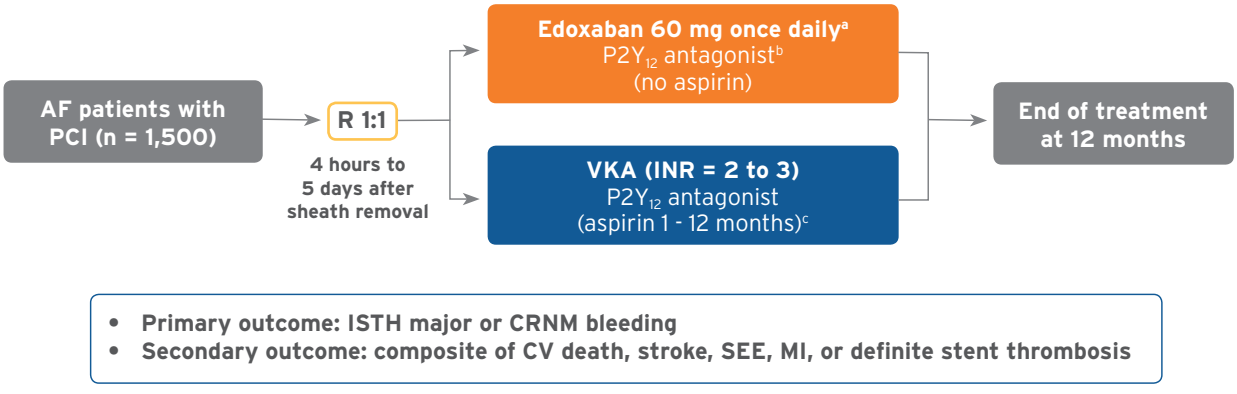
The Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention [ENTRUST-AF PCI; NCT02866175] study achieved the primary safety endpoint of non-inferiority in bleeding for edoxaban-based dual therapy compared with vitamin K antagonist (VKA)-based triple antithrombotic in atrial fibrillation (AF) patients following stent placement [Vranckx P et al. *Lancet*. 2019].

Andreas Goette, MD, St Vincenz Hospital, Paderborn, Germany, presented the results of ENTRUST-AF PCI, a prospective, multinational, multicentre, randomised, open-label phase 3b study with blinded endpoint evaluation. The study was designed to evaluate safety and efficacy of an edoxaban-based antithrombotic regimen versus a VKA-based antithrombotic regimen in subjects with AF, following percutaneous intervention (PCI) with stenting. The study enrolled 1,506 patients with AF following stent placement for acute coronary syndrome (51.6%) or stable coronary artery disease (48.4%). One arm received edoxaban 60 mg once daily in combination with a $P2Y_{12}$ inhibitor for 12 months, while the other arm received a VKA, such as warfarin, in combination with a $P2Y_{12}$ inhibitor and aspirin 100 mg once daily (see Figure 13). The aspirin duration was for 1 to 12 months, based on the investigators' judgement.

The dose of edoxaban was reduced from 60 mg to 30 mg if certain factors were present: renal impairment (creatinine clearance 15 to 50 mL/min), body weight ≤ 60 kg, and/or use of prespecified potent P-glycoprotein inhibitors. The choice of $P2Y_{12}$ inhibitor was left to the treating physician. The primary objective of the ENTRUST-AF PCI trial was to compare the incidence of major or clinically relevant non-major International Society on Thrombosis and Haemostasis (ISTH)-defined bleeding over a 12-month period of an edoxaban-based antithrombotic regimen against a VKA-based regimen. This occurred in 17% of the edoxaban group (annualised event rate, 20.7%) vs 20% of the triple therapy group (annualised event rate, 25.6%; HR, 0.83; 95% CI, 0.654 to 1.047; *P* for non-inferiority = .001; *P* for superiority = .1154), demonstrating non-inferiority of the edoxaban-based dual therapy for the 12 months post-PCI. Similar rates of the main efficacy composite outcome of cardiovascular death, stroke, systemic embolic events, spontaneous myocardial infarction, and definite stent thrombosis were observed for the edoxaban-based dual therapy regimen and the VKA-based triple therapy regimen. However, the trial was not powered for investigation of individual efficacy endpoints.

In conclusion, in patients with AF who had had PCI, edoxaban plus a $P2Y_{12}$ inhibitor was non-inferior to a VKA-based triple regimen for bleeding with no significant differences in ischaemic events.

Figure 13. ENTRUST-AF PCI Study Design



[a] Or edoxaban 30 mg dose adjusted if CrCl ≤ 50 mL/min, body weight ≤ 60 kg, or concomitant therapy with certain P-gp inhibitors. [b] Clopidogrel 75 mg once daily, or in case of a documented clinical need, prasugrel (5 or 10 mg once daily) or ticagrelor (90 mg twice daily). [c] Aspirin 100 mg once daily guided by clinical presentation (ACS or stable coronary disease), CHA_2DS_2-VASc and HAS-BLED score.

ACS, acute coronary syndrome; AF, atrial fibrillation; CrCL, creatinine clearance; CRNM, clinically relevant non-major; CV, cardiovascular; INR, international normalised ratio; ISTH, International Society on Thrombosis and Haemostasis; PCI, percutaneous coronary intervention; SEE, systemic embolic events; VKA, vitamin K antagonist.

Modified from Vranckx P et al. Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement: Rationale and design of the ENTRUST-AF PCI trial. *Am Heart J*. 2018;196:105-112.

Effects of Omega-3 Fatty Acids on Arrhythmias in Diabetes Patients: an Update

Written by **Michiel Tent**

Additional data from A Study of Cardiovascular Events iN Diabetes (ASCEND) showed no effect on non-fatal arrhythmias of 1 g daily of omega-3 fatty acid (FA) capsules in patients with diabetes and no known cardiovascular disease (CVD). There was no statistically significant effect on atrial fibrillation (AF), nor on the composite outcome of any cardiac arrhythmia. There may, however, be a dose-related protective effect on coronary events.

Observational studies have suggested that higher fish consumption may have a protective effect against coronary heart disease (CHD). However, a meta-analysis in 2018 of 10 large randomised trials of 0.5 to 2 g daily omega-3 FA supplementation (with EPA and DHA, found in fish) did not show convincing benefit on CVD [Aung T et al. *JAMA Cardiol* 2018]. Sarah Parish, BSc, MSc, DPhil, University of Oxford, United Kingdom, pointed out that 3 new large trials have since been reported. Evidence from 12 low-dose studies showed a dose-dependent mean reduction in the rate ratio (RR) of coronary heart disease events of 8% (3% to 13%) per 1 g daily. In addition, the REDUCE-IT trial, applying a 4-g dose of a purified form of EPA among participants with high triglyceride levels, also reported a highly statistically significant 25% reduction in various cardiovascular outcomes corresponding to 7% (4% to 10%) per 1 g daily [Bhatt DL et al. *N Engl J Med* 2019]. In that study, however, supplementation was also associated with a larger percentage of patients who were hospitalised for AF or flutter (3.1% vs 2.1%, *P* = .004).

Secondary Analysis of ASCEND

In the original ASCEND study [ASCEND Study Collaborative Group *N Engl J Med* 2018] there was no evidence, based on patient-reported outcomes, of an effect of omega-3 FA supplementation on arrhythmias. Prof. Parish presented a secondary analysis of ASCEND, which assessed the effects of omega-3 FA supplementation on arrhythmias more comprehensively with additional data for 97% of participants with linkage to electronic Hospital Episode Statistics (HES) data during the trial (and for 14 years before randomisation).

In ASCEND, 15,480 participants with diabetes but without atherosclerotic cardiovascular disease had been randomised to 1 g omega-3 FA or matching placebo daily. Almost all participants with known prior AF were excluded. In the secondary analysis, key arrhythmia outcomes considered were: 1) AF in participants without known prior AF; 2) non-fatal ventricular arrhythmia; and 3) any non-fatal cardiac arrhythmia. During a mean follow-up of 7.4 years, HES data captured arrhythmias in an additional 1,137 participants over the 455 that had self-reported arrhythmia adverse events during the trial. The incidence of non-fatal arrhythmias and cardiac deaths are shown in Table 15.

Prof. Parish concluded that, in ASCEND, 1 g omega-3 FA did not show a statistically significantly effect on AF or on the composite outcome of any non-fatal cardiac arrhythmia. Prof. Parish added that systematic reporting of arrhythmia outcomes in existing and future trials is warranted. The ongoing STRENGTH trial of 4 g daily supplementation will add new insights after completion in 2020.

Table 15. Effect of Omega-3 Fatty Acid Supplements on Arrythmias and Cardiac Deaths

	Omega-3 FA (n = 7,740)	Placebo (n = 7,740)	
Non-fatal arrhythmias	**n (%)***	**n (%)***	**Rate ratio (95% CI)**
Atrial fibrillation	595 (7.7%)	582 (7.6%)	1.02 (0.91 to 1.15)
Ventricular arrhythmia	81 (1.0%)	54 (0.7%)	1.49 (1.06 to 2.09)
Any cardiac arrhythmia	807 (10.4%)	769 (9.9%)	1.05 (0.95 to 1.16)
Cardiac deaths			
Coronary death	100 (1.3%)	127 (1.6%)	0.79 (0.61 to 1.02)
Non-coronary death	33 (0.4%)	42 (0.5%)	0.78 (0.50 to 1.23)
Any cardiac death	133 (1.7%)	169 (2.2%)	0.79 (0.63 to 0.98)

* Participants with events.

CI, confidence interval; FA, fatty acid.

New Treatment Updates

The Inflammatory Hypothesis: Learning from the CANTOS and CIRT Trials

Written by **Rachel Giles**

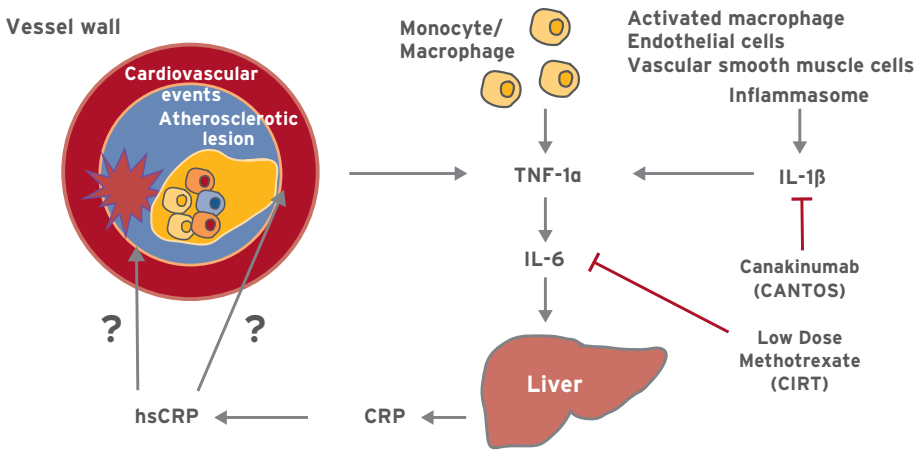
Over the last decades we learnt to appreciate atherosclerosis as an inflammatory disease based on solid evidence deriving from experimental studies and epidemiological association between inflammatory markers and cardiovascular events, Donato Santovito, MD, PhD, Institute for Cardiovascular Prevention (IPEK), Ludwig Maximilian University, Munich, Germany, began his presentation. "We were missing an important piece of science though, that treating inflammation would indeed improve cardiovascular outcomes," Dr Santovito added. In the last 2 years, with 2 large clinical trials specifically designed to test the inflammation hypothesis of atherothrombosis have been presented, however, with somewhat contradictory results.

First, the 10,061 patient Cardiovascular Risk Reduction Study: Canakinumab Anti-inflammatory Thrombosis Outcomes Study [CANTOS; NCT01327846] demonstrated that specific targeting of interleukin (IL)-1β can significantly reduce cardiovascular risk independent of lipid or blood pressure lowering. In CANTOS, canakinumab given at doses of either 150 or 300 mg subcutaneously once every 3 months lowered the inflammatory biomarkers IL-6 and C-reactive protein (hsCRP) by 35% to 40% when compared with placebo; effects that led to a 17% reduction in rates of the composite outcome of recurrent myocardial infarction (MI), stroke, hospitalisation for unstable angina leading to urgent need for revascularisation, or cardiovascular death ($P < .001$) [Ridker PM et al. *N Engl J Med* 2017]. As such, CANTOS has provided proof-of-principle regarding the inflammation hypothesis of atherothrombosis.

Canakinumab was well tolerated. However, while rates of total infection were similar in the canakinumab and placebo groups, fatal infections were increased with active therapy at a rate of approximately 1 per 1,000 treated patients ($P = .02$ comparing all doses of canakinumab to placebo). Moreover, the elevated costs make canakinumab not cost-effective for prevention of recurrent cardiovascular events [Sehested TSG et al. *JAMA Cardiol*. 2019]. Altogether, these aspects prompted research into additional therapeutic agents and targets.

The Cardiovascular Inflammation Reduction Trial [CIRT; NCT01594333] was designed in parallel with CANTOS to evaluate the hypothesis that an alternative approach to inflammation inhibition using low-dose methotrexate might also lower vascular events rates. Thus, whereas CANTOS used a narrow-spectrum approach to inflammation inhibition through use of a targeted anti-IL-1β monoclonal antibody, CIRT elected to use a broader spectrum anti-inflammatory approach known to have clinical efficacy in multiple systemic disorders, but with a low-dose of an agent where far less is known about its mechanisms of effect (Figure 14). In CIRT, investigators

Figure 14. Illustration of the Molecular Rationale Behind Inhibition of IL-1β (in CANTOS trial) or IL-6 (in CIRT trial)



CRP, C-reactive protein; hsCRP, high-sensitivity CRP; IL, interleukin; TNF, tumour necrosis factor.

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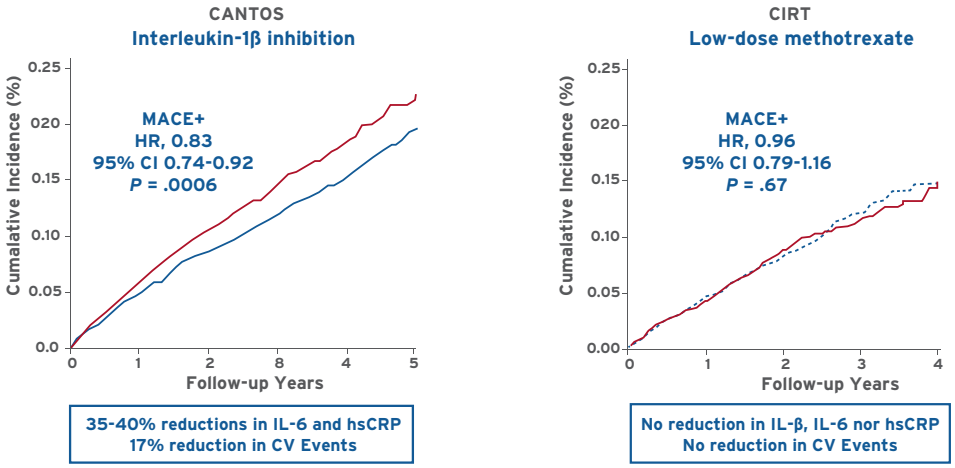
Figure 15. Cumulative Incidence of Recurrent Myocardial Infarction, Stroke, need for Urgent Revascularisation, or Cardiovascular Death (MACE-plus) in the CANTOS (left) and CIRT (right) Trials



CI, confidence interval; CV, cardiovascular; HZ, hazard ratio; IL, interleukin; MACE, major adverse cardiovascular events.

Reprinted from Ridker PM et al. Anti-inflammatory therapy for atherosclerosis: interpreting divergent results from the CANTOS and CIRT clinical trials. *J. Intern. Med.* 2019;285(5):503-509. Copyright 2019. With permission from John Wiley and Sons.

randomised patients with previous MI or multivessel coronary artery disease in addition to type 2 diabetes or metabolic syndrome to low-dose methotrexate (15 to 20 mg) or matching placebo. The trial was halted by the Data and Safety Monitoring Board after a median of 2.3 years for futility, at which point 4,786 of the 6,158 eligible patients had been randomised to treatment. More than 60% of patients qualified for the trial with a previous MI.

The data indicated that low-dose methotrexate had no effect on IL-1β, IL-6, or CRP levels, all markers of inflammation. In terms of the original primary endpoint, the use of methotrexate did not reduce the risk of non-fatal MI, non-fatal stroke, or cardiovascular death (HR, 1.01; 95% CI, 0.82 to 1.25; *P* = .91), effectively eliminating it as an inexpensive option for treating residual inflammatory risk among patients receiving background statin therapy (Figure 15) [Ridker PM et al. *N Engl J Med* 2019]. In January 2018, the primary endpoint was expanded to include hospitalisation for unstable angina that led to urgent revascularisation. The purpose of the expanded endpoint was to provide greater statistical power with a smaller overall sample size. However, even with the expanded endpoint, the trial was stopped for futility (HR, 0.96; 95% CI, 0.79 to 1.16; *P* = .67). There was no treatment effect on any of the secondary endpoints.

The CIRT data suggests that the mechanism of low-dose methotrexate, likely mediated through adenosine signalling, comprises an entirely different pathway for inflammation inhibition that is less relevant for atherothrombosis. Therefore, these 2 contemporary trials – 1 positive and 1 informative but with neutral result – highlight the different relevance of inflammatory pathways on cardiovascular diseases and guide future pharmacologic attention away from broad spectrum anti-inflammatory treatments and towards specific targeted inhibition upstream (e.g., the NLRP3 inflammasome) or downstream the IL-1/IL-6 pathway of innate immunity, which is currently tested in clinical trials (e.g., colchicine is tested in the LoDoCo2, COLCOT, and CONVINCE). Furthermore, novel emerging novel immuno-therapeutic targets are currently considered to become future therapeutic opportunities for cardiovascular diseases [Lutgens E et al. *Eur Heart J* 2019]. The independent effects of lipid-lowering and inflammation inhibition are attractive as combination therapies addressing both of these atherogenic pathways to provide maximal clinical benefit.

Empagliflozin Induces Effective Decongestion in Type 2 Diabetes Patients with ADHF

Written by **Michiel Tent**

Empagliflozin as add-on therapy can achieve effective decongestion without increasing the risk of worsening renal function in patients with type 2 diabetes (T2DM) with acute decompensated heart failure (ADHF). These were the results of a randomised study in 38 consecutive Japanese T2DM patients admitted for ADHF.

Empagliflozin is indicated for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise. The agent has been shown to reduce the risk of hospitalisation for HF in T2DM patients with cardiovascular disease. This may be partly explained by natriuresis and osmotic diuresis caused

by empagliflozin, leading to plasma volume contraction and decongestion. However, little is known about the therapeutic effect of empagliflozin on decongestion and its association with renal function in T2DM patients with ADHF. Shunsuke Tamaki, MD, PhD, Osaka General Medical Center, Japan, and colleagues, therefore, evaluated the effect of empagliflozin as add-on therapy on plasma B-type natriuretic peptide (BNP) level, haemoconcentration, plasma volume contraction, and renal function in T2DM patients with ADHF, in a prospective, randomised controlled study.

The study enrolled 38 consecutive T2DM patients admitted for ADHF. Exclusion criteria were severe primary valvular heart disease; acute coronary syndrome; mechanical circulatory support device; sodium-glucose cotransporter 2 inhibitor use; severe infection; and history of acute coronary syndrome, stroke, or transient ischaemic attack in the past month. Within 96 hours of admission, participants were randomly assigned to either empagliflozin (10 mg/day) add-on therapy (EMPA(+); n = 20) or conventional glucose-lowering therapy (EMPA(-); n = 18). There were no significant baseline differences in body mass index, left ventricular ejection fraction, plasma BNP level, haematocrit, or serum creatinine level between the 2 groups. Regarding renal function, baseline prevalence rates of hyperuricaemia, serum uric acid level, and fractional excretion of uric acid did not significantly differ between groups either.

Left ventricular ejection fraction was measured at baseline using echocardiography. Body weight and vital signs, such as blood pressure and heart rate, were measured, and blood and urine samples were collected at baseline and 1, 2, 3, and 7 days after randomisation. Haemoconcentration was defined as a ≥ 3% absolute increase in haematocrit. The percentage change in plasma volume was calculated using the Strauss formula. Worsening renal function was defined as an increase in serum creatinine ≥ 0.3 mg/dL above baseline within 7 days of randomisation.

Main Results

Seven days after randomisation, empagliflozin as add-on therapy resulted in a similar change in body weight, a significantly lower plasma BNP level (Figure 16), and more frequent haemoconcentration (Figure 17) compared with conventional glucose-lowering therapy. Also, the decrease in plasma volume was larger in the EMPA(+) group than in the EMPA(-) group at 2 days (-8.74% vs 1.14%, *P* = .0228), 3 days (-11.28% vs -0.02%, *P* = .0121), and 7 days after randomisation (-10.62% vs 0.97%, *P* = .0211).

A reduction of plasma volume is often associated with worsening renal function [Ronco C et al. *J Am Coll Cardiol*. 2012]. In this study, however, the incidence of worsening renal function did not significantly differ between the EMPA(+) and EMPA(-) groups: 15% vs 22%. Yet, there was a significant difference in serum uric acid level change from baseline at 2, 3, and 7 days after randomisation between groups. As a result, serum uric acid level was significantly lower in the EMPA(+) group than in the EMPA(-) group 7 days after randomisation (6.2 ± 1.8 mg/dL vs 7.8 ± 1.8 mg/dL, *P* = .0127), likely related to increased urinary excretion.

Figure 16. Plasma B-Type Natriuretic Peptide Level at Day 7

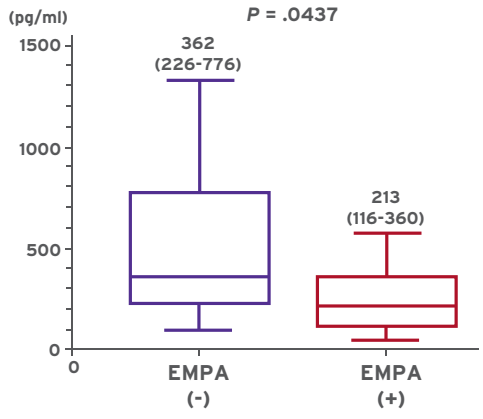


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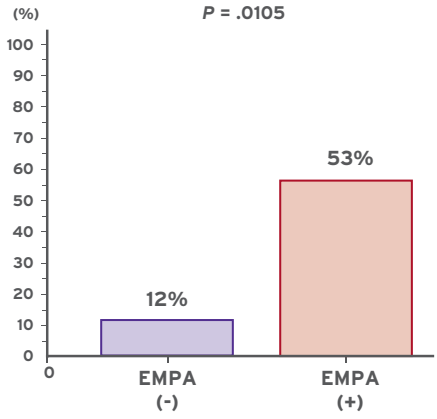
Figure 17. Incidence of Haemoconcentration at Day 7



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