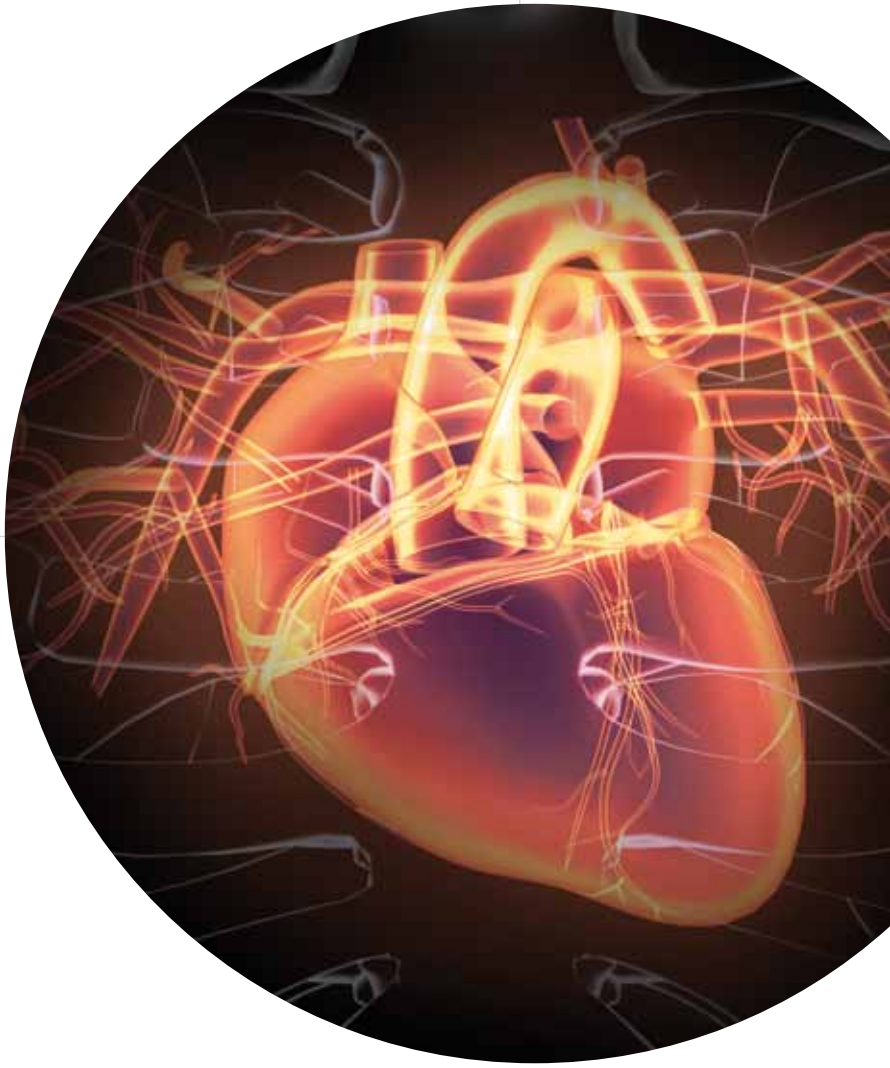
ESC Congress 2017 In Review

Official peer-reviewed highlights

Main Edition



In This Issue

Overview of the 2017 ESC Clinical Practice Guidelines

The European Society of Cardiology unveiled 4 new guideline updates, covering acute myocardial infarction in patients with ST-segment elevation, peripheral arterial disease, dual antiplatelet therapy, and valvular heart disease. These guidelines summarise the available evidence on the topics, providing a valuable clinical decision-making tool for practicing clinicians.

Also PCSK9 Inhibition of Cholesterol · Clinical Trial Highlights · Heart Failure in Patients With Diabetes

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ESC European Society of Cardiology

Dear Colleagues,

In this issue of *ESC Congress 2017 in Review*, we are delighted to share with you the peer-reviewed highlights of the European Society of Cardiology Congress 2017 held in Barcelona, Spain. Over the 5 days of the congress –in addition to the educational programme– 41 Hot Line presentations, 22 Clinical Trial Updates, 23 Registry presentations, 4 new ESC Clinical Practice Guidelines, and 4514 abstracts were presented. The Congress spotlight was "40 years of PCI" to showcase the impact that percutaneous coronary interventions have had on all aspects of cardiovascular care over the past 4 decades.

The articles selected for this issue of *ESC Congress 2017 in Review*, the official highlights report for ESC Congress 2017, will summarise the most newsworthy, cutting-edge, and clinically relevant topics presented in Barcelona. The trials –including COMPASS, CANTOS, RE-DUAL PCI, and ORION-1– will influence cardiovascular care and will allow us to better understand diseases and manage patients.

The ESC Clinical Practice Guidelines presented at ESC Congress 2017 include guidelines on the management of acute myocardial infarction in patients presenting with ST-segment elevation, on the diagnosis and treatment of peripheral arterial diseases, and on the management of valvular heart disease, as well as a focused update on dual antiplatelet therapy.

We are confident that the articles in this edition of *ESC Congress 2017 in Review* will be useful for your clinical practice. Please also be reminded that ESC Congress 365, the ESC Congress online library, provides unlimited year-round access to all abstracts, slides, and presentations, along with ESC TV interviews and other material from ESC Congress 2017. To access this unique source of up-to-date information, visit us online at www.escardio.org/365.

We hope you will enjoy this issue of *ESC Congress 2017 in Review* and look forward to seeing you in Munich for ESC Congress 2018. For more information, please visit www.escardio.org/ESC2018.

Professor Stephan Achenbach, FESC
Chairman, ESC Congress Programme Committee 2016-2018

Dear Practitioner,

We are pleased to share with you highlights from the European Society of Cardiology (ESC) Congress 2017 held in Barcelona, Spain.

The featured article provides a topline summary of the new guidelines released by the ESC during the Congress. It covers the management of acute myocardial infarction (MI) in patients presenting with ST-segment elevation, the diagnosis and treatment of peripheral arterial diseases (PAD), the management of valvular heart disease, and a focused update on dual antiplatelet therapy in patients.

A number of highly anticipated and potentially practice-changing clinical trials were presented at ESC Congress 2017, including the results from the COMPASS, CANTOS, and ORION-1 studies. COMPASS extended the results from ATLAS TIMI-51 demonstrating that rivaroxaban 2.5 mg BID plus aspirin was superior to aspirin alone for prevention of cardiovascular (CV) death, stroke, or MI in patients with stable CAD or PAD. The CANTOS study of canakinumab, a human monoclonal antibody directed against IL-1β, in patients with CAD and residual inflammatory risk was the first trial to target inflammation to reduce CV events. The results showed that canakinumab significantly reduced the risk of CV events when added to a background of optimal medical therapy without affecting lipids, they also help to validate the hypothesis of a connection between inflammation and atherosclerosis. Furthermore, a reduction in fatal lung cancers was an added benefit although tempered somewhat by an increase in deaths due to infection. The ORION-1 study showed that inclisiran, an oligonucleotide that interferes with the mRNA encoding for the PCSK9 protein, delivered at a dose of 300 mg subcutaneously twice per year, lowered low-density lipoprotein cholesterol (LDL-C) by approximately 50% for up to 1 year in patients with high CV risk and elevated LDL-C.

In addition to the results from Hot Line session clinical trials and registry updates, you will also find information on selected areas of CV medicine including cholesterol-lowering therapy for primary and secondary prevention, a look at future therapies for heart failure, and the prevention and management of acute stroke.

We hope that you find the articles and practical perspectives that are contained in the pages of this issue of *ESC Congress 2017 in Review* helpful in integrating this new information into your clinical practice.

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Main Session

Late-Breaking Clinical Trials

Late-Breaking Science

Selected Content

Overview of the 2017 ESC Clinical Practice Guidelines

Written by **Toni Rizzo**

The European Society of Cardiology (ESC) unveiled 4 new guideline updates developed by expert task forces and peer-reviewers, covering acute myocardial infarction in patients with ST-segment elevation (AMI-STEMI), peripheral arterial disease (PAD), dual antiplatelet therapy (DAPT), and valvular heart disease (VHD). These guidelines summarise the available evidence on the topics, providing a valuable clinical decision-making tool for practicing clinicians.

Management of AMI in Patients With STEMI

The 2017 ESC Guidelines for the Management of AMI in Patients Presenting With ST-Segment Elevation [Ibanez B et al. *Eur Heart J*. 2017] were developed by the ESC Task Force led by Stefan James, MD, Uppsala University, Uppsala, Sweden, and Borja Ibanez, MD, PhD, University Hospital Fundación Jiménez Díaz, Madrid, Spain. Levels of recommendations have been changed for several management options, including radial access, drug-eluting stent over bare-metal stent, complete revascularisation, thrombus aspiration, bivalirudin and enoxaparin therapy, early hospital discharge, and the use of tenecteplase tissue plasminogen activator.

The updated guidelines include a number of new and revised concepts since the previous version was published in 2012 (Figure 1). For example, important changes have been made in the definition of "time 0" to choose a reperfusion strategy. Ambiguous terms such as "door-to-balloon" and "door-to-door" have

Figure 1. AMI-STEMI: New and Revised Concepts

MINOCA and Quality Indicators:
- New chapters dedicated to these topics

Strategy Selection and Time Delays:
- Clear definition of first medical contact
- Definition of "time 0" to choose reperfusion strategy (ie, the strategy clock starts at the time of "STEMI diagnosis")
- Selection of PCI over fibrinolysis: when anticipated delay from "STEMI diagnosis" to wire crossing is ≤120 min
- Maximum delay time from "STEMI diagnosis" to bolus of fibrinolysis agent is set to 10 min
- "Door-to-Balloon" term eliminated from guidelines

Time Limits for Routine Opening of an IRA:
- 0-12h (Class I); 12-48h (Class IIa)

Electrocardiogram at Presentation:
- Left and right bundle branch block considered equal for recommending urgent angiography if ischaemic symptoms

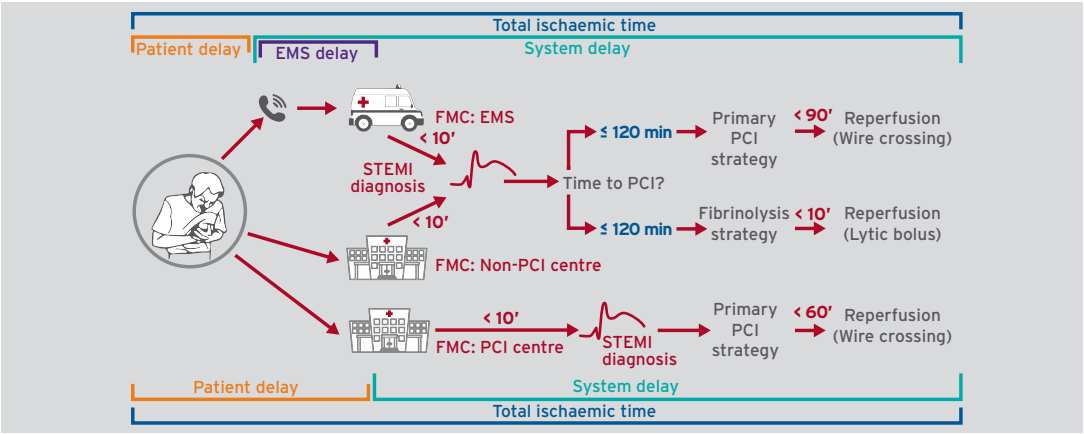
Time to Angiography after Fibrinolysis:
- Recommended between 2-24h after successful fibrinolysis

Patients Taking Anticoagulants:
- Acute and chronic management presented

IRA, infarct-related artery; MINOCA, myocardial infarction with nonobstructive coronary arteries; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Reprinted from Ibanez B and James S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2017. doi:10.1093/eurheartj/ehx393. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Figure 2. Flowchart for Reperfusion Strategy in Patients With STEMI



EMS, emergency medical system; FMC, first medical contact; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

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been eliminated. Time 0 is the time of STEMI diagnosis, defined as the time at which the electrocardiogram of a patient with ischaemic symptoms is interpreted as presenting ST-segment elevation or the equivalent.

A new flowchart outlines the criteria for selection of reperfusion strategy (Figure 2).

The selection of reperfusion strategy is based on the estimated time from STEMI diagnosis to percutaneous coronary intervention (PCI)-mediated reperfusion. Fibrinolysis should be initiated as soon as possible, preferably in the prehospital setting. Patients receiving primary fibrinolysis should be transferred immediately after to a PCI centre. The 2017 ESC Pocket Guidelines (offline and online app) include interactive tools for calculating antithrombotic agent doses.

Long-term maintenance therapies should include antiplatelet and lipid-lowering therapy for all patients with STEMI. Most patients should receive β-blockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). Mineralocorticoid receptor antagonists (MRA) are recommended for patients with left ventricular dysfunction and heart failure (HF) after STEMI. The recommendations for routine lipid lowering therapy, β-blockers, ACE inhibitors, ARBs, and MRAs are shown in Table 1.

The new guidelines also contain revised recommendations for management of STEMI patients with acute HF, cardiogenic shock, and atrial fibrillation (AF). A flowchart on MI with nonobstructive coronary arteries focuses on determining aetiology rather than specific treatments.

Diagnosis and Treatment of PADs

The 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS) were updated from the 2011 version [Aboyans V et al. *Eur Heart J*. 2017]. These guidelines address atherosclerotic disease of all the arteries except the coronary arteries and the aorta. ESC Task Force Chairperson, Victor Aboyans, MD, PhD, Dupuytren University, Limoges, France, and co-Chairperson, Jean-Baptiste Ricco, MD, University of Poitiers, Poitiers, France, presented an overview of the recommendations for lower-extremity artery disease (LEAD), renal artery disease (RAD), and cerebrovascular PADs.

Management of patients with PADs involves addressing general cardiac risk and prevention and related symptoms at the specific site. The guidelines recommend a multidisciplinary approach with a Vascular Team at all centres.

Table 1. Recommendations for Routine Therapies in the Acute, Subacute, and Long-term Phases of STEMI

Recommendations	Class	Level
Lipid-lowering therapy		
It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term.	I	A
A LDL-C goal of 70 mg/dL or a reduction of at least 50% if the baseline LDL-C is between 70 and 135 mg/dL is recommended.	I	B
It is recommended to obtain a lipid profile in all STEMI patients as soon as possible after presentation.	I	C
In patients with LDL-C ≥ 70 mg/dL despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered.	IIa	A
β-blockers		
Intravenous β-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with no signs of acute HF, and with an SBP > 120 mm Hg.	IIa	A
Intravenous β-blockers must be avoided in patients with hypotension, acute HF, or AV block or severe bradycardia.	III	B
Oral treatment with β-blockers is indicated in patients with HF and/or LVEF ≤40% unless contraindicated.	I	A
Routine oral treatment with β-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications.	IIa	B
ACE inhibitors and ARBs: LVEF ≤40% and/or HF		
ACE inhibitors are recommended, starting within the first 24 hours of STEMI in patients with evidence of HF, LV systolic dysfunction, diabetes, or an anterior infarct.	I	A
An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with HF or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors.	I	B
ACE inhibitors should be considered in all patients in the absence of contraindications.	IIa	A
MRAs: LVEF ≤40% and HF		
MRAs are recommended in patients with an LVEF ≤40% and HF or diabetes, who are already receiving an ACE inhibitor and a β -blocker, provided there is no renal failure or hyperkalaemia.	I	B

AV, atrioventricular; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.

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The ankle-brachial index measurement is recommended for diagnosis of asymptomatic at-risk patients and patients with clinical suspicion or at risk for LEAD. Among asymptomatic patients, the guidelines individualised a subset of patients with "Masked LEAD" (ie, generally old patients with other comorbidities limiting walking so that the classical symptoms cannot be revealed) with the risk of sudden severe presentation. For management of patients with claudication, the guidelines recommend cardiovascular disease prevention and exercise therapy with or without revascularisation. Patients with chronic limb-threatening ischaemia should be referred to a vascular team for risk stratification and management (Table 2).

Renal artery disease (RAD) is a strong independent predictor of mortality. Medical therapy with ACE inhibitors or ARBs is recommended for treatment of hypertension in patients with bilateral severe or unilateral renal artery stenosis and in some cases of stenosis in a single functioning kidney. Revascularisation is not recommended for RAD secondary to atherosclerosis but may be considered in patients with significant stenosis and particular clinical scenarios such as flash pulmonary oedema.

For patients with asymptomatic extracranial carotid artery disease, optimal medical therapy reduces the risk of stroke [Abbott AL et al. *Int J Stroke*. 2007; Naylor AR et al. *Semin Vasc Surg*. 2008]. Best medical treatment is recommended for all asymptomatic patients; and with a 60-99% stenosis, carotid endarterectomy should be considered in the presence of clinical and/or more imaging characteristics that may be associated with an increased

Table 2. Management of Chronic Limb-Threatening Ischaemia

Recommendations	Class	Level
Early recognition of tissue loss and/or infection and referral to the vascular team is mandatory to improve limb salvage.	I	C
In patients with CLTI, assessment of the risk of amputation is indicated.	I	C
In patients with CLTI and diabetes, optimal glycaemic control is recommended.	I	C
For limb salvage, revascularisation is indicated whenever feasible.	I	B
In patients with CLTI with below-the-knee lesions, angiography including foot runoff should be considered prior to revascularisation.	IIa	C

CLTI, chronic limb-threatening ischaemia.

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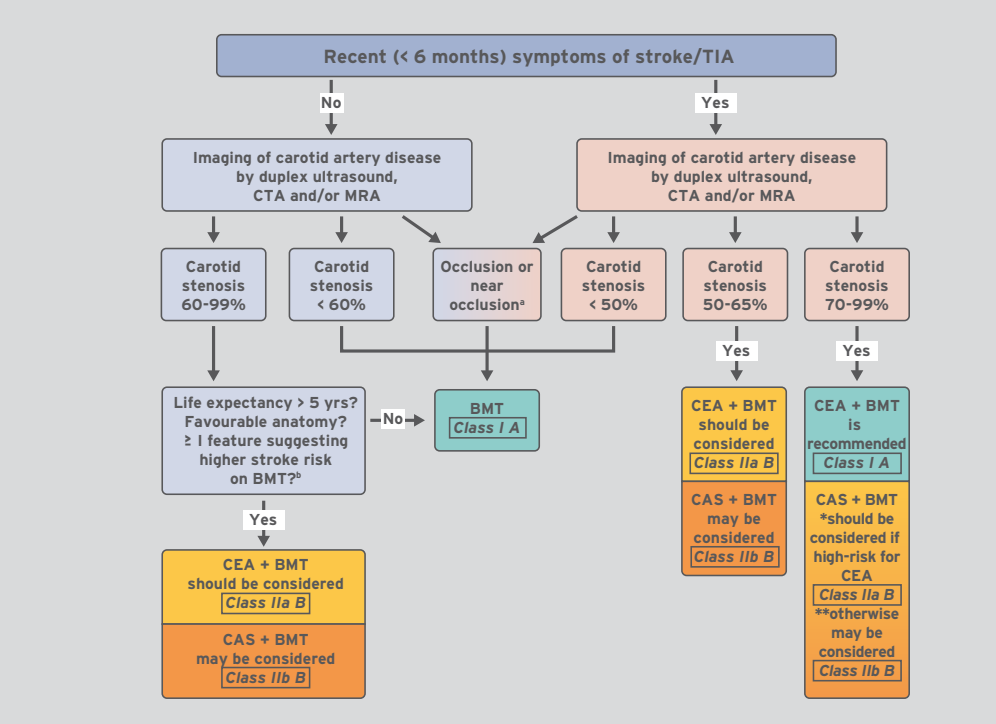
Figure 3. Management of Extracranial Carotid Artery Disease



BMT, best medical therapy; CAS, carotid artery stenting; CEA, carotid endarterectomy; CTA, computed tomography angiography; MRA, magnetic resonance angiography; TIA, transient ischaemic attack.

[a] With post-stenotic internal carotid artery narrowed to the point of near occlusion.

[b] Ipsilateral silent brain infarction, stenosis progression > 20%, embolisation on transcranial Doppler, large plaques (> 40 mm^2), echolucent plaques, intraplaque haemorrhage.

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risk of ipsilateral stroke, provided documented perioperative stroke/death rates are < 3% and life expectancy exceeds 5 years (Figure 3). Revascularisation in patients with symptomatic 50% to 99% carotid stenosis should be performed within 14 days of symptom onset.

Dual Antiplatelet Therapy in CAD

The 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease was developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). ESC DAPT Task Force Chairperson, Marco Valgimigli, MD, Inselspital Universitätsspital Bern, Bern, Switzerland, overviewed the updated DAPT guideline. The recommendations highlight the need for personalised use of DAPT in terms of type and duration to maximise ischaemic protection and minimise bleeding risk in patients with CAD.

All of the prior recommendations on DAPT have been revised in the updated guideline (Figure 4).

According to the recommendations, clinicians may consider the use of risk scores designed to evaluate the benefits and risks of different DAPT durations. The DAPT and PRECISE-DAPT scores have been validated for making decisions about the duration of DAPT.

DAPT is not indicated for patients with stable CAD and no history of prior MI who are undergoing medical therapy only. After PCI with stent placement, DAPT is considered standard of care. DAPT may be considered for a limited duration in patients with stable CAD treated with PCI who are at high bleeding risk (Table 3).

In patients with acute coronary syndrome (ACS) undergoing PCI or coronary artery bypass graft (CABG), DAPT is indicated for 12 months in patients without high bleeding risk (aspirin plus prasugrel, ticagrelor, or clopidogrel) and for 6 months in patients at high bleeding risk (aspirin plus clopidogrel or ticagrelor). There is no indication for DAPT in patients with stable CAD undergoing CABG unless there is a concomitant or prior indication.

Table 3. DAPT in High Bleeding-Risk Patients With Stable CAD Treated With PCI

Recommendations	Class	Level
In patients with stable CAD considered at high bleeding risk (eg, PRECISE-DAPT ≥25), DAPT for 3 months should be considered.	IIa	B
In patients with stable CAD in whom 3-month DAPT poses safety concerns, DAPT for 1 month may be considered.	IIb	C

CAD, coronary artery disease; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

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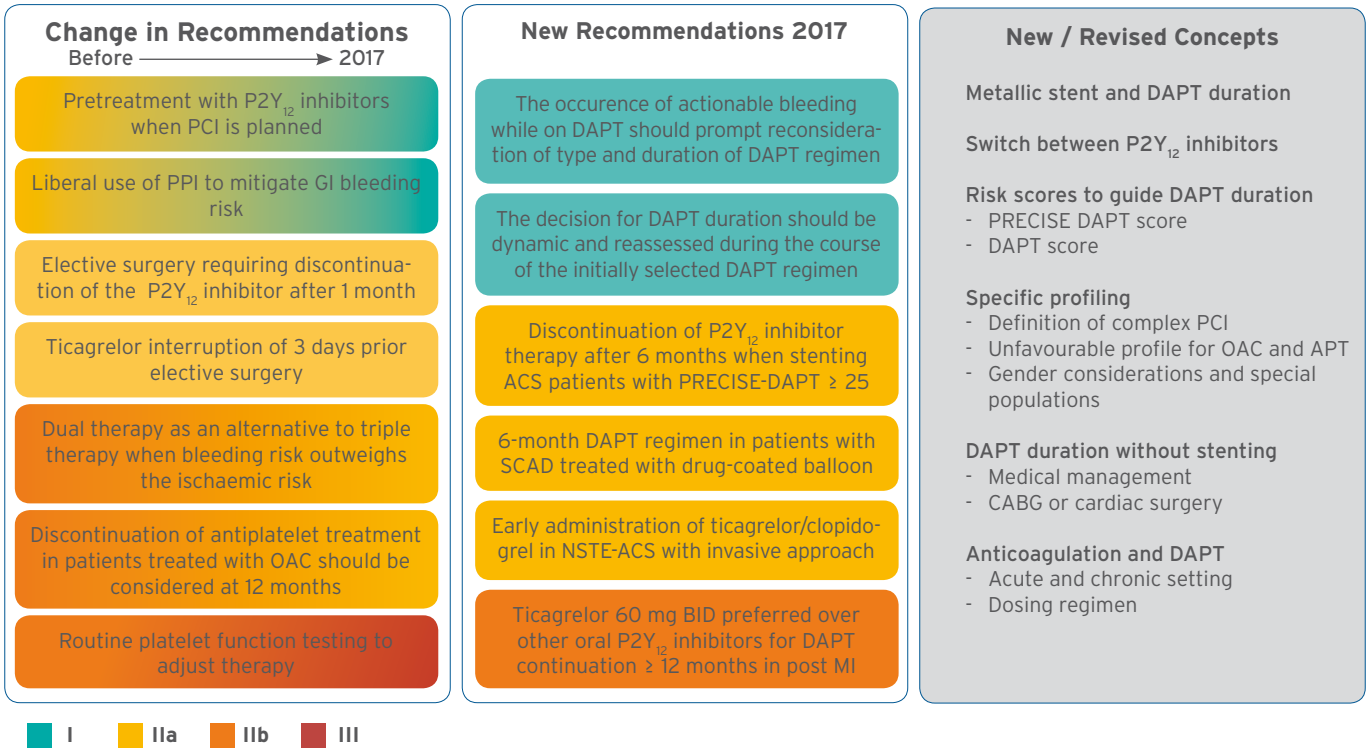
Figure 4. Changes in the 2017 Focused Update on DAPT



ACS, acute coronary syndrome; APT, antiplatelet therapy; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; GI, gastrointestinal; MI, myocardial infarction; NSTE, non-ST-segment elevation; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; SCAD, stable coronary artery disease.

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DAPT is indicated for 12 months in patients with ACS without high bleeding risk (aspirin plus ticagrelor or clopidogrel) treated with medical therapy and for ≥ 1 month in those with high bleeding risk (aspirin plus clopidogrel).

Among patients with an indication for oral anticoagulation who are scheduled for PCI, clopidogrel is the only option to establish a DAPT regimen. The guidelines include an algorithm for making decisions about the choice and duration of therapy (Figure 5).

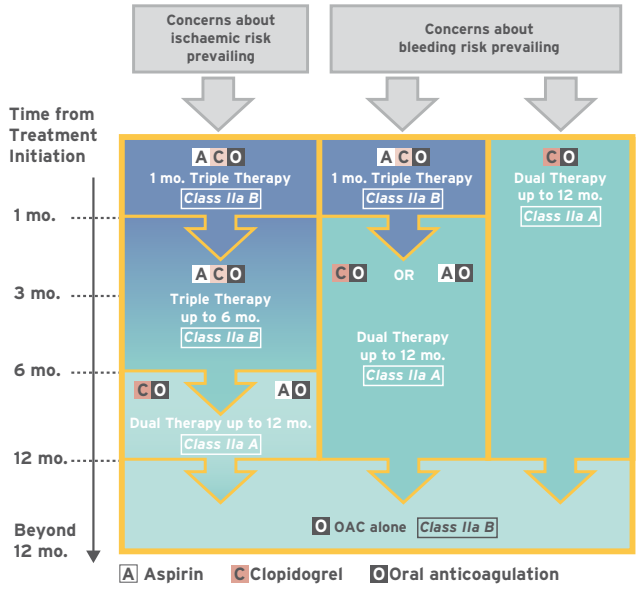
The recommendations for DAPT based on gender and in special populations are shown in Table 4.

Management of Valvular Heart Disease

The updated 2017 ESC/EACTS Guidelines for the Management of VHD has major changes compared with the 2012 version. Developed jointly by the ESC and EACTS, the guidelines overview was presented by ESC Chairperson, Helmut Baumgartner, MD, University Hospital Münster, Münster, Germany, and the EACTS Chairperson, Volkmar Falk, MD, German Heart Center, Berlin, Germany.

Major changes in the new guidelines address heart valve centres and the heart team, the role of transcatheter interventions, indications for surgery in asymptomatic VHD, and medical therapy. The recommended requirements for a heart valve centre are shown in Table 5.

Figure 5. Choice and Duration of Therapy in Patients With an Indication for Oral Anticoagulation Undergoing PCI



DAPT, dual antiplatelet therapy; MI, myocardial infarction; OAC, oral anticoagulant.

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Non-vitamin K antagonist oral anticoagulants (NOACs) are not approved for AF associated with VHD (ie, rheumatic mitral stenosis) but recent trials support the use of NOACs for patients with degenerative aortic stenosis, aortic regurgitation, or mitral regurgitation presenting with AF. Recommendations for the management of AF in patients with VHD are summarised in Table 6.

Table 4. Gender Considerations and Special Populations

Recommendations	Class	Level
Similar type and duration of DAPT are recommended in male and female patients.	I	A
It is recommended to reassess the type, dose, and duration of DAPT in patients with actionable bleeding complication while on treatment.	I	C
Similar type and duration of DAPT should be considered in patients with and without diabetes mellitus.	IIa	B
Prolonged (ie, ≥ 12 months) DAPT duration should be considered in patients with prior stent thrombosis, especially in the absence of correctable causes (eg, lack of adherence or correctable mechanical stent-related issues).	IIa	C
Prolonged (ie, > 12 months) DAPT duration may be considered in CAD patients with LEAD.	IIb	B
Prolonged (ie, > 6 months) DAPT duration may be considered in patients who underwent complex PCI.	IIb	B

CAD, coronary artery disease; DAPT, dual antiplatelet therapy; MI, myocardial infarction; LEAD, lower extremity artery disease; PCI, percutaneous coronary intervention.

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Table 5. Recommended Requirements of a Heart Valve Centre

Requirements
Multidisciplinary teams with competencies in valve replacement, aortic root surgery, mitral, tricuspid and aortic valve repair, as well as transcatheter aortic and mitral valve techniques including reoperations and reinterventions. The Heart Teams must meet on a regular basis and work with standard operating procedures.
Imaging, including 3D and stress echocardiographic techniques, perioperative TOE, cardiac CT, MRI, and PET-CT.
Regular consultation with community, other hospitals, and extracardiac departments, and between noninvasive cardiologists and surgeons and interventional cardiologists.
Back-up services including other cardiologists, cardiac surgeons, intensive care, and other medical specialties.
Data review: • Robust internal audit processes including mortality and complications, repair rates, durability of repair, and reoperation rate with a minimum of 1-year follow-up. • Results available for review internally and externally. • Participation in national or European quality databases.

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; TOE, transoesophageal echocardiography.

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Table 6. Management of AF in Patients VHD

Recommendations	Class	Level
Anticoagulation		
NOACs should be considered as an alternative to VKAs in patients with aortic stenosis, aortic regurgitation, and mitral regurgitation presenting with AF.	IIa	B
NOACs should be considered as an alternative to VKAs after the third month of implantation in patients who have AF associated with a surgical or transcatheter aortic valve bioprostheses.	IIa	C
The use of NOACs is not recommended in patients with AF and moderate to severe mitral stenosis.	III	C
NOACs are contraindicated in patients with a mechanical valve.	III	B
Surgical Interventions		
Surgical ablation of AF should be considered in patients with symptomatic AF who undergo valve surgery.	IIa	A
Surgical ablation of AF may be considered in patients with asymptomatic AF who undergo valve surgery, if feasible, with minimal risk.	IIb	C
Surgical excision or external clipping of the LA appendage may be considered in patients undergoing valve surgery.	IIb	B

AF, atrial fibrillation; LA, left atrial; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

Most of the recommendations for aortic regurgitation have remained the same as in the 2012 version. A new recommendation on repairing valves states that while most patients with aortic insufficiency will receive a valve replacement, patients with tricuspid valve prolapse and an enlarged root should be considered for aortic valve repair. The threshold for ascending aortic replacement was lowered to an ascending aortic diameter of ≥ 45 mm in patients with a *TGFBR1* or *TGFBR2* mutations and to 40 mm in women with these mutations and low body surface area, patients with a *TGFBR2* mutation, and patients with severe extra-aortic features.

The changes in recommendations for patients with aortic stenosis are shown in Table 7.

Table 7. Changes in Recommendations for Aortic Stenosis

Changes in Recommendations	
2012	**2017**
Indications for intervention in symptomatic aortic stenosis	
IIb C Intervention may be considered in symptomatic patients with low-flow, low-gradient aortic stenosis and reduced ejection fraction without flow (contractile) reserve.	**IIa C** Intervention should be considered in symptomatic patients with low-flow, low-gradient aortic stenosis and reduced ejection fraction without flow (contractile) reserve, particularly when CT calcium scoring confirms severe aortic stenosis.

CT, computed tomography.

The indications for surgery in patients with asymptomatic aortic stenosis are shown in Table 8.

Table 8. Indications for Surgery in Asymptomatic Aortic Stenosis

2012	2017
IIb C Markedly elevated BNP levels.	**IIa C** Markedly elevated BNP levels (> 3-fold age- and sex-corrected normal range) confirmed by repeated measurements without other explanations.
IIb C Increase of mean pressure gradient with exercise by > 20 mm Hg.	**Removed**
IIb C Excessive LV hypertrophy in the absence of hypertension.	**Removed**
2017 New Recommendation	
IIa C Severe pulmonary hypertension (systolic pulmonary artery pressure at rest > 60 mm Hg confirmed by invasive measurement) without other explanation.	

BNP, brain natriuretic peptide; LV, left ventricular.

The recommendations for choice of intervention in symptomatic aortic stenosis are shown in Table 9.

Table 9. Recommendations for Choice of Intervention in Symptomatic Aortic Stenosis

Recommendations	Class	Level
Aortic valve interventions should only be performed in centres with both departments of cardiology and cardiac surgery onsite, and with structured collaboration between the two, including a Heart Team (heart valve centres).	I	C
The choice of intervention must be based on careful individual evaluation of technical suitability and weighing of risks and benefits of each modality. In addition, the local expertise and outcomes data for the given intervention must be taken into account.	I	C
SAVR is recommended in patients at low surgical risk (STS or EuroSCORE II < 4% or logistic EuroSCORE I < 10% and no other risk factors not included in these scores, such as frailty, porcelain aorta, sequelae of chest radiation).	I	B
TAVI is recommended in patients who are not suitable for SAVR as assessed by the Heart Team.	I	B
In patients who are at increased surgical risk (STS or EuroSCORE II ≥ 4% or logistic EuroSCORE I ≥ 10% or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation), the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics, with TAVI being favoured in elderly patients suitable for transfemoral access.	I	B
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients or in patients with symptomatic severe aortic stenosis who require urgent major noncardiac surgery.	IIb	C
Balloon aortic valvotomy may be considered as a diagnostic means in patients with severe aortic stenosis and other potential cause for symptoms (ie, lung disease) and in patients with severe myocardial dysfunction, prerenal insufficiency, or other organ dysfunction that may be reversible with balloon aortic valvotomy when performed in centres that can escalate to TAVI.	IIb	C

SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

Tables 6-9 reprinted from Baumgartner H, Falk V et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2017. doi:10.1093/eurheartj/ehx391. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Refer to Table 10 for aspects to be considered by the Heart Team for the decision between SAVR and TAVI in patients at increased surgical risk.

Table 10. Aspects to Be Considered by the Heart Team for the Decision Between SAVR And TAVI in Patients at Increased Surgical Risk

	Favours TAVI	Favours SAVR
Clinical characteristics		
STS/EuroSCORE II < 4% (logistic EuroSCORE I < 10%)		+
STS/EuroSCORE II ≥ 4% (logistic EuroSCORE I ≥ 10%)	+	
Presence of severe comorbidity (not adequately reflected by scores)	+	
Age < 75 years		+
Age ≥ 75 years	+	
Previous cardiac surgery	+	
Frailty	+	
Restricted mobility and conditions that may affect the rehabilitation process after the procedure	+	
Suspicion of endocarditis		+
Anatomical and technical aspects		
Favourable access for transfemoral TAVI	+	
Unfavourable access (any) for TAVI		+
Sequelae of chest radiation	+	
Porcelain aorta	+	
Presence of intact coronary bypass grafts at risk when sternotomy is performed	+	
Expected patient-prosthesis mismatch	+	
Short distance between coronary ostia and aortic valve annulus		+
Size of aortic valve annulus out of range for TAVI		+
Aortic root morphology unfavourable for TAVI		+
Valve morphology (bicuspid, degree of calcification, calcification pattern) unfavourable for TAVI		+
Presence of thrombi in aorta or LV		+
Cardiac conditions in addition to aortic stenosis that require consideration for concomitant intervention		
Severe CAD requiring revascularisation by CABG		+
Severe primary mitral valve disease, which could be treated surgically		+
Severe tricuspid valve disease		+
Aneurysm of the ascending aorta		+
Septal hypertrophy requiring myectomy		+

CABG, coronary artery bypass surgery; CAD, coronary artery disease; LV, left ventricular; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgery; TAVI, transcatheter aortic valve implantation.

Table 11 summarises changes in the 2017 VHD guidelines regarding primary and secondary mitral regurgitation.

Table 11. Changes in the 2017 Valvular Heart Disease Recommendations

Changes in Recommendations	
2012	**2017**
Indications for intervention in symptomatic aortic stenosis	
IIb C Surgery may be considered in asymptomatic patients with preserved LV function, high likelihood of durable repair, low surgical risk, and: • Left atrial dilatation (volume index ≥ 60 mL/m² BSA) and sinus rhythm.	**IIa C** Surgery should be considered in asymptomatic patients with preserved LVEF (> 60%) and LVESD 40-44 mm when a durable repair is likely, surgical risk is low, the repair is performed in heart valve centres, and the following finding is present: presence of significant LA dilatation (volume index ≥ 60 mL/m² BSA) in sinus rhythm.
Pulmonary hypertension on exercise (SPAP ≥ 60 mm Hg at exercise.	**Recommendation removed**
Indications for mitral valve intervention in secondary mitral regurgitation	
IIa C Surgery should be considered in patients with moderate secondary mitral regurgitation undergoing CABG.	**Recommendation removed**
IIb C When revascularisation is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and LVEF > 30%, who remain	**IIb C** When revascularisation is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and LVEF > 30%, who remain symptomatic despite optimal medical management (including CRT if indicated), and have a low surgical risk.
	IIb C When revascularisation is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF > 30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.
	IIb C In patients with severe secondary mitral regurgitation and LVEF > 30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularisation, the Heart Team may consider percutaneous edge-to-edge procedure or valve surgery after careful evaluation for ventricular assist device or heart transplant according to individual patient characteristics.

BSA, body surface area; LA, left atrial; CABG, coronary artery bypass grafting; CRT, cardiac resynchronisation therapy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; SPAP, systolic pulmonary artery pressure.

Several new recommendations have been added to the guideline. After transcatheter or surgical implantation of a bioprosthetic valve, echocardiography, including measurement of transprosthetic gradients, should be performed within 30 days after valve implantation, 1 year after implantation, and annually thereafter. Also added is the recommendation for INR self-management (with appropriate training and quality control) for patients with a prosthetic heart valve or valve repair receiving antithrombotic therapy.

Table 12 summarises new recommendations for the management of prosthetic valve dysfunction.

Table 12. New Recommendations for the Management of Prosthetic Valve Dysfunction

Recommendations	Class	Level
Anticoagulation using a VKA and/or UFH is recommended in bioprosthetic valve thrombosis before considering reintervention.	I	C
Reoperation is recommended if paravalvular leak is related to endocarditis or causes haemolysis requiring repeated blood transfusions or leading to severe symptoms.	I	C
Transcatheter closure may be considered for paravalvular leaks with clinically significant regurgitation in surgical high-risk patients (Heart Team decision).	IIb	C
Transcatheter valve-in-valve implantation in aortic position should be considered by the Heart Team depending on the risk of reoperation and the type and size of prosthesis.	IIa	C

UFH, unfractionated heparin; VKA, vitamin K antagonist.

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The editors would like to thank the many members of the ESC Congress 2017 presenting faculty who generously gave their time to ensure the accuracy and quality of the articles in this publication

ORION-1 Shows Inclisiran Provides Robust and Consistent LDL-C Lowering

Written by **Maria Vinall**

Inclisiran is a chemically synthesised small interfering RNA designed to target PCSK9 messenger RNA. Final primary outcome results from the ORION-1 trial [NCT02597127], found that after 6 months, inclisiran (either a 1 or 2-dose regimen) produced dose-dependent reductions in PCSK9 and low-density lipoprotein cholesterol (LDL-C) levels among patients at high cardiovascular risk with elevated LDL-C levels [Ray KK et al. *N Engl J Med*. 2017]. Kausik K. Ray, MB ChB, MPhil, Imperial College London, London, United Kingdom, reported extended results from ORION-1 and the impact of inclisiran on LDL-C at 1 year.

ORION-1 enrolled 501 patients aged ≥ 18 years with atherosclerotic cardiovascular disease (ASCVD) or high ASCVD risk and in whom LDL-C was > 70 mg/dL or 100 mg/dL, respectively, despite maximally tolerated statin therapy. Participants were randomised to either a 1-dose starting regimen of 200, 300, or 500 mg of inclisiran or placebo administered subcutaneously (SC) or a 2-dose starting regimen of 100, 200, or 300 mg of inclisiran or matching placebo administered SC on days 1 and 90. LDL-C and other lipoproteins were measured monthly through to 1 year or until LDL-C had returned to within 20% of starting levels. A total of 497 patients were treated and 483 completed the end of study visit and entered extended follow-up to 360 days.

Participants were a mean age of 63 years, mostly (65%) men. The use of statins was common (73% of patients) with about 50% being on a high-dose regimen. LDL-C at baseline was 128 mg/dL. The 1-dose starting regimen was associated with robust and sustained reductions in LDL-C. The 300-mg dose was considered optimal with reductions of 50.9%, 38.4%, and 19.0%, at 60, 180, and 360 days after the first injection on the 1-dose regimen.

The addition of a second 300 mg dose at days 90 was associated with LDL-C reductions of 55.5% at day 150, 52.6% at day 180, and 31.4% at day 360.

Both regimens produced sustained reductions over time. Time-averaged reductions were −37% and −46% for the 300 mg dose for the 1- and 2-dose regimens respectively. Patients returned toward baseline in a stable manner with both regimens. With a single dose, the time adjusted LDL-C reduction for 6 months was 41% but with a second dose at day 90 this increased to 51%, in both cases with a tight interquartile range. There was minimal within-patient variability in LDL-C reduction over time. The adverse event profile was similar with both regimens. There were no liver function elevations, no differences in the incidence of myalgias or creatine phosphokinase (CPK) enzyme elevations, and no study drug-related deaths. Injection-site reactions occurred in 5% of the patients who received injections of inclisiran and no patients on placebo.

Inclisiran provides robust sustained reductions in LDL-C over 1 year with a low injection burden. The optimal starting dose is 300 mg SC at day 1 and day 90. The suggested maintenance dose is 300 mg SC at day 270, then every 180 days. This regimen provides a 46% time-averaged reduction over 12 months and a 51% time-averaged reduction over 6-month dosing interval.

Results From the COMPASS Study

Written by **Maria Vinall**

Cardiovascular disease (CVD) affects 300 million persons worldwide, about 4% of the worlds' population. Aspirin is the most widely used preventive treatment but it reduces CV events by only 19% long-term. The ATLAS TIMI-51 trial [Mega JL et al. *N Engl J Med*. 2012] established the efficacy of low doses of rivaroxaban, a selective direct factor Xa inhibitor, in patients with acute coronary syndrome. John W. Eikelboom, MD, McMaster University, Hamilton, Ontario, Canada, presented the primary results of the COMPASS trial [Eikelboom JW et al. *N Engl J Med*. 2017], which aimed to extend the results from ATLAS TIMI-51 by evaluating whether rivaroxaban plus aspirin or rivaroxaban alone is superior to aspirin alone for prevention of CV death, stroke, or myocardial infarction (MI) in patients with stable coronary artery disease (CAD) or peripheral arterial disease (PAD).

COMPASS recruited a selected high-risk population with CAD or PAD. The definition of CAD was prior MI, multivessel coronary disease, or prior coronary revascularisation. The definition of PAD was prior peripheral revascularisation or amputation, claudication with a low ankle brachial index or asymptomatic carotid disease.

The population was further enriched for risk in that patients aged < 65 years who had also multivessel coronary disease or at least 2 additional risk factors (diabetes mellitus, smoking, renal dysfunction, heart failure, or nonlacunar stroke).

The primary outcome was a composite of CV death, stroke, or MI. Secondary endpoints included the composite of ischaemic stroke, MI, acute limb ischaemia (ALI), or death from coronary heart disease; the composite of ischaemic stroke, MI, ALI, or CV death; and death from any cause. The main safety outcome was a modification of the ISTH criteria for major bleeding and the net clinical benefit was a composite of the primary outcome and fatal or critical organ bleeding.

Between March 2013 and May 2016, 27,395 patients from 602 centres in 33 countries were randomised (1:1:1) to treatment with rivaroxaban 2.5 mg BID plus aspirin 100 mg QD, rivaroxaban 5 mg BID, or aspirin 100 mg daily. At baseline, patients were a mean age of 68.2 years (22% women); 91% had CAD and 27% had PAD. The trial was stopped at the first formal analysis, as overwhelming efficacy in favour of rivaroxaban plus aspirin was noted. Mean follow-up was 23 months and maximum follow-up was 47 months.

Compared with aspirin alone, rivaroxaban 2.5 mg BID plus aspirin 100 mg QD significantly reduced the composite rate of CV death, stroke, and MI by 24% (4.1% vs 5.4%; HR, 0.76; 95% CI, 0.66 to 0.86; $P \leq .001$). The rivaroxaban 5 mg BID alone arm did not significantly reduce the primary endpoint (Figure 1). Benefits of the rivaroxaban 2.5 mg BID plus aspirin arm versus aspirin alone were generally consistent across the components of the primary endpoint.

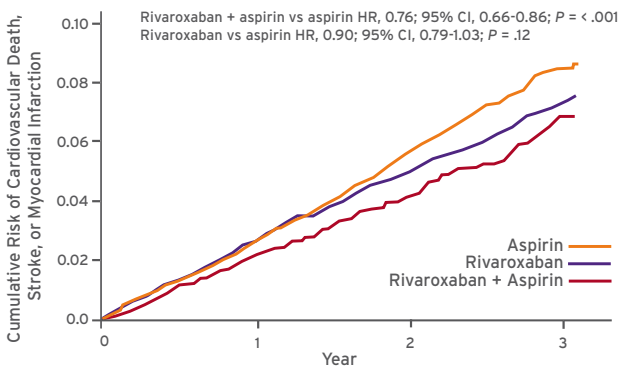
The secondary composite outcomes were significantly improved with the combination therapy (all $P \leq .01$) compared with aspirin alone. There was a trend towards lower mortality with the rivaroxaban 2.5 mg plus aspirin arm versus aspirin alone (3.4% vs 4.1%; $P = .01$), however this did not meet the threshold P value for significance of .0025.

Both rivaroxaban arms caused more major bleeds than aspirin alone. The aspirin plus rivaroxaban 2.5 mg arm increased major bleeding by 70% (3.1% vs 1.9%; HR, 1.70; 95% CI, 1.40 to 2.05; $P < .001$) while the rivaroxaban only arm increased major bleeding by 51% ($P < .001$). Rates of fatal bleeding or symptomatic intracranial haemorrhage were low and were not significantly increased with rivaroxaban plus aspirin versus aspirin (HR, 1.23; $P = .40$); there was a trend toward an increase with rivaroxaban 5 mg alone compared with aspirin (HR, 1.59; $P = .05$). Both rivaroxaban arms increased bleeding leading to transfusion versus aspirin alone (HR, 1.97; $P < .001$ for rivaroxaban 2.5 mg; HR, 1.50; $P = .03$ for rivaroxaban 5 mg).

Overall with rivaroxaban 2.5 mg twice daily added to aspirin versus aspirin alone over a median of 23 months there was a 1.3% absolute reduction in the primary endpoint versus a 1.2% increase in major bleeding. The prespecified net clinical benefit weighing only fatal or critical organ bleeding against the primary composite efficacy outcome was superior for rivaroxaban 2.5 mg with aspirin compared with aspirin alone (4.7% vs 5.9%; HR, 0.80; 95% CI, 0.70 to 0.91; $P < .001$).

The COMPASS trial demonstrated that in high-risk patients with CAD and/or PAD rivaroxaban 2.5 mg BID plus aspirin 100 mg QD reduces the composite of CV death, stroke, or MI compared with aspirin alone while rivaroxaban 5 mg BID monotherapy does not. Major bleeding is increased with rivaroxaban with aspirin or alone but without a significant increase in fatal, intracranial or critical organ bleeding.

Figure 1. Primary Outcome: Cardiovascular Death, Stroke, or Myocardial Infarction



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Risk Factor Driven Treatment Is Beneficial in Early Persistent Atrial Fibrillation and Heart Failure

Written by **Brian Hoyle**

A therapeutic approach that aggressively treats risk factors, including lifestyle changes, is feasible and effective in improving and maintaining sinus rhythm in heart failure (HF) patients in the early stages of persistent atrial fibrillation (AF).

Findings of the [NCT00877643] were presented by Isabelle C. Van Gelder, MD, PhD, Netherlands Heart Institute and the University of Groningen, Groningen, The Netherlands.

The prospective, randomised, open-label RACE 3 superiority trial conducted at 14 centres in the Netherlands

and 3 in the United Kingdom addressed the concept of risk factor-driven upstream therapy—interventions that are intended to modify the atrial substrate and lessen the detriments of AF-related risk factors and diseases. The therapy included the highest tolerable doses of mineralocorticoid receptor antagonists (MRAs), angiotensin-converting-enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs); a target blood pressure of < 120/80 mm Hg; statins; and physical/dietary cardiac rehabilitation.

The study hypothesised that upstream therapy is superior to conventional therapy in maintaining sinus rhythm in patients with early persistent AF and HF.

The 245 patients were enrolled between 2009 and 2015. Inclusion criteria were age ≥ 40 years, confirmed early symptomatic persistent AF and early HF, as well as a history of treatment of underlying heart diseases. Exclusion criteria included paroxysmal, transient, or asymptomatic AF; anti-arrhythmic drug use, MRA drug use, left atrial size > 50 mm, left ventricular ejection fraction (LVEF) < 25%, unstable cardiovascular conditions, and inability to perform a cardiovascular rehabilitation programme.

The patients were randomised to risk factor-driven upstream therapy (n = 119) or conventional therapy (n = 126), with stratification for LVEF ≥ 45% and < 45%. Myocardial extracellular volume was determined in both groups 3 weeks later. Rhythm control and HF therapy were delivered in both groups, as was 7-day monitoring of heart activity at 1 year. The primary endpoint was sinus rhythm present during the 1-year heart activity monitoring period. The 2 groups were comparable at baseline for demographic and clinical characteristics.

The aggressive approach significantly enhanced patient care compared with the conventional therapy group in terms of MRA use (85% vs 4%; $P < .001$) and statin use (93% vs 48%; $P < .001$), and greater use of ACEIs and/or ARBs (87% vs 76%). Rhythm control during the 1-year follow-up was similar in both groups.

The aggressive upstream approach was superior to conventional therapy for the primary endpoint of sinus rhythm at 1 year (OR, 1.766; $P = .021$). Analyses of a variety of clinical subgroups consistently favoured upstream rhythm control. Secondary endpoints did not differ significantly between the groups.

As expected, the upstream therapy was associated with more treatment-related safety signals (MRA adverse events 31% vs 0%, statin adverse events 17% vs 3%, ACEI and/or ARB adverse events 12% vs 6%), which were usually tolerable.

According to Prof Van Gelder, the RACE 3 findings demonstrate that the risk factor-driven upstream therapy, which includes treatment of risk factors and necessary lifestyle modifications, is "effective and feasible" in improving the maintenance of sinus rhythm in patients with early persistent AF and HF. Addressing risk factors, rather than atrial remodeling, was a favourable approach.

Prof Van Gelder added that the findings could help shift the focus to risk factor modification to improve AF outcomes.

Beta-Blockers May Benefit Patients in Sinus Rhythm Who Have Heart Failure Including Those With Reduced LVEF

Written by **Brian Hoyle**

An individual patient-level meta-analysis of randomised controlled trials (RCTs) involving over 17,000 patients with heart failure (HF) indicates that β-blockers can improve left ventricular ejection fraction (LVEF) and lessen death in HF patients in sinus rhythm with both reduced and mid-range LVEF.

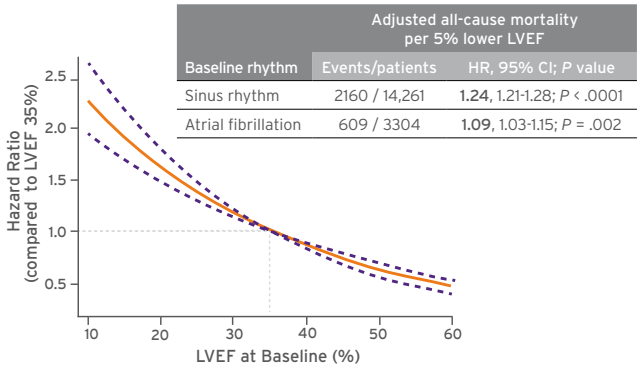
The effect of β-blockers in HF patients with reduced LVEF (< 40%), mildy reduced LVEF (40 - 49%), and preserved LVEF (≥ 50%) is unclear, according to presenter and lead researcher Dipak Kotecha, PhD, University of Birmingham, Birmingham, United Kingdom. Current ESC guidelines [Ponikowski P et al. *Eur Heart J*. 2016] suggest that mid-range LVEF be managed similarly to preserved LVEF. However, no double-blind RCTs have specifically addressed treatment of patients in these LVEF categories.

The researchers performed a meta-analysis of 11 placebo-controlled, double-blind RCTs. Each trial enrolled > 300 patients. The trials had reported mortality as the major endpoint with at least a 6-month follow-up.

The researchers examined individual patient-level data (n = 18,637), which allowed a more robust analysis. After exclusions, 17,312 patients were analysed. The researchers were able to determine when patients had commenced β-blocker therapy, allowing categorisation of the patients to the reduced (n = 16,274), mildly reduced (n = 721), or preserved (n = 317) LVEF groups. Patients were also stratified based upon sinus rhythm (n = 14,261) or atrial fibrillation (AF; n = 3,024) on the baseline electrocardiogram.

The primary outcomes were all-cause and cardiovascular (CV) mortality. Patients were followed for a mean of 1.5 years. Patients with the lowest LVEF at baseline were associated with a greater risk of all-cause mortality, particularly in those patients with baseline sinus rhythm (Figure 1).

Figure 1. LVEF and Mortality



LVEF, left ventricular ejection fraction.

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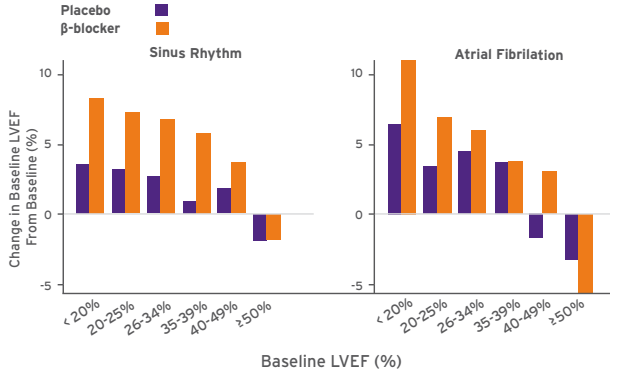
Figure 2. Effect of β-blockers in Survivors



LVEF, left ventricular ejection fraction.

Reproduced with permission from D Kotecha, MD.

In patients in sinus rhythm, β-blockers consistently lowered the risks of all-cause and CV mortality across the spectrum of LVEF, except for patients with preserved LVEF. In the latter group, β-blockers appeared not to reduce the risk of death. A disconnect was evident for AF patients, with β-blockers not appearing to lessen the risk of death across the entire LVEF spectrum.

Survival analyses for patients in sinus rhythm revealed a nearly 30% risk reduction in all-cause and CV mortality in patients with reduced LVEF treated with β-blockers (log-rank $P < .001$). The response pattern was similar for patients in the mildly reduced LVEF group, where CV death was halved with β-blockers (adjusted HR, 0.48; 95% CI, 0.24-0.97; log-rank $P = .042022$). No effect of β-blockers was evident in the small subgroup of patients in sinus rhythm with preserved LVEF (log-rank $P = .51$), nor in those with AF regardless of LVEF. In the nearly 5600 patients who survived and had a second measurement of LVEF, those in sinus rhythm (n = 4,601; Figure 2A) and AF (n = 996; Figure 2B) had greater improvements in LVEF with β-blockers than those receiving placebo as long as their LVEF was < 50%. For sinus rhythm, these findings were consistent with the mortality data. A disconnect was evident for AF patients; β-blockers did not appear to lessen the risk of death across the entire LVEF spectrum despite increasing LVEF although the number of patients included was lower.

Limitations include the small number of patients with LVEF ≥ 50%, and lack of data on brain natriuretic peptide, and diastolic and atrial function. The use of double-blind RCT data and the examination of individual patient data are study strengths.

The data suggest that HF patients in sinus rhythm categorised as reduced and mildly reduced LVEF should receive β-blockers to lower their risk of all-cause and CV death.

Canakinumab Improves Atherothrombotic Outcomes and Alters Cancer Progression

Written by **Maria Vinall**

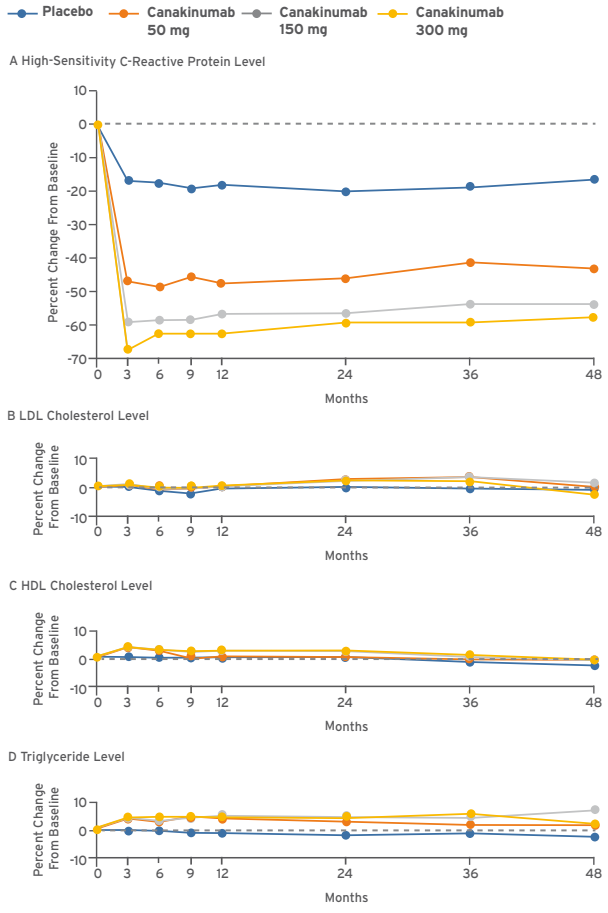
Canakinumab is a human monoclonal antibody that binds to the pro-inflammatory cytokine IL-1β and lowers systemic inflammation via reduction of IL-6, resulting in a decrease in the downstream inflammatory biomarker, high-sensitivity C-reactive protein (hsCRP). It is currently indicated for the treatment of IL-1β driven inflammatory diseases. Plasma levels of both hsCRP and IL-6 predict first and recurrent cardiovascular (CV) events independent of lipid levels [Ridker P. *J Am Coll Cardiol*. 2016]. Paul M. Ridker, MD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the results of a randomised double-blind, placebo-controlled trial, which showed that canakinumab reduces CV event rates and potentially reduces rates of incident lung cancer and lung cancer mortality without an effect on lipids.

CANTOS [Ridker PM et al. *N Engl J Med*. 2017] was designed to directly test whether inflammation reduction can reduce CV event rates in patients with stable coronary artery disease (CAD) and residual inflammatory risk, defined by an hsCRP > 2 mg/L. Participants (n = 10,061) were randomised to 1 of 3 doses of canakinumab (50, 150, or 300 mg) or placebo given subcutaneously (SC) once every 3 months. HsCRP, IL-6, and lipid levels were assessed at regular intervals during the trial. The primary endpoint was the first occurrence of nonfatal myocardial infarction (MI), nonfatal stroke, or CV death (MACE). The key secondary CV endpoint was MACE plus unstable angina requiring urgent revascularisation (MACE+). Critical non-CV safety endpoints included cancer and cancer mortality and infection and infection mortality.

Patients were a mean age of 61 years; most were men. About 24% were smokers and 40% were diabetic. Median LDL cholesterol was ~82 mg/dL and hsCRP was 4.1 mg/L. More than 93% of patients were on lipid lowering therapy; 80% were taking a renin-angiotensin inhibitor, and 95% an oral antithrombotic. Most (80%) had undergone prior coronary interventions.

Canakinumab decreased hsCRP in a dose-dependent manner, but had no effect on LDL-C or HDL-C, and only a 4-5% increase in triglycerides (Figure 1).

Figure 1. CANTOS: Dose-dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)



HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

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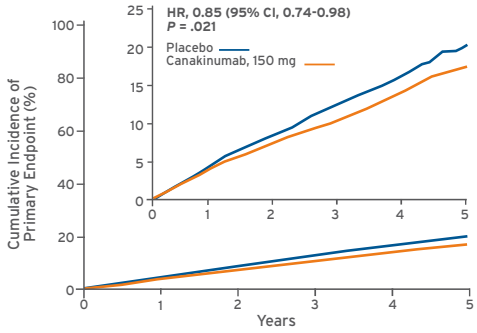
When given SC every 3 months canakinumab, at a median follow-up of 3.7 years, had a significant effect for the primary endpoint of MACE (nonfatal MI, nonfatal stroke, or CV death) was observed in the 150-mg group (Figure 2). The effect was also significant for the 300-mg group (HR 0.86; *P* = .0314); however, the *P*-value did not meet the prespecified threshold for significance. No significant effect was observed for the 50-mg group (HR, 0.93; *P* = .30).

The 150-mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary CV endpoints.

Figure 2. Primary Endpoint With Canakinumab, 150 mg vs Placebo



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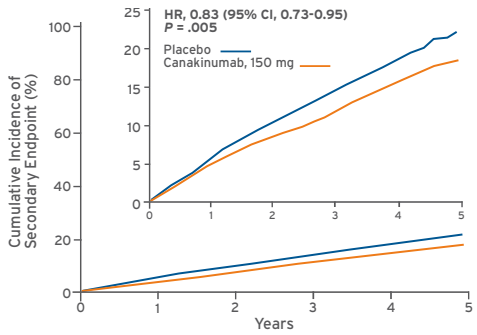
The 150-mg dose of canakinumab was also associated with significant (*P* = .005) reductions in the key secondary CV endpoint (the components of the primary endpoint plus hospitalisation for unstable angina that led to urgent revascularisation; Figure 3).

Figure 3. Key Secondary Endpoint With Canakinumab, 150 mg vs Placebo



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In addition to the primary and secondary endpoints, there were consistent and significant HR reductions in MI, unstable angina leading to urgent revascularisation, and any coronary revascularisation for the 150 mg dose (all $P \leq .02$). There was no significant effect on stroke

(HR, 0.98; 95% CI, 0.71 to 1.35; *P* = .91), cardiovascular death (HR, 0.88; 95% CI, 0.70 to 1.12; *P* = .30) or all-cause mortality (HR, 0.92; 95% CI, 0.80 to 1.11; *P* = .33). Leukopenia and fatal infections were more common with canakinumab, while fatal malignancy and arthritis (including osteoarthritis and gout) were less common.

In an exploratory analysis stratified by on-treatment hsCRP, patients with an hsCRP less than the median achieved value of 1.8 mg/L at 3 months appeared to have a greater benefit (HR, 0.73; 95% CI, 0.63 to 0.83; *P* = .0001) compared with those above the median achieved hsCRP (HR, 0.95; 95% CI, 0.84 to 1.08; *P* = .47); however, formal statistical testing for effect modification by achieved hsCRP was not presented.

Tumor initiation, promotion, malignant conversion, invasion, and metastasis can all be impacted by inflammation [Grivennikov SI et al. *Cell*. 2010]. IL-1 is abundant at tumour sites, where it may affect the process of carcinogenesis, tumour growth, and invasiveness and the patterns of tumour-host interactions [Apte RN et al. *Cancer Metastasis Rev*. 2006]. Subclinical chronic inflammation, as defined by an elevated hsCRP, is associated with an increased risk of inflammatory cancers, including lung cancer [Chaturvedi AK et al. *J Clin Oncol*. 2010]. As a result of these observations, it has been suggested that blocking IL-1β might be a good treatment approach for human metastatic disease [Dinarrello CA. *Cancer Metastasis Rev*. 2010]. Therefore, a clinical events committee of oncologists was established at trial initiation to adjudicate incident cancer in CANTOS.

Notably, patients in the CANTOS study were at unusually high risk for certain inflammatory cancers, such as lung cancer, due to older age, high rates of past and current smoking and chronic inflammation as evidenced by an elevated hsCRP. Canakinumab (300 mg) reduced death from any cancer by 51% (HR, 0.49; 95% CI, 0.31 to 0.75; *P* = .0009) and fatal lung cancer by 77% (HR, 0.23; 95% CI, 0.10 to 0.54; *P* = .0002) [Ridker PM et al. *Lancet*. 2017]. The effect appeared to be dose-dependent for both endpoints where the *P* value for trend with increasing canakinumab doses were .0007 and .0002, respectively. These findings are exploratory and will need to be replicated in future studies.

CANTOS was designed to directly test the inflammatory hypothesis of atherothrombosis. In this study, SC canakinumab administered once every 3 months lowered the inflammatory biomarkers hsCRP and IL-6 but did not reduce atherogenic lipids in patients with stable CAD and an elevated hsCRP at baseline. In summary, during the average 3.7-year follow-up period, the 150 mg dose of canakinumab showed significant reductions in the primary and secondary study endpoints, as well as the individual endpoints of MI, unstable angina requiring urgent coronary revascularisation and any coronary revascularisation. Stroke, CV death, and all-cause mortality were not significantly reduced with canakinumab. Leukopenia and fatal infections were increased with canakinumab, while fatal malignancies and arthritis were reduced.

As a consequence, patients being treated with canakinumab will require monitoring for early signs and symptoms of infection as is the current policy for individuals taking other biologic anti-inflammatory agents. Exploratory analyses suggested that residual inflammatory risk, defined by an elevated on-treatment hsCRP, may be associated with greater benefit. Another exploratory analysis suggests that patients at high risk for inflammatory cancers may experience a reduction in incident fatal malignancies, including lung cancer.

In Dr Ridker's opinion, the CANTOS trial demonstrates that targeting the IL-1β to IL-6 pathway with canakinumab reduces CV event rates and potentially reduces rates of incident lung cancer and lung cancer mortality. These data provide proof that inflammation inhibition, even in the absence of lipid lowering, can improve atherothrombotic outcomes and potentially alter the progression of some fatal cancers. Furthermore, the exploratory analyses with acheived hsCRP levels and malignancy may provide a framework for a personalised approach to initiating or continuing canakinumab in patients with stable CAD and elevated hsCRP.

Apixaban Decreases Stroke Risk in AF Patients Undergoing Cardioversion

Written by **Nicola Parry**

Michael D. Ezekowitz, MBChB, DPhil, Sidney Kimmel Medical College at Thomas Jefferson University, Lankenau and Bryn Mawr hospitals, Philadelphia, Pennsylvania, USA, reported results from the EMANATE trial [NCT02100228], showing that, compared with usual care (heparin/vitamin K antagonist), apixaban was noninferior regarding the risk of stroke in patients with atrial fibrillation (AF) undergoing cardioversion, with even fewer stroke or systemic embolic (SE) events in patients randomised to apixaban. Rates of bleeding were similar in both groups.

According to Dr Ezekowitz, the EMANATE trial aimed to prospectively compare the rates of stroke, SE, major bleeding, clinically relevant nonmajor (CRNM) bleeding, and death in anticoagulation-naïve patients (having received < 48 hours of anticoagulation therapy) in patients with AF scheduled for cardioversion [Dauriz M et al. *Diabetes Care*. 2017].

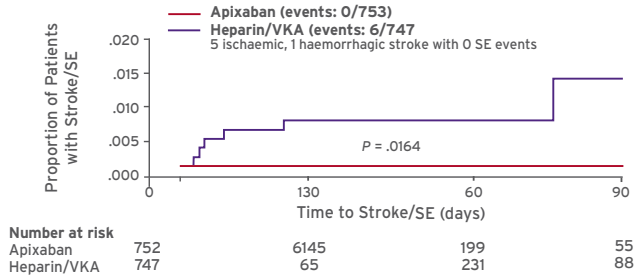
The trial included 1,500 patients (intention-to-treat [ITT] population) who were randomised to receive oral

apixaban (n = 753) or parenteral heparin and transition to warfarin (n = 747). Dr Ezekowitz noted that, prior to randomisation, 61% of the patients had not received any anticoagulation therapy.

Patients in the apixaban group could be treated with a loading dose of 10 mg unless they were aged ≥80 years, weighed ≤ 60 kg, or had a serum creatinine level ≥ 1.5 mg/dL. Patients who met 2 of these criteria received a loading dose of 5 mg.

In the ITT population, apixaban treatment significantly reduced the rate of strokes compared with usual care (0 vs 6; *P* = .0164). SE events did not occur in either group (Figure 1). However, the trial was not powered to show differences in efficacy results.

Figure 1. Stroke and Systemic Embolism Outcomes in EMANATE



One patient's adjudicated stroke date was one day prior to randomisation; thus at day 0, only 1499 were at risk for stroke. No patients had SE. ITT population.

ITT, intention-to-treat; SE, systemic embolism; VKA, vitamin K antagonist.

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The investigators assessed safety outcomes in a safety population (n = 1,456) who were randomised and received one or more doses of the study drug. Major bleeding occurred in 3 patients in the apixaban subgroup and 6 in the usual care subgroup, while CRNM bleeding occurred in 11 and 13 patients, respectively, in the 2 subgroups. Two patients in the apixaban subgroup and 1 patient in the usual care subgroup died, said Dr Ezekowitz. He noted that 342 of the 753 patients in the apixaban subgroup received a loading dose. In this subgroup, there were no strokes or SE events; however, 1 death, 1 major bleed, and 4 CRNM bleeds occurred in this subgroup, he added.

To assess the role of image guidance accompanying cardioversion, the investigators performed imaging in 840 patients prior to cardioversion. Using echocardiography, investigators identified left atrial appendage thrombi in 61 patients; 30 of these patients were receiving apixaban and 31 were receiving heparin/VKA. Complete follow-up occurred in these 61 patients, and no outcome events occurred in either subgroup. The investigators repeated imaging studies after a mean of 37 days in 23 patients receiving apixaban and 18 receiving heparin/VKA. They found that the thrombi had resolved in 12 patients receiving apixaban and in 10 patients receiving heparin/VKA, and these patients with evidence of thrombus resolution underwent cardioversion.

The results of this trial support use of apixaban in patients with AF undergoing cardioversion, concluded Dr Ezekowitz.

Results of the HPS3/TIMI55-REVEAL Trial

Written by **Phil Vinall**

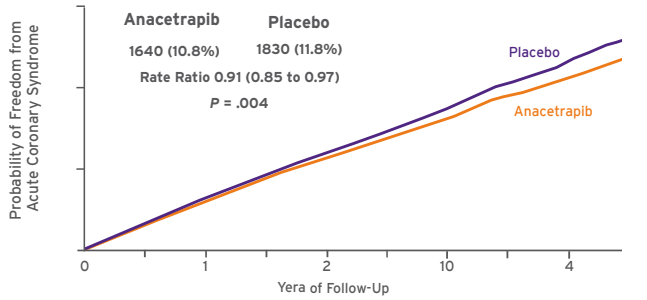
Anacetrapib is a potent inhibitor of cholesteryl ester transfer protein (CETP). Trials of other CETP inhibitors have been stopped early due to unexpected cardiovascular hazards or apparent lack of efficacy. REVEAL trial [NCT01252953], assessed the efficacy and safety of adding anacetrapib to effective doses of atorvastatin among patients with established atherosclerotic vascular disease. The primary results, presented by Martin J. Landry, MD, University of Oxford, London, United Kingdom, showed that the addition of anacetrapib to intensive therapy with atorvastatin reduced major coronary events [HPS3/TIMI55-REVEAL Collaborative Group. *N Engl J Med*. 2017].

REVEAL was a randomised, double-blind, placebo-controlled clinical trial in patients with pre-existing atherosclerotic vascular disease. The primary outcome was the first major coronary event, defined as the occurrence of coronary death, myocardial infarction (MI), or coronary revascularisation. Secondary outcomes were major atherosclerotic events (coronary death, MI or presumed ischaemic stroke), major vascular events (major coronary event or presumed ischaemic stroke), and presumed ischaemic stroke on its own.

The study comprised individuals aged > 50 years with pre-existing atherosclerotic vascular disease on a background atorvastatin regimen (20 or 80 mg daily). Patients (mean age 67 years; 84% men) were randomised to anacetrapib 100 mg daily or matching placebo. At the randomisation visit (after at least 8 weeks on a protocol-defined atorvastatin regimen) 88% of patients had coronary heart disease, 22% cerebrovascular disease, 8% peripheral arterial disease, and 37% had diabetes mellitus. Mean plasma LDL-C was 61 mg/dL, HDL-C was 40 mg/dL, and non-HDL-C was 92 mg/dL.

Follow-up (median duration of 4.1 years) is 99.8% complete. During the median follow-up of about 4 years, 90% of patients were adherent to the blinded therapy, and significantly fewer major coronary events had occurred in patients treated with anacetrapib (rate ratio [RR], 0.91; 95% CI, 0.85 to 0.97; *P* = .004) compared with placebo (Figure 1).

Figure 1. Primary Outcome: Major Coronary Events*



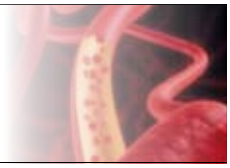
*Coronary death, myocardial infarction, or coronary revascularisation.

For the individual components of the primary outcome significant reductions were noted for MI, coronary death or MI, coronary revascularisation, and major coronary event (all $P < .01$) but not coronary death.

All lipid levels improved. HDL-C increased by 104%, LDL-C decreased by 41% (direct method), and apolipoprotein B and non-HDL-C decreased by 18% each. The absolute reduction in non-HDL-C was proportional to the reduction in coronary death or MI.

No significant evidence of differential proportional effects among 23 prespecified subgroup categories was noted. Small reductions in risk of new-onset diabetes mellitus were noted. There were no excess symptomatic side effects with anacetrapib, although levels in adipose tissue rose with continued treatment. There was also no excess of mortality, cancer, or other serious adverse events. There were small increases in blood pressure and small reductions in kidney function.

Clinical outcomes will be followed for at least an additional 2 years after the end of the treatment period to assess longer-term safety, as well as efficacy.



FOURIER Trial Shows the Reduction of LDL-C to Extremely Low Levels is Safe and Associated With a Reduction in CV Events

Written by **Maria Vinall**

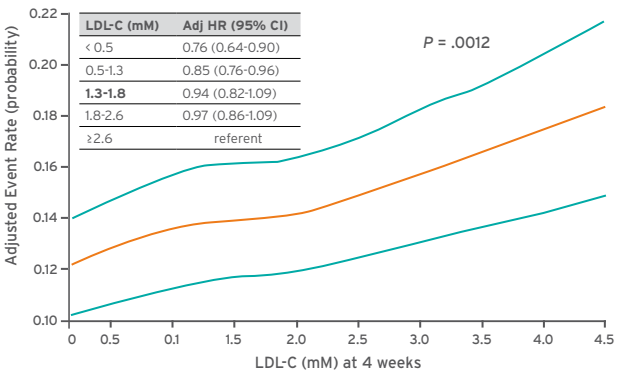
The FOURIER trial [Sabatine MS et al. *N Engl J Med*. 2017] comprised 27,564 patients (aged 40 to 85 years) with stable cardiovascular disease (CVD), on statin therapy, and with LDL-C levels ≥ 1.8 mM or a non-HDL-cholesterol level ≥ 2.6 mM. Patients were randomised to subcutaneous evolocumab (140 mg Q2W or 420 mg QM) or placebo. The main results of the FOURIER trial were a 59% reduction in LDL-C and significant reductions in CV outcomes. Evolocumab was safe and well-tolerated. Robert P. Giugliano, MD, SM, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the results of a prespecified secondary analysis from FOURIER that assessed the efficacy and safety associated with achieving progressively lower LDL-C levels [Giugliano RP et al. *Lancet*. 2017].

Patients were stratified by achieved LDL-C at 4 weeks. The primary efficacy endpoint was the composite of CV death, myocardial infarction (MI), stroke, coronary revascularisation, or unstable angina. The key secondary endpoint was the composite of CV death, MI, or stroke. Prespecified safety events included overall rates of serious adverse events (SAEs), AEs leading to study drug discontinuation, and AEs of interest (aspartate transaminase/alanine transaminase > 3x upper limit of normal [ULN], creatinine kinase > 5x ULN, neurocognitive events, new diabetes mellitus, cancer, haemorrhagic stroke, cataracts, and non-CV death). Patients with an event prior to 4 weeks were excluded. The data were pooled for both treatment groups and analysed using multivariate modelling adjusting for baseline factors associated with achieved LDL-C and randomised treatment arm. Cognition was assessed using the Cambridge Neuropsychological Test Automated Battery [Giugliano RP et al. *N Engl J Med*. 2017] and a patient survey of everyday cognition.

Of the 25,982 patients analysed, the proportions of patients who achieved LDL-C values < 0.5, 0.5-1.3, 1.3-1.8, 1.8-2.6, and ≥ 2.6 mM were 10%, 31%, 13%, 29%, and 17%, respectively. Patients achieving the lowest LDL-C values were more likely to have received evolocumab. They also had lower baseline LDL-C, total cholesterol, and lipoprotein(a) levels and were more likely older, male, and non-white.

For the primary composite endpoint of CV death, MI, stroke, coronary revascularisation or unstable angina, the adjusted event rates were reduced by 24%, 15%, 6%, and 3% for patients achieving LDL-C levels < 0.5, 0.5-1.3, 1.3-1.8, and 1.8-2.6 mM, respectively, compared with the group achieving a LDL-C > 2.6 mM at 4 weeks. Importantly, there was a significant (*P* = .0012) and progressive relationship between lower LDL-C and reductions in adverse CV events down to 0.2 mM LDL-C (Figure 1). For the secondary composite endpoint of CV death, MI, or stroke, there was a significant (*P* = .0001) and almost linear reduction in risk.

Figure 1. Adjusted Primary Endpoint Rate by LDL-C



LDL-C, low-density lipoprotein cholesterol.

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There was no significant association between achieved LDL-C and safety outcomes, either for all SAEs or other AEs of interest (adjusted *P* values for trend > .10 for each). Cognition as assessed by the CANTAB tool did not differ across the groups and the patient survey of everyday congition showed similar to slightly improved results with lower achieved LDL-C levels.

An exploratory analysis showed that patients with LDL-C < 0.26 mM at 4 weeks (n = 504) had the best outcomes (primary outcome: adjusted HR, 0.69; 95% CI, 0.49 to 0.97; *P* = .03; secondary outcome: adjusted HR, 0.59; 95% CI, 0.37 to 0.92; *P* = .02) with no difference in SAEs or AEs leading to drug discontinuation.

These data suggest that future guidelines should consider lower LDL-C levels than are currently recommended for patients with atherosclerotic CVD, patients and healthcare providers should be reassured that very low LDLs levels are safe, and laboratories should not consider a very low LDL-C abnormal.

Results From RE-DUAL PCI

Written by **Nicola Parry**

Christopher P. Cannon, MD, Harvard Medical School, Baim Institute for Clinical Research, Boston, Massachusetts, USA, reported data from the RE-DUAL PCI trial, showing that dual antithrombotic therapy with dabigatran and a $P2Y_{12}$ inhibitor reduced bleeding when compared to triple therapy with warfarin in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI).

According to Dr Cannon, although triple antithrombotic therapy comprising warfarin plus dual antiplatelet therapy is standard care after PCI for patients with AF, this triple combination leaves these individuals at high risk for bleeding events. The WOEST trial suggested that removing aspirin from the triple-therapy regimen could be done safely [Dewilde WJ et al. *Lancet*. 2013]. Dr Cannon and colleagues conducted the RE-DUAL PCI trial to investigate the efficacy and safety of dual therapy with dabigatran and a $P2Y_{12}$ inhibitor in AF patients after PCI [Cannon CP et al. *N Engl J Med*. 2017].

This multicentre, open-label trial randomised 2725 patients with AF who had undergone PCI to receive either triple therapy (warfarin, plus a $P2Y_{12}$ inhibitor [clopidogrel or ticagrelor] and aspirin) or dual therapy (dabigatran [110 mg or 150 mg BID] plus a $P2Y_{12}$ inhibitor [clopidogrel or ticagrelor]).

The study's primary endpoint was time to first ISTH major or clinically relevant nonmajor bleeding (CRNM).

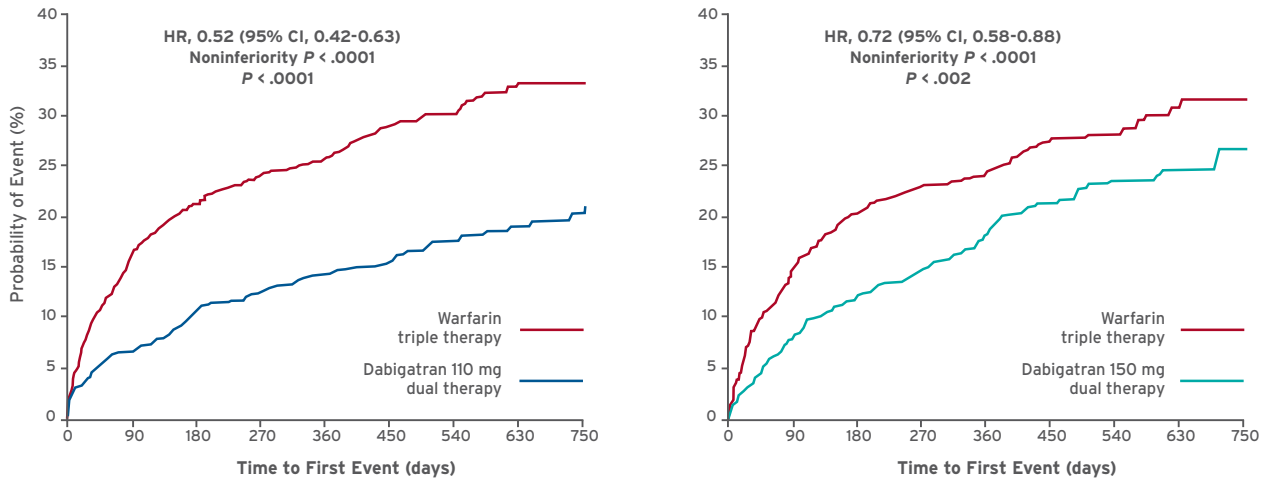
Compared with the triple-therapy regimen, treatment with dabigatran 110 mg with a $P2Y_{12}$ inhibitor reduced by almost 50% the incidence of major or CRNM bleeds at 14 months (15.4% vs 26.9%; HR, 0.52; 95% CI, 0.42 to 0.63, $P < .001$ for noninferiority, $P < .001$ for superiority; Figure 1). Dr Cannon noted that this was consistent with an absolute risk reduction (ARR) of 11.5%. Dual therapy using dabigatran 150 mg was also associated with fewer bleeds (20.2% vs 25.7%; HR, 0.72; 95% CI, 0.58 to 0.88; $P < .001$ for noninferiority, $P = .002$ for superiority; Figure 1), representing a 5.5% ARR.

Compared with the triple-therapy regimen, both dual-therapy groups also had lower rates of intracranial haemorrhage, with a 0.7% ARR (HR, 0.3; 95% CI, 0.08 to 1.07; $P = .064$) using dabigatran 110 mg, and a 0.9% ARR (HR, 0.12; 95% CI, 0.02 to 0.98; $P = .047$) using dabigatran 150 mg.

The investigators also performed a prespecified analysis of thrombotic events that occurred during the trial, evaluating the effect of dual versus triple therapy on the incidence of a composite of death, thromboembolic events (myocardial infarction, stroke, or systemic embolism), or unplanned revascularisation. Combining the 2 dabigatran dose groups, they found that dual therapy met the threshold for noninferiority for the composite endpoint (incidence, 13.7% vs 13.4%; HR, 1.04; 95% CI, 0.84 to 1.29; $P = .005$ for noninferiority). In the patients treated with 110-mg dual therapy, the incidence of death, thromboembolic events, or unplanned revascularisation was 15.2% versus 13.4% in the triple-therapy group (HR, 1.13; 95% CI, 0.90 to 1.43; $P = .30$). In the patients treated with 150-mg dual therapy, the incidence was 11.8% versus 12.8% in the triple-therapy group (HR, 0.89; 95% CI, 0.67 to 1.19; $P = .44$).

Dr Cannon concluded that these dabigatran dual-therapy regimens, using doses approved worldwide for stroke prevention, offer clinicians 2 additional options for managing AF patients following PCI.

Figure 1. Rates of Major Bleeding or Clinically Relevant Nonmajor Bleeding in RE-DUAL



From *The New England Journal of Medicine,* Cannon CP et al, Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. EPub 28 August 2017. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Empagliflozin Reduces Adverse HF Outcomes in Diabetes Patients, Regardless of HF Risk

Written by **Nicola Parry**

Empagliflozin is a selective sodium-glucose cotransporter 2 inhibitor that reduces hyperglycaemia in patients with type 2 diabetes (T2D) by reducing renal glucose reabsorption, and thereby increasing urinary glucose excretion. In the EMPA-REG OUTCOME trial, when compared with placebo, empagliflozin (10 or 25 mg daily) was shown to significantly reduce the incidence of death from cardiovascular [CV] causes and hospitalisation for heart failure (HHF) in patients with T2D and established CV risk (HR, 0.86; 95% CI, 0.74 to 0.99; *P* = .04 for superiority) [Zinman B et al. *N Engl J Med*. 2015].

Javed Butler, MD, MPH, Stony Brook School of Medicine, Stony Brook, New York, USA, reported the results of an analysis of data from patients in the EMPA-REG OUTCOME trial demonstrating that the risk reductions seen in the main study occur across all spectrums of HF risk [Fitchett D et al. *Eur Heart J*. 2017].

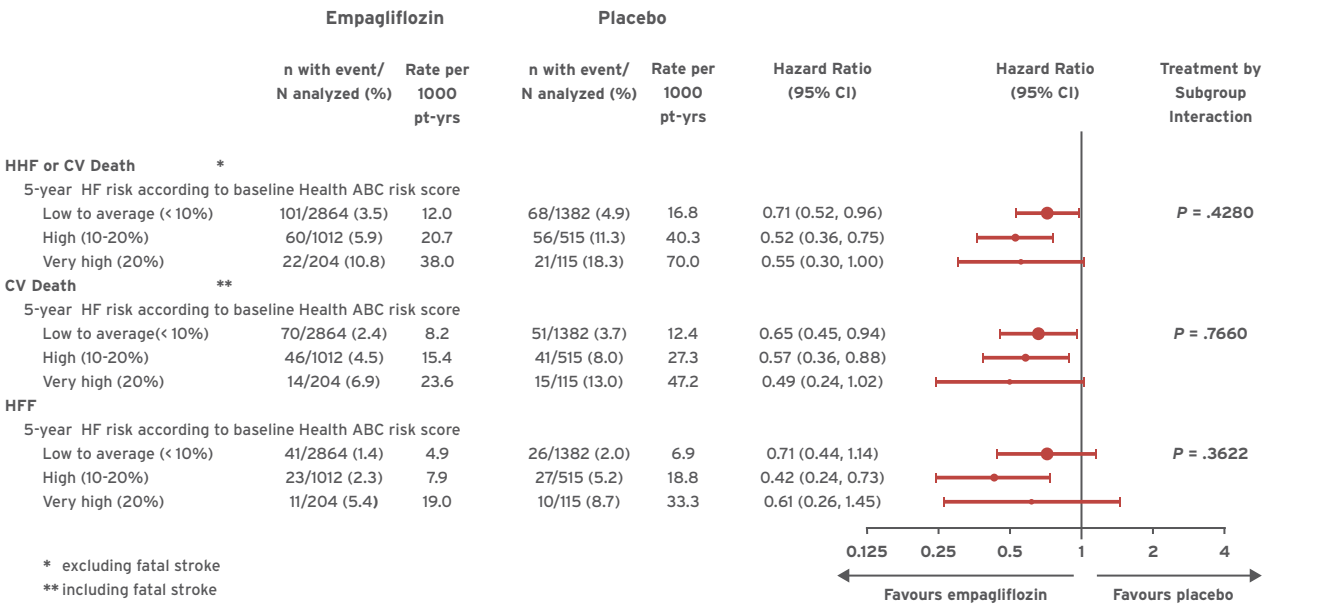
The primary objective of this analysis was to investigate the effects of empagliflozin in patients across the spectrum of HF and HF risk. Patients who did not have HF at baseline (89.9%; 6,314 of 7,028) were stratified as to their 5-year risk for incident HF using the 9-variable Health ABC HF Risk score [Butler J et al. *Circ Heart Fail*. 2008; Kalogeropoulos A et al. *Circ Heart Fail*. 2010]; 67.2% were classified as being at low-to-average (5-year HF risk < 10%), 24.2% as high risk (10-20%), and 5.1% as very high risk (≥ 20%). Patients with HF at baseline or those with an incident HF episode during follow-up were grouped and defined as patients with 'HF burden.' The outcomes of HHF or CV death (excluding fatal stroke), HHF, and CV death (including fatal stroke) were assessed in relation to HF-baseline risk using a time-to-first-event approach. Data were pooled for the empagliflozin dose groups.

Regardless of their HF risk category, empagliflozin reduced the risk of the primary endpoint in patients without HF at baseline. The effect was consistent across all 3 groups: low-to-average HF (HR, 0.71; 95% CI, 0.52 to 0.96), high risk (HR, 0.52; 95% CI, 0.36 to 0.75), and very high risk (HR, 0.55; 95% CI, 0.30 to 1.00; *P* for interaction .4; Figure 1), occurred early and persisted for the duration of the trial.

In the placebo group, the incident HF hospitalisation rate or CV death risk per 100 patient-years increased with increasing HF risk profile: 1.68 (95% CI, 1.31 to 2.10) in the low-to-average risk group; 4.03 (95% CI, 3.06 to 5.13) in the high-risk group; and 7.0 (95% CI, 4.33 to 10.29) in the very-high-risk group. The incident HF hospitalisation rate or CV death risk in those with prevalent baseline HF was 8.55 (95% CI, 6.33 to 11.11) per 100 patient-years.

These findings demonstrate that in patients with T2D and established CV disease, a sizeable proportion without HF at baseline are at high or very high risk for HF outcomes. Empagliflozin reduced HF hospitalisation rate and CV death risk regardless the presence of HF at baseline and across the spectrum of HF risk in those without HF, Dr Butler concluded.

Figure 1. Effect of Empagliflozin on Heart Failure Hospitalisation and Cardiovascular Death According to Heart Failure Risk



ABC, Health ABC Heart Failure Risk score; CI, confidence interval; CV, cardiovascular; HF, heart failure; HHF, hospitalisation for heart failure; pt-yrs, patient-years.

Reprinted from Fitchett D et al. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalisation across the spectrum of heart failure risk in the EMPA-REG OUTCOME trial. *Eur Heart J*. 2017; doi:10.1093/eurheartj/ehx511. By permission of Oxford University Press on behalf of the European Society of Cardiology.

A Look Ahead in the Treatment of Heart Failure

Written by **Brian Hoyle**

According to Alexandre Mebazaa, MD, PhD, FESC, Hôpitaux Universitaires Saint Louis–Lariboisière, Paris, France, mechanical circulatory support devices continue to improve in design and performance, and are leading to more prolonged survival in advanced heart failure (HF). However, left ventricular assisted devices (LVADs) remain burdened by postimplantation complications.

Advanced HF patients who are stable but require assistance in weakening or strengthening the force of muscular contractions in the heart can benefit, in some cases, from cardiac resynchronisation in case of large QRS [Milliez P et al. *Eur J Heart Fail*. 2008].

LVADs can be considered in patients with end-stage HF with reduced ejection fraction (HRrEF) who have received appropriate medical/device therapy, either as a bridge to heart transplantation or, in those not eligible for a transplant, to reduce the risk of premature death. There are a number of eligibility criteria (Table 1) [Ponikowski P et al. *Eur J Heart Fail*. 2016].

Table 1. Eligibility Criteria for Implantation of LVADs

Patients with > 2 months of severe symptoms despite optimal medical and device therapy and more than one of the following:
LVEF < 25% and, if measered, peak VO_2 < 12 mL/kg/min.
≥ 3 HF hospitalisations in previous 12 months without an obvious precipitating cause.
Dependence on intravenous inotropic therapy.
Progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥ 20 mm Hg and SBP ≤ 80-90 mm Hg or CI ≤ 2 L/min/m^2).
Absence of severe right ventricular dysfunction together with severe tricuspid regurgitation.

CI, cardiac index; LVEF, left ventricular ejection fraction; HF, heart failure; PCWP, pulmonary capillary wedge pressure; SPB, systolic blood pressure; VO_2, volume of oxygen.

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Refinements of LVADs and the repertoire of devices have led to their increasing use. Devices capable of providing continuous flow are available. Immediate installation of an LVAD improves the patient's condition. But, the immediate short-term benefit should not obscure the reality that complications like infection, stroke, and major bleeding frequently occur and need to be handled immediately by a multidisciplinary care team. Patients need to be educated concerning the possibility of setbacks and the ongoing need for care.

Right ventricular dysfunction can develop following installation of a LVAD. A very recent systematic review and meta-analysis clarified the predictive factors of right ventricular problems [Bellavia D et al. *Eur J Heart Fail*. 2017].

Patient-driven future developments in LVADs include devices that automatically adapt to the changing cardiac demands of exercise and a fully implantable device that would enable a person to swim.

The DOSE-AHF [Felker GM et al. *N Engl J Med*. 2011] and CARRESS-HF [Bart BA et al. *N Engl J Med*. 2012] clinical trials highlighted that the outcome of acute HF (AHF) continues to be poor. In DOSE-AHF and CARRESS-HF, 40% of patients were hospitalised or had died by 60 days following treatment randomisation, according to Gerasimos Filippatose, MD, PhD, Athens University Hospital Attikon, Greece.

Improving the outlook calls for better diagnosis and classification, increased knowledge of the disease epidemiology and pathophysiology, and better disease management. In terms of classification, the 2016 ESC guidelines for the diagnosis and treatment of HF [Ponikowski P et al. *Eur Heart J*. 2016] stratified HF into categories of reduced, mid-range, and preserved ejection fraction (Figure 1).

Figure 1. European Society of Cardiology Classification of Heart Failure

Heart Failure With Preserved, Mid-range, and Reduced EF

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± Signs	Symptoms ± Signs	Symptoms ± Signs
	2	LVEF < 40%	LVEF 40-49%	LVEF ≥ 50%
	3	-	1. Elevated levels of natriuretic peptides, 2. At least one additinal criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction.	1. Elevated levels of natriuretic peptides, 2. At least one additinal criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction.

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LAE, left atrial enlargement; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

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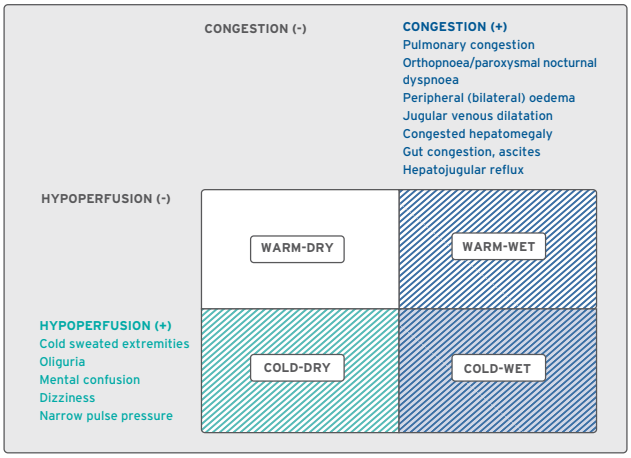
Whether this classification or others, such as a proposed staging system of HF that is similar to the TNM-like system used in cancer [Fedele F et al. *J Am Coll Cardiol*. 2014], could be useful for AHF remain unclear. A potentially useful clinical approach for AHF in the ESC 2016 guidelines is based on congestion and hypoperfusion (Figure 2). Other factors useful in the initial assessment and management of AHF include clinical severity, blood pressure, heart rate/rhythm, and comorbidities.

Figure 2. Clinical Profiles of AHF Patients Based on Congestion and Hypoperfusion



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More knowledge of the epidemiology of HF is crucial. Studies from different countries have highlighted the need for standardised definitions and clinical indications for AHF. The global data that will accrue in the REPORT-HF Registry [Filippatos G et al. *Eur J Heart Fail*. 2015] will hopefully improve the situation.

The pathophysiology of AHF is also unclear, which has hindered the development of diagnostic tools. Having a proven diagnostic tool, like electrocardiography that is used for acute myocardial infarction (AMI), is the goal of AHF. Improvement in disease management is also needed. Patients discharged with congestion are significantly more likely to die within the next year than those discharged without pulmonary or peripheral congestion [Metra M et al. Circ Heart Fail. 2012]. The complex pathophysiology of AHF makes it unlikely that a single target, like thrombus in AMI, will be involved in AHF.

Pharmacologic treatment of AHF involves diuretics to reduce fluid volume, vasodilators, and, if needed, inotrope-mediated augmentation of contractility. Trials are underway to evaluate new drugs. Further on the horizon, wireless monitoring of pulmonary arterial pressure is being explored.

Other future therapeutic approaches were discussed by Marco Metra, MD, University of Brescia, Brescia, Italy. Ultrafiltration is being refined as a decongestion strategy [Costanzo MR et al. *J Am Coll Cardiol*. 2017]. Definitive clinical trial data is lacking with the premature termination of the AVOID-HF trial [Costanzo MR et al. *JACC Heart Fail*. 2016] due to slower than expected enrolment. The PURE-HF trial [NCT03161158] which is designed to evaluate whether tailored, peripheral ultrafiltration complementary to low-dose diuretics is associated with a reduction in cardiovascular mortality and HF will hopefully provide evidence-based rigour.

Intravenous inotropes are not currently recommended, except for symptomatically hypotensive or hypoperfused patients, due to increased mortality in analyses from clinical trials. But, earlier data indicated a benefit of levosimendan in advanced HF [Parissis JT et al. *Heart*. 2006; Parissis JT et al. *J Am Coll Cardiol*. 2006]. Ambulatory treatment involving pulsed infusions of levosimendan did not improve the primary outcomes, though with favourable effects on quality of life and a tendency to reduced hospitalisations [Altenberger J et al. *Eur J Heart Fail*. 2014]. However, a recent meta-analysis has suggested a reduction in hospitalisations with repeated infusions [Silvetti S et al. *ESC Heart Fail*. 2017] supporting the idea that more research on inotropes is warranted.

Another approach is the oral use of omecamtiv mecarbil, a drug that targets the cardiac protein myosin to increase the duration of ejection time. Benefits were demonstrated in the phase 2 COSMIC-HF trial [Teerlink JR et al. *Lancet*. 2016]. The phase 3 GALACTIC-HF trial [EudraCT number 2016-002299-28], designed to determine if treatment with omecamtiv mecarbil when added to standard of care is well tolerated and reduces the risk of cardiovascular death or HF events in patients with chronic HFrEF, is underway.

Other drugs in earlier stages of development include the second-generation nitroxyl donor, BMS-986231, for treatment of HFrEF [Tita C et al. *Eur J Heart Fail*. 2017], the partial adenosine A1-receptor agonist, capadenoson, shown to improve left ventricular function in an experimental model [Sabbah HN. *Eur J Heart Fail*. 2016], and targeted treatment of mitochondrial dysfunction using elamipretide [Sabbah HN. *Eur J Heart Fail*. 2016].

Regenerative therapy may someday be used to rebuild myocardial tissue that is defective. The results with stem cell therapies for other applications certainly indicate the potential of this approach. The CHART-1 trial of cardiopoietic regenerative therapy in congestive HF has been recently concluded [Bartunek J et al. *Eur J Heart Fail*. 2016] and an exploratory analysis identified a subgroup of patients who may benefit from cardiopoietic cell therapy. The CHART-2 trial [NCT02317458] will further explore this therapy in patients with chronic HF secondary to ischaemic cardiomyopathy.

LVAD implantation is now an important option either as destination therapy or as a bridge to transplantation. Lastly, when medical treatment has failed and no device can be indicated because of patient age, comorbidities and/or right ventricular dysfunction, palliative care must be considered.

Heart Failure in Patients With Diabetes

Written by **Nicola Parry**

In a symposium on heart failure (HF) and diabetes, speakers shared data from recent studies investigating the effects of diabetes in the HF population.

Effect of CV Risk Factors on CV Mortality in Patients Receiving Empagliflozin

The EMPA-REG OUTCOME was a randomised, double-blind, placebo-controlled trial to assess the effect of once-daily empagliflozin (at a dose of either 10 mg or 25 mg), a selective inhibitor of sodium glucose cotransporter 2, versus placebo on cardiovascular (CV) events in 7,028 adults with type 2 diabetes mellitus (T2DM) at high CV risk versus usual standard of care. The primary outcome was a composite of death from CV causes, nonfatal myocardial infarction (MI; excluding silent MI), or nonfatal stroke [Zinman B et al. *N Engl J Med*. 2015].

The trial showed significant reduction in CV mortality and all-cause mortality with empagliflozin in patients with T2DM and CV disease, with similar benefits at the 2 doses of empagliflozin used.

There was a lower rate of the primary composite CV outcome in patients with T2DM who received empagliflozin than in those who received placebo (10% in the pooled empagliflozin group vs 12.1%; HR, 0.86; 95% CI, 0.74 to 0.99; $P = .04$). Although there were no significant between-group differences in the rates of MI (4.8% vs 5.4%; HR, 0.87; 95% CI, 0.70 to 1.09; $P = .23$) or stroke (3.5% vs 3.0%; HR, 1.18; 95% CI, 0.89 to 1.56; $P = .26$), patients who received empagliflozin had significantly reduced rates of death from CV causes (HR, 0.62; 95% CI, 0.49 to 0.77; $P < .001$ and from all causes (HR, 0.68; 95% CI, 0.57 to 0.82; $P < .001$).

Although the mechanism of the mortality reduction is unclear, David Fitchett, MD, University of Toronto, Toronto, Canada, noted that empagliflozin treatment also resulted in small reductions in blood pressure (BP) and HbA1c, and small increases in LDL-C during the trial.

Dr Fitchett and colleagues therefore performed a study to investigate how these risk factors affected the reduction in mortality with empagliflozin versus placebo during the EMPA-REG OUTCOME trial [Zinman B et al. *Eur Heart J*. 2017].

After adjusting for control of BP, LDL-C and HbA1c, and for all 3 risk factors together there was no effect on the point estimate of the hazard ratio for CV mortality (HR, 0.61; 95% CI, 0.48 to 0.76). Similarly, the adjustment for the single factor and for the all 3 factors together did not influence the point estimate of the hazard ratio for all-cause mortality (HR, 0.67; 95% CI, 0.56 to 0.81).

This suggests that reductions in CV mortality and all-cause mortality in patients receiving empagliflozin in the EMPA-REG OUTCOME trial were not driven by control of these CV risk factors during the study.

Effect of Diabetes on HFmrEF

Diabetes is associated with worse long-term survival and is an independent predictor of mortality in patients with HF relative to patients with diabetes without HF [Johansson I et al. *Eur Heart J*. 2017], emphasised Isabelle Johansson, MD, Karolinska Institute, Stockholm, Sweden. However, she noted that data on the recently introduced subtype of heart failure with mid-range ejection fraction (HFmrEF) are still lacking. Using data from the Swedish Heart Failure Registry, Dr Johansson and colleagues therefore aimed to investigate characteristics and prognostic implications of T2DM in HFmrEF (left ventricular EF 40-49%) in a contemporary HF population [Johansson I et al. *Eur J Heart Fail*. 2014].

They found that 21% (n = 6,483) of the total HF population had HFmrEF; and among those with HFmrEF, 24% (n = 1,562) had T2DM.

Compared with HFmrEF patients without T2DM, those with T2DM had more comorbidities, especially ischaemic heart disease, hypertension, and chronic kidney disease ($P < .0001$ for all). They also had a worse survival rate (adjusted HR for all-cause mortality, 1.51; 95% CI, 1.39 to 1.65; $P < .0001$) at a median follow-up of 4 years.

The investigators also compared HFmrEF patients with those with preserved-range ejection fraction (HFpEF) and reduced-range ejection fraction (HFrEF) subtypes. Diabetes was an independent predictor of mortality in all 3 types of HF, and increased the risk of mortality by 51% in HFmrEF (HR, 1.51; 95% CI, 1.39 to 1.65), 46% in HFrEF (HR, 1.46; 95% CI, 1.39 to 1.54), and 32% in HFpEF (HR, 1.32; 95% CI, 1.22 to 1.43).

They found similar characteristics and prognoses in patients with HFmrEF or HFrEF who also had diabetes. Thus, in the diabetes setting, Dr Johansson indicated that introducing the HFmrEF has added limited information to the pre-existing 2 HF-subtypes, and may even confuse clinicians.

Effect of Diabetes on Iron Status in HF

The effect of T2DM on iron status in HFrEF patients remains unclear because although some studies have established

diabetes as a risk factor that promotes iron overload, others have also shown that some diabetes patients may be iron deficient [Ponikowska B et al. *Diabetes Care*. 2013].

Marcin Drozd, MD, Wroclaw Medical University, Wroclaw, Poland, and colleagues therefore performed a study to assess if the concomitance of diabetes mellitus in patients with HF and EF ≤45% affects iron status established based on standard and novel circulating biomarkers (soluble transferrin receptor [sTfR] and hepcidin) [Drozd M et al. *Eur Heart J*. 2017].

The study included 622 men with stable HFrEF, 188 (30%) of whom also had diabetes. The prevalences of iron deficiency (25% vs 20%), anaemia (8% vs 10%), and iron deficiency anaemia (9% vs 13%) were similar in those with and without diabetes (P = .2).

Levels of sTfR and hepcidin were abnormal in 50% of HFrEF patients with diabetes, compared with 25% of those without diabetes. Compared with HFrEF patients without diabetes, those with diabetes had higher sTfR levels (25% vs 41%) and lower hepcidin levels (5% vs 18%; P = .01 for both).

Transferrin saturation (TSAT) and sTfR levels correlated with left ventricular EF only in patients without diabetes, Dr Drozd added.

However, there were no differences in haematinic parameters between the 2 patient groups, and erythropoiesis was preserved in the whole study cohort.

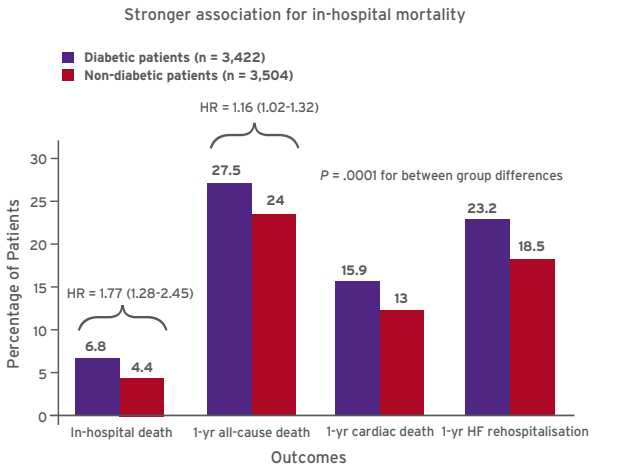
Although the presence of iron deficiency using standard biomarkers such as ferritin and TSAT did not differ between HF patients with and without diabetes, Dr Drozd emphasised that changes in the novel markers sTfR and hepcidin may indicate differences between the 2 groups. Patients with diabetes are prone to having low hepcidin (reflective of depleted iron stores) and high sTfR levels (reflective of intracellular iron depletion), he said, despite having similar levels of ferritin and TSAT.

Effect of Diabetes on Acute and Chronic HF

According to Ovidiu Chioncel, MD, PhD, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, diabetes is highly prevalent in patients hospitalised for acute HF (AHF; about 49%) and ambulatory chronic HF (CHF; about 31%). He shared recent data from the European Society of Cardiology and Heart Failure Association Long-Term Registry, a prospective, observational study collecting epidemiological information and 1 -year follow-up data in AHF and CHF patients, including 211 cardiology centres from 21 European and Mediterranean countries, all members of the ESC [Chioncel O et al. *Eur J Heart Fail*. 2017; Targher G et al. *Eur J Heart Fail*. 2017].

In AHF patients, diabetes was an independent predictor of in-hospital death (HR, 1.77; 95% CI, 1.28 to 2.45) and 1-year all-cause mortality (HR, 1.16; 95% CI, 1.02 to 1.32; P < .0001 for between-group differences; Figure 1).

Figure 1. Effect of Diabetes on Outcomes in Acute Heart Failure



Reprinted from Targher G et al. In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;19(1):54–65. doi: 10.1002/ejhf.679. By permission of Oxford University Press on behalf of the European Society of Cardiology.

However, in CHF patients, diabetes was an independent predictor of 1-year all-cause mortality only in patients with reduced EF (< 40%; OR, 1.419; 95% CI, 1.160 to 1.735; P = .0007).

The results showed no graded relationship between baseline levels of glycaemia and outcomes. Interestingly, however, the study found a west-to-east gradient in diabetes prevalence in patients with AHF and CHF in different geographic regions, Dr Chioncel added.

The results of this study therefore provide important new insights into the impact of diabetes on outcomes of patients with AHF and CHF.

Lowering Cholesterol in Primary and Secondary CV Prevention

Written by **Maria Vinall**

John B. Kostis, MD, Cardiovascular Institute, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA, reviewed some of the studies examining the relationship between statin use and cataracts in the Cholesterol-lowering Therapy for Primary and Secondary Prevention session on 29 August 2017. This became an issue during the development of lovastatin, when it was noted that dogs given very high doses of statins developed cataracts.

The connection was suggested to be related to the very high cholesterol content of the lens fibre and bidirectional effects of statins on oxidation and inhibition of appropriate lens epithelial cell development that may promote cataract development [Dobrzynski JM, Kostis JB. *Curr Atheroscler Rep*. 2015]. Publications

on this issue have been inconsistent. One meta-analysis showed a 19% decrease in cataracts among statin users in observational studies [Kostis JB, Dobrzynski JM. *J Cardiovasc Pharmacol Ther.* 2014]. Another, that examined the incidence of cataracts in 110,214 patients in 12 studies who received proprotein convertase subtilisin-kexin type 9 (PCSK9) antibodies or statins, found that they neither caused nor prevented cataracts. Sequential analysis showed the same results; however, funnel plot analysis, revealed the potential for publication bias. Only 1 of the 12 studies indicated the potential for an increase in cataracts with low LDL-C levels and only one indicated a decrease in cataract with LDL-C lowering. Meta-regression was essentially flat. In summary, based on currently available information, there is no evidence of a relationship between incidence of cataracts with either statins or PCSK9 antibodies or with very low LDL [Kostis JB et al. ESC Congress 2017. (Abstract 5967)]. Nevertheless, collection of data on cataracts in studies of cholesterol-lowering medications under development remains important.

Luiz Sérgio Carvalho, MD, PhD, State University of Campinas, São Paulo, Brazil, presented a meta-analysis showing that there a trend towards increased risk of type 2 diabetes mellitus (T2DM) in patients achieving very low levels of LDL-C.

Individuals with gain of function mutations in PCSK9 have reduced plasma levels of LDL-C, while loss of function mutations with PCSK9 are associated with more LDL-C [Horton JD et al. *J Lipid Res*. 2009]. PCSK9 loss of function mutations are also associated with increased risk of prediabetes and diabetes [Ference BA et al. *N Engl J Med*. 2016] by impairing β-cell function [Rutti S et al. *Endocrinology*. 2009]. With this background information, Dr Carvalho's team conducted a systematic review and meta-analysis of 20 high-quality randomised controlled trials (RCTs) with PCSK9 inhibitors. The primary outcome was change in HbA1c and fasting blood glucose from baseline. Secondary outcomes included risk of incident T2DM and/or worsening of T2DM during follow-up.

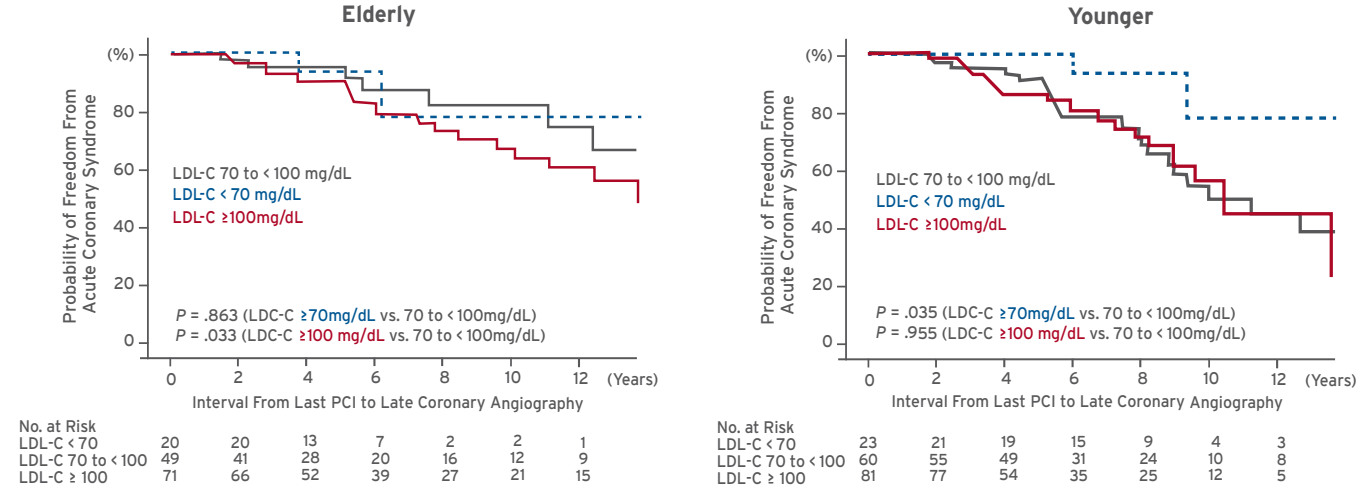
After a mean follow-up of 42 weeks, PCSK9 inhibition was associated with a 0.032% increase in HbA1c and with a 1.88 mg/dL increase fasting plasma glucose (both $P < .001$). PCSK9 inhibition did not increase or decrease T2DM. The study was limited due to the rarity of the outcome and the relatively short-term follow-up. Although the PCSK9 inhibitors increased plasma glycaemia and HbA1c, the effect on T2DM was only apparent among individuals who achieved very low levels of LDL-C after treatment.

Akihiro Endo, MD, Shimane University Faculty of Medicine, Division of Cardiology, Izumo, Japan, reported that reducing LDL-C to < 70 mg/dL is effective for reducing the incidence of recurrent acute coronary syndrome (ACS) in younger Japanese patients; however, a similar effect was not found in elderly Japanese patients.

With the aging of the population, the number of elderly patients with cardiac ischaemia is increasing. LDL-C-lowering therapy with statins is effective for primary and secondary prevention of atherosclerotic cardiovascular diseases in Japanese patients [Nakamura H et al. *Lancet*. 2006]. The target values are < 140 mg/dL for primary prevention and < 100 mg/dL for secondary according to Japanese guidelines. Most RCTs have excluded elderly patients, however.

The present study examined whether LDL-C lowering with statins is equally effective in elderly and younger patients with a history of percutaneous coronary intervention following recurrent cardiac ischaemia. The probability of freedom from recurrent ACS was significantly

Figure 1. Probability of Freedom From Recurrent Acute Coronary Syndrome



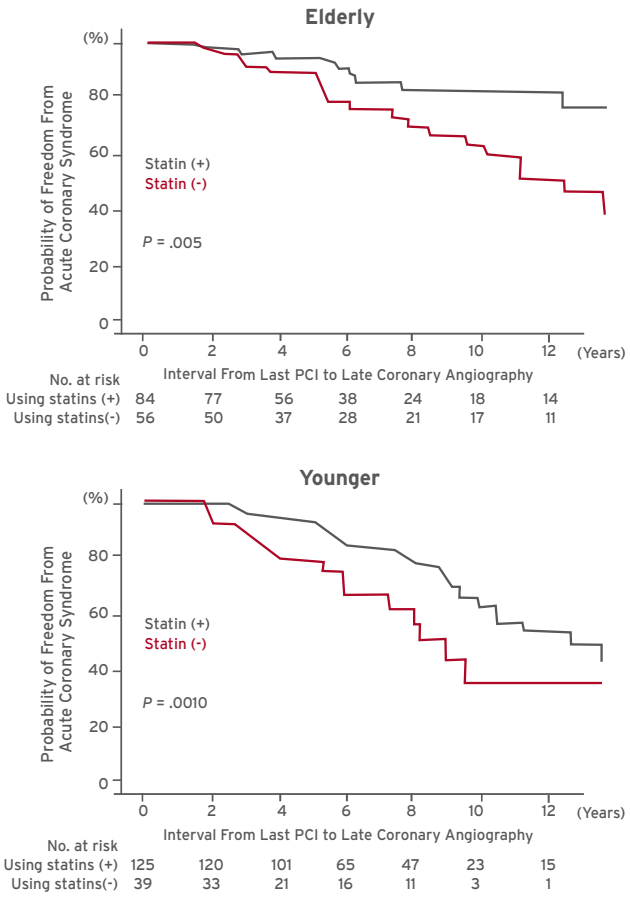
ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol.

Reproduced with permission from A Endo, MD.

higher in younger patients with LDL-C < 70 mg/dL than in those with LDL-C 70 to < 100 mg/dL; however, there was no event differences between these LDL-C levels in the elderly group (Figure 1).

The probability of freedom from any late revascularisation significantly decreased in patients with LDL-C ≥ 100 mg/dL in both groups of patients. Use of statins reduced the incidence of recurrent ACS in both the elderly and younger groups (Figure 2).

Figure 2. Probability of Freedom From Recurrent Acute Coronary Syndrome in Patients Who Were or Were Not Using Statins



ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

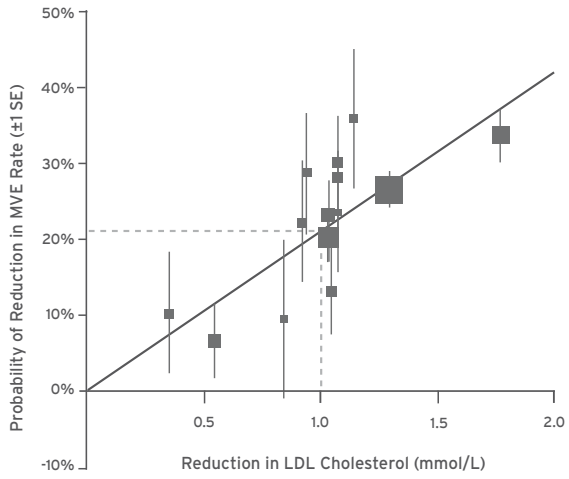
Reproduced with permission from A Endo, MD.

Strict control of LDL-C to < 70 mg/dL was effective for reducing the incidence of recurrent ACS in younger patients. However, LDL-C < 100 mg/dL might be sufficient as the target value of LDL-C–lowering therapy for secondary prevention in elderly Japanese patients.

Jennifer G. Robinson, MD, MPH, University of Iowa, Iowa City, Iowa, USA, discussed the benefits of statin use for primary and secondary prevention of cardiovascular disease (CVD) risk.

Statins reduced CVD risk in all subgroups of patients studied except those with class III-IV heart failure and end-stage renal disease/haemodialysis. The reduction is in direct proportion to the magnitude of LDL-C reduction (22% decrease in major vascular events for every 1 mmol/L reduction in LDL-C; Figure 3) [Baigent C et al. *Lancet*. 2005] with a greater reduction occurring in younger patients [Cholesterol Treatment Trialists' Collaborators et al. *Lancet*. 2012]. Twenty-six trials have shown the safety of statins; only a slight risk of an increase T2DM has been noted. Statin discontinuation is associated with increased risk of myocardial infarction and death from CVD [Nielsen SF et al. *Eur Heart J*. 2016].

Figure 3. Reduction in Major Vascular Events vs Reduction in LDL-C



LDL-C, low-density lipoprotein cholesterol; MVE, major vascular events.

Reprinted from *Lancet*. Baigent C et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins;366:1267-78. Copyright 2005. With permission from Elsevier.

Statins are particularly important in patients with clinical atherosclerotic cardiovascular disease (ASCVD), LDL-C ≥ 190 mg/d, diabetes age 40 to 75 years, and ≥ 7.5% 10-year ASCVD risk. The guidelines are evolving as goals and new lipid-lowering agents enter therapy use. Once a patient is maximised on statin therapy, the physician may consider adding a nonstatin (PCSK9 inhibitor) to boost therapy benefits.

The largest absolute CVD risk reduction from adding a nonstatin is achieved in higher-risk patients with higher LDL-C levels despite maximal statin therapy. The focus should be on treating high-risk patients with high LDL-C, who have the lowest numbers-needed-to-treat to prevent one CVD event [Robinson JG. *J Am Coll Cardiol*. 2016]. Titration to cholesterol goals is not cost-effective with current drug pricing. The treatment paradigm is evolving from treat to goal, toward a focus on specific statin benefit groups to an evaluation of the individual patient's potential for net benefit.

Expert Opinion on Prevention of Recurrent Stroke

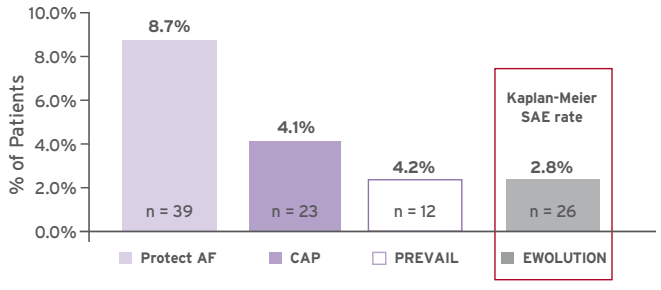
Written by **Phil Vinall**

As part of the Prevention and Management of Acute Stroke session on 29 August 2017, Lucas Boersma, MD, PhD, St. Antonius Hospital, Nieuwegein, The Netherlands, reviewed data from the general population EWOLUTION Registry showing that the WATCHMAN left atrial appendage (LAA) closure procedure was associated with higher success of implant and sealing with less procedural adverse events (AEs) than noted in prior large randomised studies.

EWOLUTION is a prospective, single-arm, multicentre registry of the WATCHMAN LAA closure technology comprising > 1,000 patients (39% with prior major bleeding or predisposition; 73% contraindicated for oral anticoagulation [OAC]). The mean $CHAD_2DS_2$-VASc score was 4.5 (± 1.6); 40% of participants had a HAS-BLED score ≥ 3. The primary analysis included procedural success and safety and the incidence of stroke, bleeding, and death after 2 years [Boersma LV et al. *Eur Heart J*. 2016].

The interim data after 1-year show that 91% of patients were still alive; implant success was 98.5% with a 99% LAA seal rate. Most patients (83%) were on antiplatelet therapy; the remainder were on either OAC or no anticoagulation (9%); device thrombus was noted in 3.7% of patients. The annual rate of ischaemic stroke was 1.1% (84% RR reduction vs a calculated stroke rate of 7.2% without the use of anticoagulation for similar CHA_2DS_2-VASc scores); the annual rate of postprocedural major bleeding was 2.3% (RR reduction of 54% vs expected rate based on HAS-BLED score) [Boersma LV et al. *Heart Rhythm*. 2017]. Procedure- and/or device-related serious AEs within the first 7 days occurred at a rate of 2.8%, lower than in prior WATCHMAN trials (Figure 1).

Figure 1. 7-Day Procedure/Device Related SAEs: All WATCHMAN Studies



Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischaemic stroke, device embolisation, and other vascular complications

SAE, serious adverse event.

Reprinted from Boersma LV et al, Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J*. 2016;37(31):2465-2474. doi:10.1093/eurheartj/ehv730. By permission of Oxford University Press on behalf of the European Society of Cardiology.

WATCHMAN stroke prevention appears effective and safe specifically given that 73% of patients were contraindicated for OACs [Boersma LV et al. *Heart Rhythm*. 2017]. Improvement in implantation techniques has led to a reduction in the composite of vascular complications compared with previous studies. Nevertheless, registries come with several important limitations; to define the role of LAA occlusion randomised clinical trial are indispensable.

Blerim Mujaj, MD, MSc, Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands, presented the results of a study that examined the association between oral antithrombotic treatment and carotid plaque composition.

The study was based on data for 1,740 patients from the Rotterdam Study with carotid plaque determined by MRI. Intraplaque hemorrhage (IPH) was defined as the presence of a hyperintense region in the atherosclerotic plaque. Participants were classified as current, past, or never antithrombotic users. Information on the use of antithrombotic treatment (vitamin K antagonists [VKA] and salicylates), including duration of use and dosage, was obtained from pharmacy records for all participants. The average international normalised ratio (INR for VKA) and daily defined dose (DDD for antiplatelet agents) were tracked. The mean age of patients was 72.9 years, and 46% were women.

Current and past use of antithrombotic treatment was associated with IPH in the carotid artery plaques. Longer durations of use for VKA (> 3 months) and durations for use of antiplatelet agents (> 30 months) were significantly associated with IPH. Among oral VKA users, INR levels > 2.97 were significantly associated with presence of IPH, whereas among the antiplatelet users DDD levels higher than 1.0 were significantly associated with presence of IPH (*P* for trend ≤ .05). No association was found with other plaque components such as lipid core or calcification. In conclusion, the use of antithrombotic treatment relates to a higher frequency of intraplaque haemorrhage in carotid atherosclerotic plaques.

Hans-Christoph Diener, MD, Department of Neurology and Stroke Center, University Hospital Essen, Essen, Germany, discussed the options for antithrombotic therapy in different subtypes of cerebrovascular ischaemic disease.

Aspirin monotherapy substantially reduces the risk of early recurrent stroke after transient ischaemic attack (TIA) and minor stroke if given early (within the first 12 weeks; Figure 2) [Rothwell PM et al. *Lancet*. 2016]. A single study in Chinese patients showed that the addition of clopidogrel to aspirin in the first 90 days after a TIA or mild stroke reduced the risk of recurrent stroke [Wang Y et al. *N Engl J Med*. 2013]. This combination is being tested in Caucasians in the currently recruiting POINT trial. Aspirin plus ticagrelor was tested in the SOCRATES trial. There was no significant reduction in the primary composite endpoint

of stroke, myocardial infarction, or death but the combination did reduce recurrent stroke [Johnston SC et al. *N Engl J Med*. 2016]. Other studies have shown that long-term combination antiplatelet therapy is not superior to monotherapy with aspirin or clopidogrel and in some cases, trial results showed a higher bleeding risk.

In Prof Diener's opinion, there are good data showing that combination antiplatelet therapy with aspirin and clopidogrel plus best medical treatment is superior to stenting for patients with intracranial large vessel disease [Derdeyn CP et al. *Lancet*. 2014]. He also believes that there are no good recommendations for patients with aortic arch plaques but that the combination of aspirin plus clopidogrel is probably as good as warfarin [Amarenco P et al. *Stroke*. 2014].

In patients with AF and previous TIA or ischaemic stroke warfarin is more effective than aspirin for secondary prevention of stroke [EAFT Study Group. *Lancet*. 1993]. For the prevention of recurrent stroke, systemic symbolism, and haemorrhagic stroke, NOACs are superior to warfarin [Ntaios G et al. *Int J Stroke*. 2017].

In patients with small vessel disease the combination of aspirin plus clopidogrel is not superior to aspirin monotherapy but carries a higher bleeding risk. Cryptogenic stroke represents about 25% of all strokes; most are thromboembolic. It has been proposed that embolic strokes of undetermined source (ESUS) are therapeutically relevant and can be defined as a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources [Hart RG et al. *Lancet Neurol*. 2014]. Two studies RESPÉCT-ESUS and NAVIGATE-ESUS trials are in progress to determine whether anticoagulation with dabigatran or rivaroxaban is superior to aspirin in patients with ESUS.

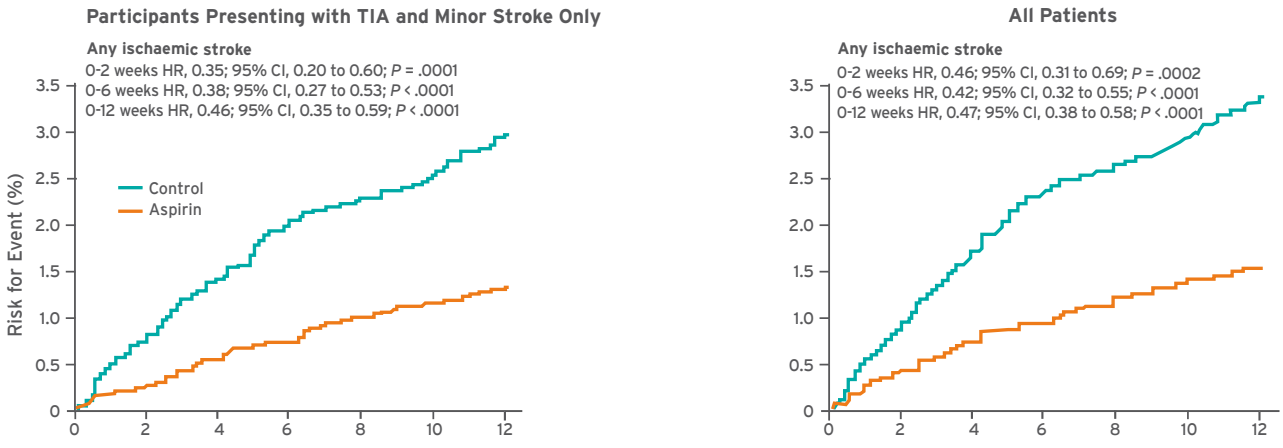
Mikael Mazighi, MD, Unité de Soins Intensifs NeuroVasculaire, Hôpital Lariboisière, Paris, France, described mechanical thrombectomy with intravenous recombinant tissue plasminogen activator (IV tPA) as the gold standard for acute ischaemic stroke.

Therapy should be started as soon as possible. IV tPA should be administered within 4.5 hours of symptom onset and thrombectomy should be performed within 6 hours [Prabhakaran S et al. *JAMA*. 2015]. There is no age limit for this procedure. A meta-analysis of data from 5 randomised controlled trials showed that thrombectomy is of benefit to most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation internal carotid artery and proximal middle cerebral artery). Disability was significantly reduced at 90 days compared with best medical therapy (adjusted common OR 2.49, 95% CI, 1.76 to 3.53; $P < .0001$) [Goyal M et al. *Lancet*. 2016] with a number needed to treat of 2.6.

A stent retriever is the first device of choice, but newer devices like the contact aspiration technique are being evaluated [Lapergue B et al. *JAMA*. 2017]. Older patients (> 80 years) and those with higher NIHSS scores appear to benefit the most from thrombectomy. The benefits of thrombectomy in patients with large stroke volume need to be confirmed.

Prof Mazighi concluded that IV-tPA remains a relevant viable treatment in association with thrombectomy for stroke ischaemia. Although effective for occlusions in carotid and middle cerebral arteries, the benefit of thrombectomy use in basilar artery occlusions and for more distal occlusions in the anterior circulation remain to be established.

Figure 2. Effects of Aspirin on Early Recurrent Stroke After TIA and Ischaemic Stroke



Source: Rothwell PM et al. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet*. 2016; 88(10042):365-375. doi: 10.1016/S0140-6736(16)30468-8.

PCSK9 Inhibition to Cholesterol

Written by **Brian Hoyle**

The successful efforts to lower levels of LDL-C over the past 4 decades were reviewed in the PCSK9 Inhibition - Cholesterol Reduction and Beyond session on 26 August 2017. The 7-year LRC trial conducted beginning in 1975 was an auspicious start, explained Steven Nissen, MD, Cleveland Clinic, Cleveland, Ohio, USA, demonstrating a nearly 20% reduction in LDL-C after 1 year of therapy, and reductions in the incidence of coronary heart disease (CHD) and nonfatal myocardial infarction (MI) [Lipid Research Clinics. *JAMA*. 1984].

The discovery of statins ushered in a new era of trials geared toward achieving even lower levels of LDL-C by inhibiting hydroxymethylglutaryl-CoA reductase using simvastatin, pravastatin, atorvastatin, and rosuvastatin. The next series of studies explored the benefits of intensive statin therapy to achieve even lower LDL with higher doses of atorvastatin [Cannon CP et al. *N Engl J Med*. 2004; Nissen SE et al. *JAMA*. 2004; LaRosa et al. *N Engl J Med*. 2005], simvastatin [Blazing MD, DeLemos et al. *JAMA* 2004] and rosuvastatin [Nissen SE et al. *JAMA*. 2006; Hsia J et al. *J Am Coll Cardiol*. 2011]. There is now clinical consensus that lowering LDL with a high-intensity statin is the preferred strategy in most high-risk patients; however, the exact strategy differs across guidelines [Stone NJ et al. *Circulation*. 2013; Lloyd-Jones DM et al. *J Am Coll Cardiol*. 2016; Catapano AL et al. *Eur Heart J*. 2016].

Subsequent to the statin trials, ezetimibe was found to improve cardiovascular (CV) outcomes in manner that was consistent with the degree of LDL reduction through a nonstatin mechanism [Cannon CP et al. *N Engl J Med*. 2015]. These findings provided further support for concept of LDL lowering as the key determinant of CV benefit, rather than the notion that the benefit was limited to statin therapy alone. Importantly, these findings set the stage for alternative strategies of LDL lowering, including those that target proprotein convertase subtilisin/kexin type 9 (PCSK9).

The role of PCSK proteins in human biology was largely unknown 2 decades ago. The intervening brief period of time has witnessed the unravelling of the protein's genetics and the demonstration of the functional importance of PCSK9 in the metabolism of cholesterol. PCSK9 is a circulating protein that binds to the receptor for LDL [Seidah NG et al. *Circ Res*. 2014] and targets the receptor for degradation in the liver, effectively blocking removal of LDL from the blood by the liver [Lambert et al. *Eur Heart J*. 2016].

As described by Stephen Nicholls, MD, PhD, South Australian Health & Medical Research Institute, Adelaide, Australia, PCSK9 is comprised of a signal peptide, and pro-, catalytic, and C-terminal domains. Various mutations in these domains can produce a gain or loss of function. Gain-of-function mutations lead to increased total cholesterol and LDL-C [Abidfadel M et. al *Nat Genet*. 2003]. Loss-of-function mutations are associated with lower LDL-C levels and a reduced risk of CHD [Rashid S et al. *Proc Natl Acad Sci USA*. 2005].

It has long been known that statins up-regulate the expression of the LDL receptor, which stimulates increased removal of LDL from the blood. More recent evidence indicates that the binding of statin to sterol regulatory element-binding protein 2 also up-regulates the expression of PCSK9, which in turn increases LDL. Thus as statin doses are escalated, the incremental decrease in LDL is counterbalanced by increases in PCSK9 levels, such that each doubling of statin doses decreases the LDL by only approximately 6%. It was hypothesised that the addition of a PCSK9 inhibitor to statin therapy should have the potential to dramatically lower LDL.

This hypothesis has been borne out in studies of monoclonal antibodies targeted against PCSK9, including evolocumab [Sabatine MS et al. *N Engl J Med*. 2015], alirocumab [Robinson JG et al. *N Engl J Med*. 2015], and bococizumab [Ridker *P et al. N Engl J Med*. 2017], each significantly and substantially reduced LDL-C by 40-70% when added to background statin therapy. PCSK9 inhibitors also reduced levels of lipoprotein(a), which has been implicated in CV disease. Dr Nicholls and colleagues have proposed that physiological concentrations of PCSK9 enhance the production of lipoprotein(a) and that inhibition of PCSK9 will reduce lipoprotein(a) levels.

Evolocumab has been shown to result in a significantly lower atheroma volume in the GLAGOV study [Nicholls S et al. *JAMA*. 2016]. Notably, in the FOURIER trial of 27,564 high-risk patients with stable atherosclerotic disease, evolocumab significantly reduced major adverse cardiac events (CV death, MI, or stroke) by 20% ($P < .001$) [Sabatine MS et al. *N Engl J Med*. 2017]. There was also a significant reduction in CV events in SPIRE 2 with bococizumab in patients at higher-risk; however, the SPIRE trials were terminated early due to development of neutralizing antibodies to this humanised murine antibody. The outcomes trial with alirocumab, ODYSSEY Outcomes, is ongoing to assess for cardiovascular benefit of LDL reduction with this agent [NCT01663402].

Therapies to reduce LDL-C and CV events must be safe in both the short and long term. PCSK9 directed therapy has been in use for a relatively short period of time (up to 4 years) and therefore longer-term safety data are needed, according to J. Woulter Jukema, MD, PhD, Leiden University Medical Centre, Leiden, The Netherlands. In the FOURIER trial, there were no safety concerns identified in the main trial (Table 1) as well as in a cognitive study known as EBBINGHAUS that was embedded within FOURIER [Giugliano RP et al. *N Engl J*

Med. 2017]. In addition, data out to 4 years with evolocumab pooled across phase 2 and 3 lipid-lowering studies have raised no safety concerns [Koren MJ et al. *JAMA Cardiol*. 2017]. Similarly, pooled data from earlier trials of alirocumab also indicate no safety concerns (Table 2).

Table 1. Safety Data From the FOURIER Trial

	Evolocumab (n = 13,769)	Placebo (n = 13,756)
Adverse events (%)		
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Treatment-related that led to discontinuation of study	1.6	1.5
Muscle-related	5.0	4.8
Cataract	1.7	1.8
Diabetes (new onset)	8.1	7.7
Neurocognitive	1.6	1.5
Laboratory Results (%)		
Binding Ab	.03	n/a
Neutralizing Ab	None	n/a

Further safety data are pending from the ODYSSEY Outcomes study with alirocumab [Schwartz GG et al. *Am Heart J*. 2014].

Interestingly, PCSK9 may have a variety of functional roles in autocrine and exocrine activities in the liver, intestinal tract, lung, kidney, pancreas, and arterial wall. This raises the hope that targeting this protein could produce benefits beyond the lowering of LDL-C. As explained by Bertrand Cariou, MD, PhD, Université de Nantes, Nantes, France, PCSK9 may be directly involved in atherogenesis independent of the level of LDL-C. In the intestines, increased PCSK9 may function in the retention of lipid in the blood following a meal and in the secretion of apolipoprotein B, the main apolipoprotein of LDL [Le May C et al. *Arterioscl Thromb Vascul Biol*. 2009]. PCSK9 may also modulate trans-intestinal cholesterol excretion [Le May C et al. *Arterioscl Thromb Vascul Biol*. 2013]. Genetic studies with pancreatic tissue have indicated a possible link between PCSK9 mutations and the increased risk of type 2 diabetes [Ference BA et al. *N Engl J Med*. 2016].

The findings highlight the need for more data on the various actions of PCSK9 in the long-term and more studies are needed to properly gauge the mode of action and long-term clinical safety of PCSK9 inhibitors.

Table 2. Pooled Data Fwrom 14 Trials Involving Alirocumab

	Pooled Control (n = 1,894)	Pooled Alirocumab (n = 3,340)	Pooled Alirocumab LDL-C < 25 mg/dL (n = 796)	Pooled Alirocumab LDL-C < 15 mg/dL (n = 288)
Infections and infestations	36.3	38.5	34.0	35.4
Musculoskeletal disorders	25.2	24.2	21.1	20.1
Injection-site reaction	3.9	5.7	3.0	3.5
Nervous system disorders	14.9	14.9	10.3	9.0
Diabetes mellitus	1.3	1.2	1.5	2.4
Neoplasms	2.5	2.5	2.8	2.4