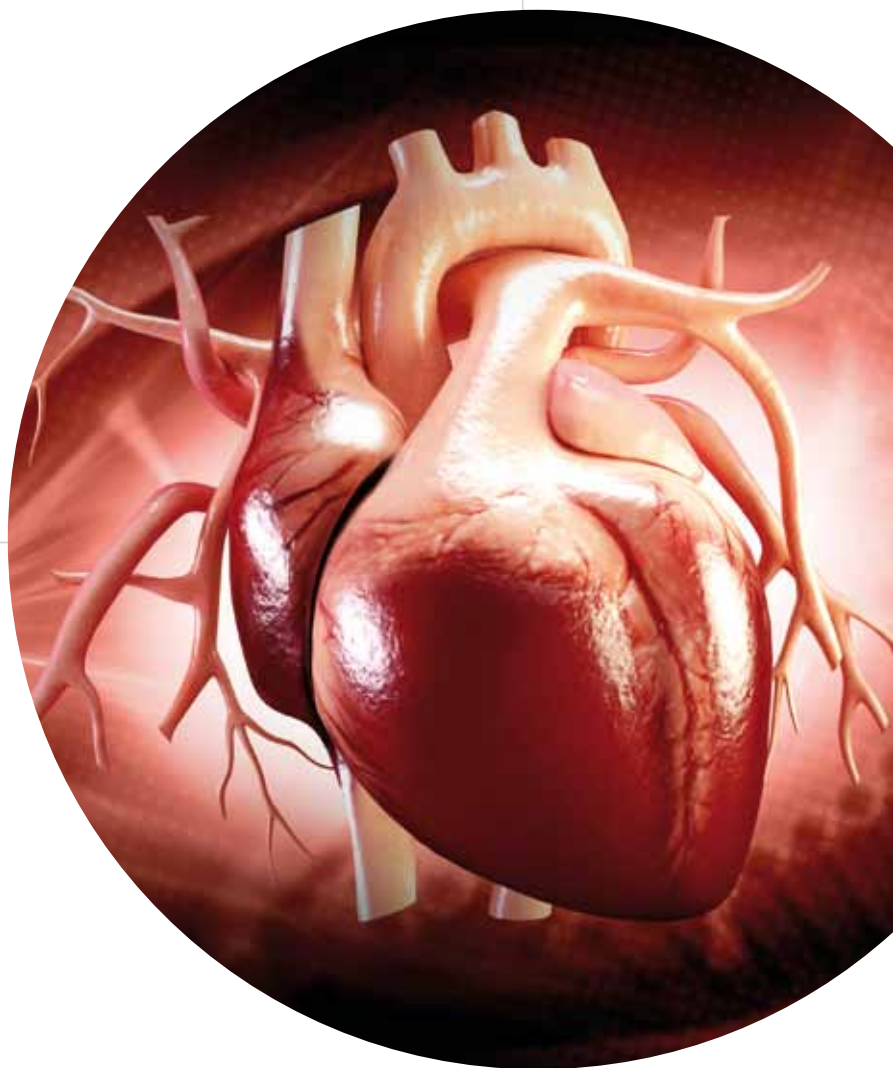# ESC Congress 2017 In Review

Official peer-reviewed highlights

Focus on CAD & ACS

In This Issue

2017 ESC Clinical Practice Guidelines for the Management of STEMI

The management of ST-segment elevation acute myocardial infarction continues to evolve as new treatments are tested out in well-conducted clinical trials. The growing evidence emanating from recent trials has been incorporated in the updated 2017 Clinical Practice Guidelines that aimed to align these recommendations with the other ESC Clinical Practice Guidelines and consensus documents.

Also
Pharmacotherapy After STEMI
Clinical Trial Highlights
$P2Y_{12}$ Inhibitors for the Treatment of ACS

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European Society of Cardiology

Dear Colleagues,

We are delighted to present this issue of *ESC Congress 2017 in Review*, focused on coronary artery disease (CAD) and acute coronary syndromes (ACS), two entities of particular importance in cardiology. The peer-reviewed highlights in this issue are based on presentations at the European Society of Cardiology (ESC) Congress 2017 held in Barcelona, Spain.

Among the articles in this issue, you will find a closer look at 2017 ESC Clinical Practice Guidelines on acute myocardial infraction (AMI) in patients presenting with persistent ST-segment elevation, which harbours significant changes to the previous version, both regarding acute care as well as long-term drug therapy.

Several Hot Line trials are covered in this issue. They include COMPASS, CANTOS, and RE-DUAL PCI. Results from RE-DUAL PCI showed that dual antithrombotic therapy with dabigatran and a $P2Y_{12}$ inhibitor was superior to triple therapy with warfarin at preventing bleeding after percutaneous coronary intervention among AF patients. COMPASS demonstrated that in high-risk patients with CAD rivaroxaban 2.5 mg BID plus aspirin 100 mg QD reduces the composite of cardiovascular death, stroke, or MI compared with aspirin alone. Data from the CANTOS trial showed that canakinumab reduces cardiovascular event rates and potentially reduces the rate of incident lung cancer as well as lung cancer mortality.

We are confident that the articles and practical perspectives presented in *ESC Congress 2017 in Review - Focus on CAD and ACS* will provide you with important new insights. To access ESC Congress content (videos, slides, abstracts, reports, and ESC TV interviews) all year long, visit us online at any time at www.escardio.org/365.

We hope to see you in Munich for ESC Congress 2018. For more information, please visit www.escardio.org/ESC2018.

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

Dear Practitioner,

We are pleased to share with you this special issue of *ESC Congress in Review 2017* with a focus on coronary artery disease (CAD) and acute coronary syndromes (ACS) from presentations at the European Society of Cardiology (ESC) Congress 2017 held in Barcelona, Spain.

The featured article reviews the newly released 2017 ESC Clinical Practice Guidelines for the Management of Acute Myocardial Infarction (MI) in Patients Presenting with ST-segment Elevation (STEMI). Changes from the 2012 guidelines include new sections dedicated to MI with nonobstructive coronary arteries; an update on caring for patients in the acute phase of MI; a change in the timing of primary percutaneous coronary intervention (PCI) and fibrinolysis now sets the start of the "strategy clock" at the time of STEMI diagnosis rather than first medical contact; and the use of longer-term therapies after STEMI.

A number of highly anticipated and potentially practice changing clinical trials were presented at ESC Congress 2017, including the results from the COMPASS and RE-DUAL PCI studies. COMPASS extended the results from ATLAS TIMI-51 demonstrating that the combination of rivaroxaban 2.5 mg BID plus aspirin was superior to aspirin alone for prevention of cardiovascular death, stroke, or MI in patients with stable CAD or PAD. There was a trade-off with more bleeding when low-dose anticoagulant was added to aspirin, but fortunately severe bleeding was not increased.

Triple antithrombotic therapy comprising warfarin plus dual antiplatelet therapy is standard care after PCI for patients with AF, but this combination can leave these patients at high risk for bleeding events. RE-DUAL PCI was designed to investigate the efficacy and safety of dual therapy with dabigatran and a $P2Y_{12}$ inhibitor in AF patients after PCI compared with standard triple therapy. Results showed that among patients with AF undergoing PCI, dual therapy was safe and effective at reducing bleeding events compared with triple therapy (absolute risk reduction of 11.5% for the 110 mg dose and 5.5% for the 150 mg dose).

In addition to the results from clinical trials and registry updates, you will also find articles that discuss the use of pharmacotherapy after STEMI and $P2Y_{12}$ inhibitors for the treatment of ACS.

We hope that you find the articles and practical perspectives that are contained in this special edition of *ESC Congress 2017 in Review – Focus on CAD & ACS* 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

ESC European Society of Cardiology

2017 ESC Clinical Practice Guidelines for the Management of STEMI

Written by **Toni Rizzo**

A goal of the 2017 update of the European Society of Cardiology (ESC) Clinical Practice Guidelines for the management of acute myocardial infarction (AMI)-STEMI [Ibanez B et al. *Eur Heart J*. 2017] was to align the recommendations with the other ESC guidelines and consensus documents, including the simultaneously published update on dual antiplatelet therapy (DAPT) [Valgimigli M et al. *Eur Heart J*. 2017].

In a session on 27 August 2017 that presented an overview of the new AMI-STEMI guidelines, Stefan James, MD, Uppsala University, Uppsala, explained that the ESC Task Force attempted to make the guidelines more user-friendly by highlighting the changes from the 2012 guidelines in flowcharts and tables. The charts in Figure 1 summarise the revised and new recommendations in the current update.

Acute Cardiac Care in Stable and Unstable STEMI
Pascal Vranckx, MD, PhD, Cardiovascular Research Centre, Hasselt, Belgium, discussed the changes in the updated guidelines on caring for patients in the acute phase of MI, from symptom recognition to emergency medical services (EMS) and emergency department evaluation and treatment.

Figure 1. Changes in the 2017 ESC STEMI Guidelines
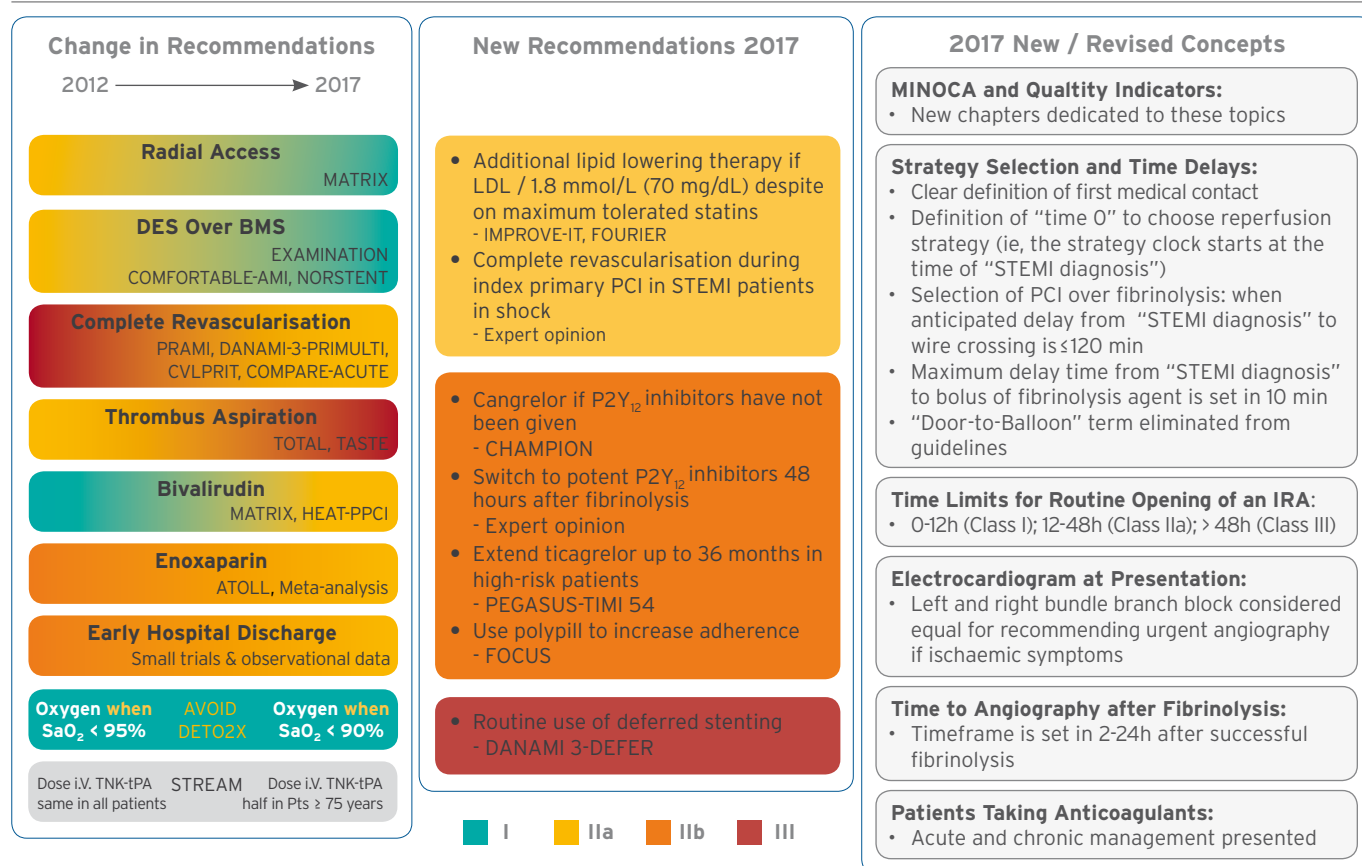
BMS, bare-metal stent; DES, drug-eluting stent; IRA, infarct-related artery; LDL, low-density lipoprotein; MINOCA, myocardial infarction with nonobstructive coronary arteries; PCI, percutaneous coronary intervention; SaO$_2$, arterial oxygen saturation; STEMI, ST-segment elevation myocardial infarction; TNK-tPA, tenecteplase tissue plasminogen activator.

For the first time, the first medical contact (FMC) is clearly defined in the guidelines, as the first contact with a physician, paramedic, nurse, or other trained EMS personnel who can obtain and interpret the electrocardiogram (ECG) and deliver initial interventions.

The guidelines on imaging and stress testing include recommendations for emergency echocardiography for certain presentations but should not delay angiography unless the diagnosis is uncertain (Table 1) and provide recommendations following primary PCI and post discharge.

Table 1. Indications for Imaging and Stress Testing in Patients With STEMI

| Recommendations	Class	Level
At presentation		
Emergency echocardiography is indicated in patients with cardiogenic shock and/or haemodynamic instability or suspected mechanical complications without delaying angiography.	I NEW	C
Emergency echocardiography before coronary angiography should be considered if the diagnosis is uncertain.	IIa IC→IIa	C
Routine echocardiography that delays emergency angiography is not recommended.	III NEW	C
Coronary CT angiography is not recommended.	III	C

CT, computed tomography.

Adapted from Ibanez B, James S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017; doi:10.1093/eurheartj/ehx419. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Figure 2. Maximum Target Times According to Reperfusion Strategy in Patients Presenting via EMS or in a non-PCI Centre
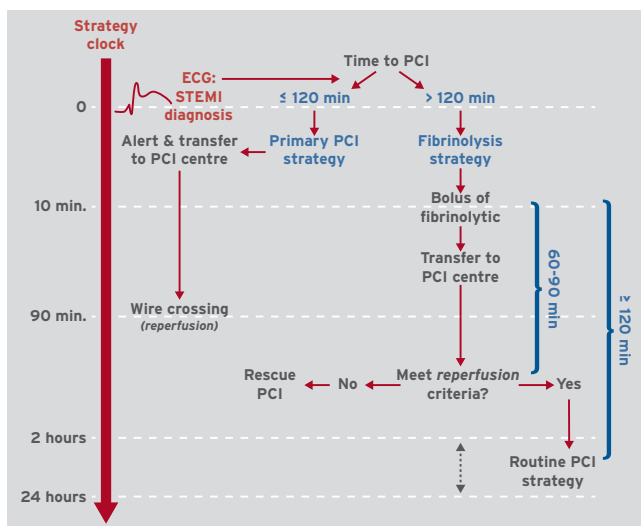
ECG, electrocardiogram; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Reprinted from Ibanez B, James S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017; doi:10.1093/eurheartj/ehx419. By permission of Oxford University Press on behalf of the European Society of Cardiology.

The maximum target times according to reperfusion strategy in patients presenting via EMS or in a non-PCI centre are shown in Figure 2.

New recommendations have been added to the guideline for management of cardiogenic shock, including the concept of the Heart Team (Table 2).

Table 2. Management of Cardiogenic Shock in STEMI

Recommendations	Class	Level
Immediate PCI is indicated for patients with cardiogenic shock if coronary anatomy is suitable. If coronary anatomy is not suitable for PCI, or PCI has failed, emergency CABG is recommended.	I	B
Invasive blood pressure monitoring with an arterial line is recommended.	I	C
Immediate Doppler echocardiography is indicated to assess ventricular and valvular functions, loading conditions, and to detect mechanical complications.	I	C
It is indicated that mechanical complications are treated as early as possible after discussion by the Heart Team.	I	C NEW
Oxygen/mechanical respiratory support is indicated according to bloodgases.	I	C
Strategy should be guided as in other STEMI patients if time from STEMI diagnosis to wire crossing is > 120 min -> immediate fibrinolysis & transfer to PCI centre. Urgent angiography upon arrival regardless of time from lytics.	IIa / IIa	C NEW! / C NEW
Intra-aortic balloon pumping should be considered in patients with haemodynamic instability/cardiogenic shock due to mechanical complications.	IIa	C NEW
Haemodynamic assessment with pulmonary artery catheter may be considered for confirming diagnosis or guiding therapy.	IIb	B
Ultrafiltration may be considered for patients with refractory congestion, who failed to respond to diuretic-based strategies.	IIb	B IIa → IIb
Inotropic/vasopressor agents may be considered for haemodynamic stabilisation.	IIb	C IIa → IIb
Short-term mechanical support may be considered in patients in refractory shock.	IIb	C
Routine intra-aortic balloon pumping is not indicated.	III	B IIb → III

CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Adapted from Ibanez B, James S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017; doi:10.1093/eurheartj/ehx419. By permission of Oxford University Press on behalf of the European Society of Cardiology.

β-blockers are now recommended for first-line rate control for atrial fibrillation, with amiodarone as second choice.

For patients presenting with ventricular arrhythmias and conduction disturbances, one new recommendation has been added recommending radiofrequency catheter ablation at a specialised ablation centre.

Primary PCI and Fibrinolysis Procedures

A key change in the guidelines for the timing of primary PCI and fibrinolysis is the start of the "strategy clock" at the time of STEMI diagnosis rather than FMC. Sigrun Halvorsen, MD, PhD, University of Oslo, Oslo, Norway, discussed the importance of time targets in the management of patients with STEMI.

Primary PCI is the preferred reperfusion strategy in patients presenting within 12 hours of symptom onset, if it can be performed within 120 minutes of STEMI diagnosis. Fibrinolytic therapy is recommended if this time target cannot be met.

The 120-minute cut-off was kept based on the available evidence, but Prof Halvorsen cautioned that no specific study has addressed the time at which the benefits of pri-

mary PCI are lost. For patients presenting within 12 to 48 hours, routine primary PCI should be considered; it should only be recommended if ongoing symptoms suggestive of ischaemia, haemodynamic instability, or life-threatening arrhythmias are present. Routine PCI is not indicated if more than 48 hours have passed.

The recommendations on the indications and procedural aspects of primary PCI are shown in Table 3.

An important addition to the antithrombotic therapy options in patients undergoing primary PCI is the addition of cangrelor (IIb, A). Based on the CHAMPION studies, cangrelor may now be considered for patients who have not received $P2Y_{12}$ receptor inhibitors [Steg G et al. *Lancet*. 2013].

Longer Term Therapies After STEMI

Eva Prescott, MD, DMSc, Bispebjerg University Hospital, Copenhagen, Denmark, briefly reviewed the recommendations for hospital stay and lifestyle interventions. For behavioural aspects, a new recommendation that use of the polypill and combination therapy to increase adherence to drug therapy may be considered has been added.

The recommendation on calcium antagonists has been omitted from the recommendations for routine medical therapies in the acute, subacute, and long-term phases. The goal for lipid-lowering therapy has been updated to an LDL-C goal of < 70 mg/dL or a reduction of ≥ 50%, if baseline is 70 to 135 mg/dL. Based on the IMPROVE-IT and FOURIER trials, further lipid-lowering therapy should be considered in patients with LDL-C ≥ 70 mg/dL despite a maximally tolerated statin dose who remain at high risk [Cannon CP et al. *N Engl J Med*. 2015; Sabatine MS et al. *N Engl J Med*. 2017].

Table 4 summarises the recommendations on maintenance antithrombotic therapy. Details of the changes are included in the 2017 focused update on dual antiplatelet therapy [Valgimigli M et al. *Eur Heart J*. 2017].

MI With Nonobstructive Coronary Arteries

The ESC 2017 AMI-STEMI guidelines include a new chapter addressing MI with nonobstructive coronary arteries (MINOCA), which was summarised by Stefan Agewall, MD, PhD, University of Oslo, Oslo, Norway. According to a recently published ESC working group position paper on MINOCA [Agewall S et al. *Eur Heart J*. 2017], the diagnosis is made immediately upon coronary angiography in a patient meeting the criteria for AMI: universal AMI criteria; nonobstructive coronary arteries on angiography, defined as no coronary artery stenosis ≥ 50% in any potential infarct-related artery; and no clinically overt specific cause for the acute presentation.

MINOCA is estimated to occur in 1-13% of patients with AMI. It is a heterogeneous condition, with several potential

Table 3. Indications and Procedural Aspects of the Primary PCI Strategy

Recommendations	Class	Level
Indications		
In the absence of ST-segment elevation, a primary PCI strategy is indicated in patients with suspected ongoing ischaemic symptoms suggestive of MI and if at least one of the following criteria is present: • Haemodynamic instability or cardiogenic shock • Recurrent or ongoing chest pain refractory to medical treatment • Life-threatening arrhythmias or cardiac arrest • Mechanical complications of MI • Acute heart failure • Recurrent dynamic ST-segment or T-wave changes, particularly with intermittent ST-segment elevation	I	C
IRA technique		
Stenting is recommended (over balloon angioplasty) for primary PCI.	I	A
Stenting with new-generation DES is recommended over BMS for primary PCI.	I	A
Radial access is recommended over femoral access if performed by an experienced radial operator.	I	A
Routine use of thrombus aspiration is not recommended.	III	A
Routine use of deferred stenting is not recommended.	III	B
Prophylactic treatment with antiarrhythmic drugs to prevent AF is not indicated.	III	B
Non-IRA strategy		
Routine revascularisation of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge.	IIa	A
Non-IRA PCI during the index procedure should be considered in patients with cardiogenic shock.	IIa	C

CABG, coronary artery bypass graft surgery; DES, drug-eluting stent; IRA, infarct-related artery; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Adapted from Ibanez B, James S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017; doi:10.1093/eurheartj/ehx419. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Table 4. Maintenance Antithrombotic Strategy After STEMI

Recommendations	Class	Level
Antiplatelet therapy with low-dose aspirin (75-100 mg) is indicated.	I	A
DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding.	I	A
A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding.	I	B
In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy.	I	C
In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.	IIa	B
In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy should be considered for 1-6 months (according to a balance between the estimated risk of recurrent coronary events and bleeding).	IIa	C
DAPT for 12 months in patients who did not undergo PCI should be considered unless there are contraindications such as excessive risk of bleeding.	IIa	C
In patients with LV thrombus, anticoagulation should be administered for up to 6 months guided by repeated imaging.	IIa	C
In high ischaemic-risk patients who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg BID on top of aspirin for longer than 12 months may be considered for up to 3 years.	IIb	B
In low bleeding-risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg BID) may be considered.	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation.	III	C

AMI, acute myocardial infarction; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LV, left ventricular; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; STEMI, ST-segment elevation myocardial infarction.
Reprinted from Ibanez B, James S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017; doi:10.1093/eurheartj/ehx419. By permission of Oxford University Press on behalf of the European Society of Cardiology.

etiologic diagnoses, and failure to identify the underlying cause might result in inadequate or inappropriate therapy. Possible causes include coronary endothelial dysfunction, such as microvascular spasm or myocardial disorders without obvious coronary artery involvement [Agewall S et al. *Eur Heart J.* 2017].

The updated AMI-STEMI guidelines include a diagnostic test flow chart for MINOCA (Figure 3).

Prof Agewall concluded that MINOCA is a working diagnosis and should lead the treating physician to investigate underlying causes. CMR might be considered a standard examination when the underlying cause is not identified.

Figure 3. Diagnostic Test Flowchart for MINOCA

CMR, cardiac magnetic resonance; IVUS, intravascular ultrasound; LV, left ventricular; MINOCA, myocardial infarction with nonobstructed coronary arteries; STEMI, ST-segment elevation myocardial infarction; TOE, transoesophageal ultrasound; TTE, transthoracic echocardiography.
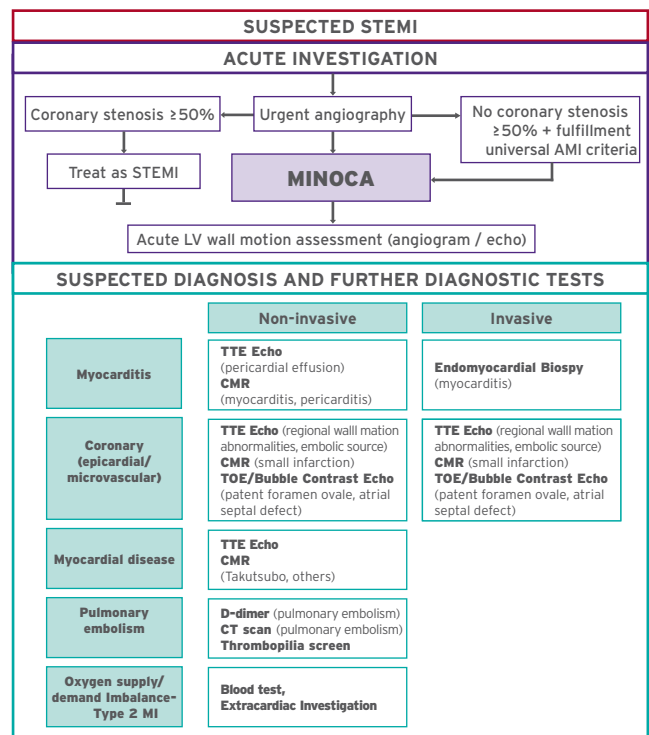
Reprinted from Ibanez B, James S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017; doi:10.1093/eurheartj/ehx419. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Quality Indicators in STEMI

Héctor Bueno, MD, PhD, University Hospital, Madrid, Spain, discussed the new chapter on quality indicators in the 2017 AMI-STEMI guidelines. The new recommendations for quality indicators were added to ensure that every patient with STEMI receives the best possible care according to accepted standards and has the best possible outcomes. The proposed quality indicators are shown in Table 5.

The quality indicators chosen for the guideline were validated in the MINAP-UK and FAST-MI studies [Bebb O et al. *Eur Heart J.* 2017; Schiele F et al. *Circ Cardiovasc Qual Outcomes.* 2017]. Prof Bueno concluded that the new quality indicators will help institutions assess the quality of care and improve the quality of care in patients with STEMI.

Future Challenges in STEMI Treatment

Borja Ibanez, MD, PhD, University Hospital Fundación Jiménez Díaz, Madrid, Spain, pointed out that of the 159 recommendations in the 2017 STEMI guidelines, almost half are level of evidence C, which is based on the consensus of expert opinions, small studies, retrospective studies, or registries. Prof Ibanez discussed several areas with gaps in the evidence and where future research is needed. Public campaigns are needed to reduce patient delay and improve prehospital management.

Although head-to-head trials have demonstrated the benefits of primary PCI over fibrinolysis, the extent to which the PCI-related time delay diminishes the advantages of PCI over fibrinolysis is not clear. The PCI-related time delay that potentially mitigates the benefits of PCI has been calculated in various studies as from 60 to 120 minutes. However, there have been no dedicated studies to determine the best cut-off time. Identification of the best cut-off time to choose a reperfusion strategy is of extreme importance and should be addressed in future studies. Among the areas highlighted were interventions to limit infarct size, optimal regimens of combination antithrombotic therapies (prehospital and long-term post discharge), the role of β-blockers in patients with reperfused MI, revascularisation of the non-infarct-related artery, and experience with novel therapies beyond clinical trials (ie, in general clinical practice [Ford I, Norrie J. *N Engl J Med*. 2016]). There is a need for less selective and less expensive pragmatic trials that are more easily generalised to clinical practice involving a wider spectrum of centres and patients across the world. More observational data from registries and clinical databases is also needed for quality assessment.

Table 5. Quality Indicators

Type of Indicator Process	Quality Indicator
Structural measures (organisation)	1. The centre should be part of a network specifically developed for the rapid and efficient management of STEMI patients with written protocols covering the following points: • Single emergency telephone number for patients to contact the emergency services • Prehospital interpretation of the ECG for diagnosis and strategy decision • Prehospital activation of the catheterisation laboratory • Transportation (ambulance-helicopter) equipped with ECG defibrillators

Performance measures for reperfusion therapy	1. Proportion of STEMI patients arriving in the first 12 h receiving reperfusion therapy.
	2. Proportion of patients with timely reperfusion therapy, defined as:
	• Patients attended to in the pre-hospital setting:
	  – 90 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI
	  – < 10 min from STEMI diagnosis to lytic bolus for reperfusion with fibrinolysis
	• Transferred patients:
	  – < 120 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI
	  – < 30 min door-in-door-out for patients presenting in a non-PCI centre (en route to a PCI centre)

Performance measures for risk assessment in hospital	1. Proportion of patients having LVEF assessed before discharge.
Performance measures for antithrombotic treatment in hospital	1. Proportion of patients without a clear and documented contraindication for aspirin and/or a $P2Y_{12}$ inhibitor, discharged on DAPT.
Performance measures for discharge medication and counselling	1. Proportion of patients without contra-indications with a statin (high-intensity) prescribed at discharge. 2. Proportion of patients with LVEF ≤ 40% or clinical evidence of heart failure and without contraindications with a β-blocker prescribed at discharge. 3. Proportion of patients with LVEF ≤ 40% or clinical evidence of heart failure without contra-indications with an ACE inhibitor (or ARB if not tolerated) prescribed at discharge. 4. Proportion of patients with smoking cessation advice/counselling at discharge. 5. Proportion of patients without contraindications enrolled in a secondary prevention/cardiac rehabilitation program at discharge.
Outcome measures	1. 30-day adjusted mortality (eg, GRACE risk score-adjusted). 2. 30-day adjusted readmission rates.
Opportunity-based composite quality indicators	1. Proportion of patients with LVEF > 40% and no evidence of heart failure receiving at discharge low-dose aspirin, a $P2Y_{12}$ inhibitor, and high-intensity statins. 2. Proportion of patients with LVEF ≤ 40% and/or heart failure receiving at discharge low-dose aspirin, a $P2Y_{12}$ inhibitor, high-intensity statins, an ACE inhibitor (or ARB), and a β-blocker.
Patient-reported outcomes	1. Availability of a program to obtain feedback regarding the patient's experience and quality of information received, including the following points: • Angina control • Explanations provided by doctors and nurses (about the disease, benefit/risk of discharge treatments, and medical follow-up) • Discharge information regarding what to do in case of recurrence of symptoms and recommendation to attend a rehabilitation program (including smoking cessation and diet counselling)

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; DAPT, dual antiplatelet therapy; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Reprinted from Ibanez B, James S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017; doi:10.1093/eurheartj/ehx419. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Supplemental Oxygen No Better Than Ambient Air: Results From the DETO2X-AMI Study

Written by **Brian Hoyle**

The findings of a registry-based randomised clinical trial (RCT) involving 6,629 patients have shown that routine oxygen therapy for nonhypoxaemic patients with suspected acute myocardial infarction (AMI) does not reduce all-cause mortality at 1 year compared with ambient air.

The results of the DETO2X-AMI study [Hofmann R et al. *N Engl J Med*. 2017] were presented by Robin Hofmann, MD, Karolinska Institutet, Stockholm, Sweden.

Oxygen therapy has been used for over a century for AMI patients, and it is recommended in clinical guidelines. The rationale of the approach is the belief that the delivery of more oxygen to the ischaemic myocardium reduces the infarct size and subsequent complications. On the other hand, above-normal oxygen levels can produce or cause coronary constriction. Data supporting the benefit of routine oxygen therapy in terms of patient survival are lacking. A recent systematic literature review confirmed conflicting data on the benefits of oxygen therapy in acute coronary syndrome patients [Shuvy M et al. *Eur Heart J*. 2013].
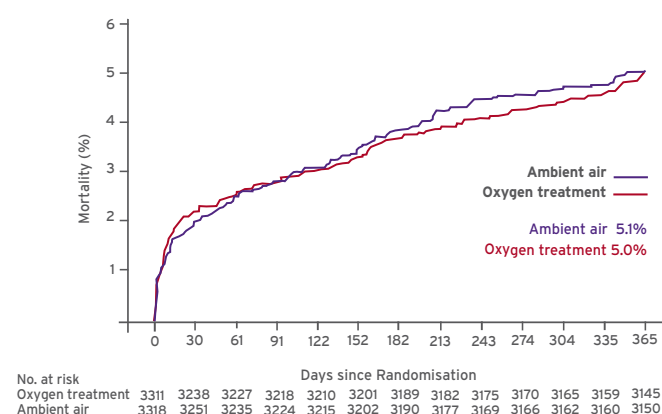
The national SWEDEHEART cardiac registry collects data from 69 Swedish hospitals that provide comprehensive coronary care, and manage over 90% of the annual AMIs in Sweden. Inclusion criteria were classical symptoms of AMI within the previous 6 hours, age ≥ 30 years, oxygen saturation ≥ 90%, and suspected myocardial damage evident by either characteristic electrocardiogram changes or elevated troponin level. Patients already receiving routine oxygen therapy were excluded, as were those who experienced a cardiac arrest before enrollment.

The 6,629 patients with suspected MI were randomised to receive supplemental oxygen delivered at a rate of 6 L/minute for 6-12 hours (median duration 11.6 hours) using an open face mask (n = 3,311) or normal breathing of ambient air (n = 3,318). The primary endpoint in the intention-to-treat population was all-cause death within 1 year post randomisation.

At baseline, the 2 groups were similar demographically and clinically. No patients were lost to follow-up for the primary endpoint.
The primary endpoint of 1-year mortality was similar among the 2 groups (5.0% in the oxygen group vs 5.1% in the ambient air group; HR, 0.97; 95% CI, 0.79 to 1.21; *P* = .80; Figure 1).

Figure 1. Primary Endpoint at 1 Year

No. at risk												
Oxygen treatment	3311	3238	3227	3218	3210	3201	3189	3182	3175	3170	3165	3159	3145
Ambient air	3318	3251	3235	3224	3215	3202	3190	3177	3169	3166	3162	3160	3150

From *The New England Journal of Medicine*, Loscalzo J et al, Oxygen Therapy Beneficial in Acute Myocardial Infarction? Simple Question, Complicated Mechanism, Simple Answer, EPub 28 August 2017. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Cardiac troponin T levels were nearly identical in the 2 groups (*P* = .97). Finally, there was no significant benefit to routine oxygen treatment across subgroups of AMI diagnosis, infarction type, sex, advanced age, smoking, diabetes, chronic kidney disease, anaemia, and prior history of MI or percutaneous coronary intervention.

In conclusion, routine use of oxygen in patients with suspected AMI without hypoxaemia did not reduce 1-year all-cause mortality.

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 International Society on Thrombosis and Haemostasis (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 BID 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. In the aspirin plus rivaroxaban 2.5 mg BID arm, major bleeding was increased by 70% (3.1% vs 1.9%; HR, 1.70; 95% CI, 1.40 to 2.05; P < .001) while the rivaroxaban 2.5 mg BID 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 BID 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 BID; HR, 1.50; P = .03 for rivaroxaban 5 mg BID).

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 BID 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
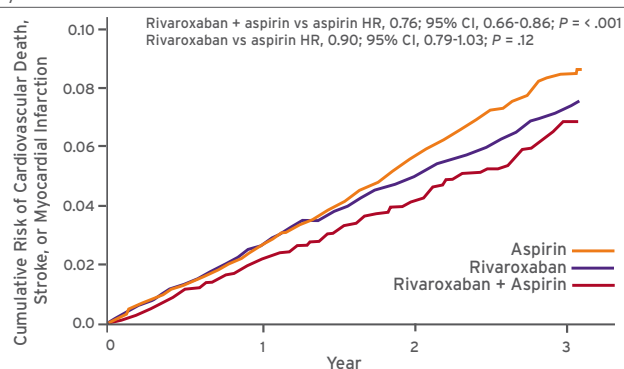
From *The New England Journal of Medicine*, Eikelboom JW et al, Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease, EPub 28 August 2017. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

CANTOS Shows 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), non-fatal 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).

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 1. CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)
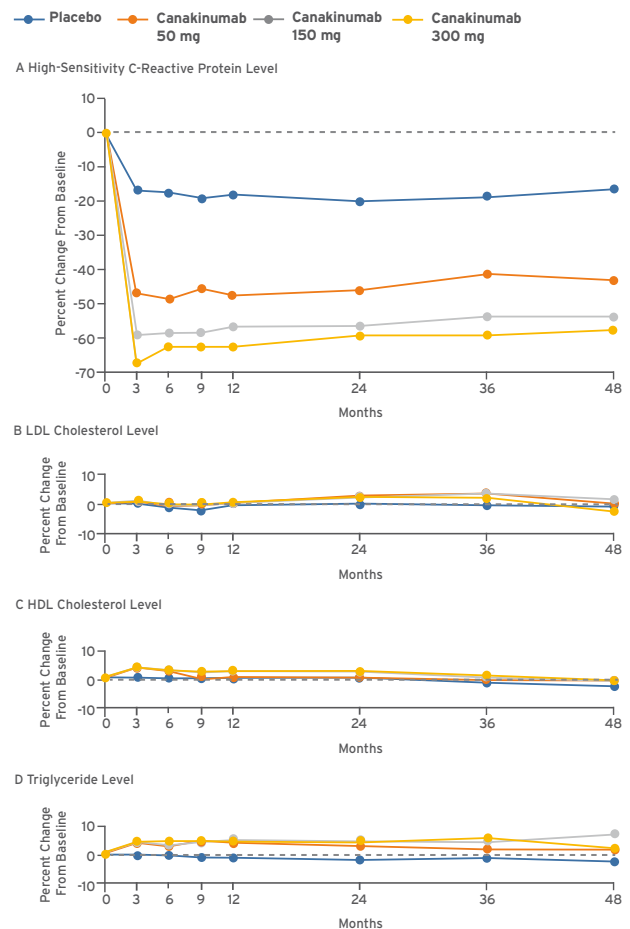
HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

From *The New England Journal of Medicine*, Ridker PM et al, Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease, EPub 27 August 2017. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Figure 2. Primary Endpoint With Canakinumab, 150 mg vs Placebo
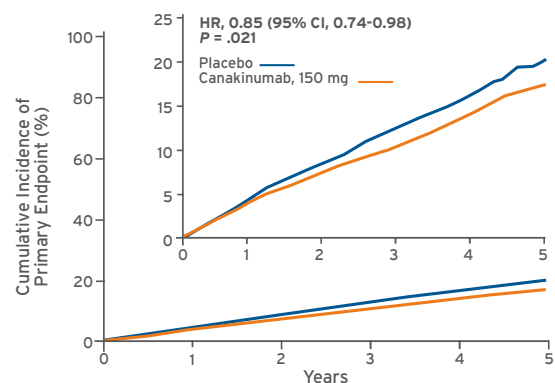
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The 150-mg dose of canakinumab was also associated with significant (*P* = .005) reductions in the key secondary CV endpoint (the components of the primary endpoint plus hospitalisation for unstable angina that led to urgent revascularisation; Figure 3).

Figure 3. Key Secondary Endpoint With Canakinumab, 150 mg vs Placebo
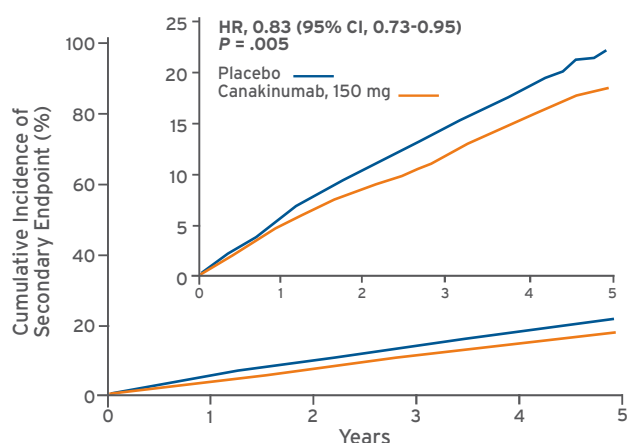
From *The New England Journal of Medicine*, Ridker PM et al, Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease, EPub 27 August 2017. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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* ≤ .02). There was no significant effect on stroke (HR, 0.98; 95% CI, 0.71 to 1.35; *P* = .91), CV death (HR, 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 1.8mg/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]. Sub-clinical 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.

VALIDATE-SWEDEHEART Trial Results

Written by **Toni Rizzo**

Bivalirudin was compared with heparin without planned use of glycoprotein IIb/IIIa inhibitors (GPI) for patients with acute coronary syndrome (ACS) in multiple studies [Cavender MA, Sabatine MS. *Lancet*. 2014]. Prior studies differed in the use of prerandomisation heparin, post-percutaneous coronary intervention (PCI), bivalirudin infusion, and use of potent P2Y$_{12}$ inhibitors [Shahzad A et al. *Lancet*. 2014; Han Y et al. *JAMA*. 2015; Schulz S et al. *Eur Heart J*. 2014]. The aim of the VALIDATE-SWEDEHEART trial [NCT02311231], presented by David Erlinge, MD, PhD, Skane University Hospital, Lund University, Lund, Sweden, was to compare bivalirudin with heparin in patients with ACS (either ST-segment elevation myocardial infarction [STEMI] or non-ST-segment elevation myocardial infarction [NSTEMI]).

In this open-label, registry-based trial, 3,005 patients with STEMI and 3,001 with NSTEMI scheduled for urgent PCI were randomised before the procedure to treatment with bivalirudin (0.75 mg/kg IV bolus followed by 1.75 mg/kg per hour infusion) or unfractionated heparin (70-100 U/kg IV bolus). The use of potent P2Y$_{12}$ inhibitors was required for all the patients prior to PCI. GPI use was not planned. PCI was performed, predominantly with radial artery access. The primary endpoint was the composite of death, MI, or major bleeding events at 180 days.

The SWEDEHEART healthcare registry was used for screening, enrolment, randomisation, case report forms, and follow-up. Study nurses phoned the patients at days 7 and 180 to register bleeding and MI events [Erlinge D et al. *Am Heart J*. 2014].

Prior to PCI, the majority of patients were treated with ticagrelor (94.9%) and the remaining patients were treated with prasugrel, or cangrelor. A total of 25 of 29 Swedish PCI centres participated in the trial. The study included 47.8% of all patients in Sweden presenting at enrolling hospitals with an initial diagnosis of STEMI or NSTEMI planned for PCI. Bailout GPIs were used in 2.4% of the bivalirudin group and 2.8% of the heparin group. After randomisation, 0.6% of patients in the bivalirudin group and 0.4% of patients in the heparin group crossed over to the other treatment group.

At 180 days, the rate of death, MI, or major bleeding events was not significantly different between the bivalirudin and heparin groups (HR, 0.96; 95% CI, 0.83 to 1.10; *P* = .54; Figure 1) [Erlinge D et al. *N Engl J Med*. 2017].

Figure 1. Primary Endpoint: Death, MI, or Major Bleeding at 180 Days
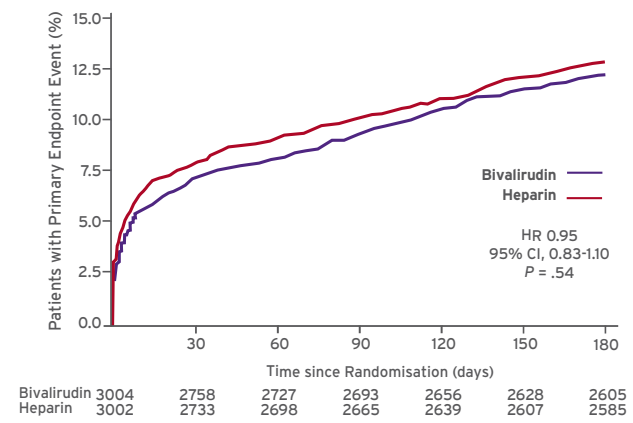
MI, myocardial infarction.

At 180 days, there were no significant differences between the groups in mortality (HR, 1.05; 95% CI, 0.78 to 1.41; *P* = .76), MI (HR, 0.84; 95% CI, 0.60 to 1.19; *P* = .33), or bleeding events (HR, 1.00; 95% CI, 0.84 to 1.19; *P* = .98). Figure 2 shows the bleeding event rates at 30 and 180 days.

Figure 2. Bleeding Event Rates at 30 and 180 Days
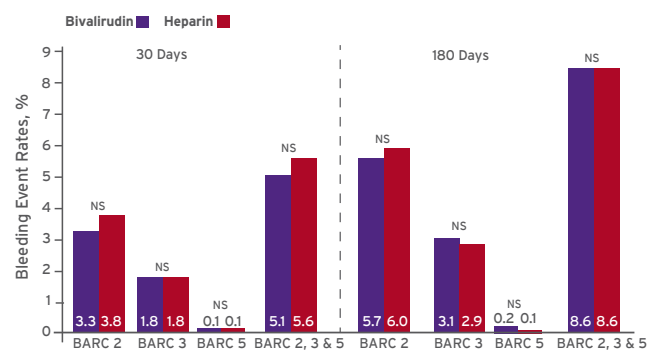
BARC, Bleeding Academic Research Consortium.
Reproduced with permission from D Erlinge, MD, PhD.

Definite stent thrombosis occurred significantly more often in the heparin versus bivalirudin group at 30 days (*P* = .03) but was not significantly different at 180 days (*P* = .09). In a prespecified subgroup analysis of the primary endpoint, there was no significant interaction for

any subgroup, although there was a borderline significantly higher event rate in the heparin versus bivalirudin group (*P* = .051) for females.

The investigators concluded that there were no significant differences between bivalirudin and heparin therapy with respect to mortality, re-infarction, or major bleeding events in patients with STEMI or NSTEMI undergoing PCI.

Virtual Histology Imaging Fails to Detect Benefit of Adding Evolocumab to Statin Therapy to Alter Plaque Composition

Written by **Phil Vinall**

The PCSK9 inhibitor evolocumab lowers LDL-C, induces plaque regression on intravascular ultrasound (IVUS), and reduces cardiovascular events in statin-treated patients with atherosclerotic cardiovascular disease. Its impact on plaque composition is unknown, however.

The GLAGOV trial [NCT01813422] compared the effects of evolocumab (420 mg) or placebo administered monthly for 78 weeks on the progression of coronary atherosclerosis as measured by serial IVUS in patients with angiographic coronary artery disease treated with optimal statin therapy. Stephen J. Nicholls, MBBS, PhD, South Australian Health and Medical Research Institute, Adelaide, Australia, presented the results of a prespecified exploratory analysis from the GLAGOV trial that evaluated the effect of evolocumab on plaque components in the patients who had ultrasound imaging that enabled virtual histology (VH) analysis.

The substudy comprised 331 patients (evolocumab, n = 164; placebo, n = 167). Participants (> 70% men) were a mean age of about 59 years; about 17% had diabetes and about 26% were smokers. Almost 60% of the patients were on high-intensity statin therapy; the rest were on a moderate-intensity statin. The primary endpoint was the absolute change in dense calcium volume from baseline to week 78. Secondary endpoints were the changes in volume occupied by necrotic, fibrofatty, and fibrotic components.

Compared with baseline, at week 78 evolocumab was associated with changes in LDL-C (–62.8%), HDL-C (+11.6%), triglycerides (–11.5%), and lipoprotein(a) (–22.7%) that remained significant after adjustment for changes in the placebo group (*P* < .001 for each, except HDL-C *P* = .02). Using conventional measures of IVUS-derived plaque burden, compared with baseline, there was a significant benefit for evolocumab combined with a statin compared with placebo and statin monotherapy in both percent (–1.20%) and total atheroma volume (–3.6 mm^3; both *P* < .0001).

For the primary endpoint of change from baseline in normalised dense calcium volume based on VH, there was a statistically significant difference in both groups compared with baseline; however, the difference between the 2 treatments was not significant.

On the secondary outcomes, there were significant reductions from baseline in both fibrofatty and fibrous volume for both treatment groups, again with no significant between group difference. There was no change in the size of the necrotic core with either therapy.

When combined with optimal statin therapy, evolocumab produces robust lowering of LDL-C and plaque regression by conventional IVUS. However, VH imaging failed to detect any difference between evolocumab combination therapy and statin monotherapy for individual plaque components. The utility of VH imaging in drug development to assess the effect of anti-atherosclerotic therapies remains uncertain.

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 had 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 2,725 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.

Figure 1. Rates of Major Bleeding or Clinically Relevant Nonmajor Bleeding in RE-DUAL
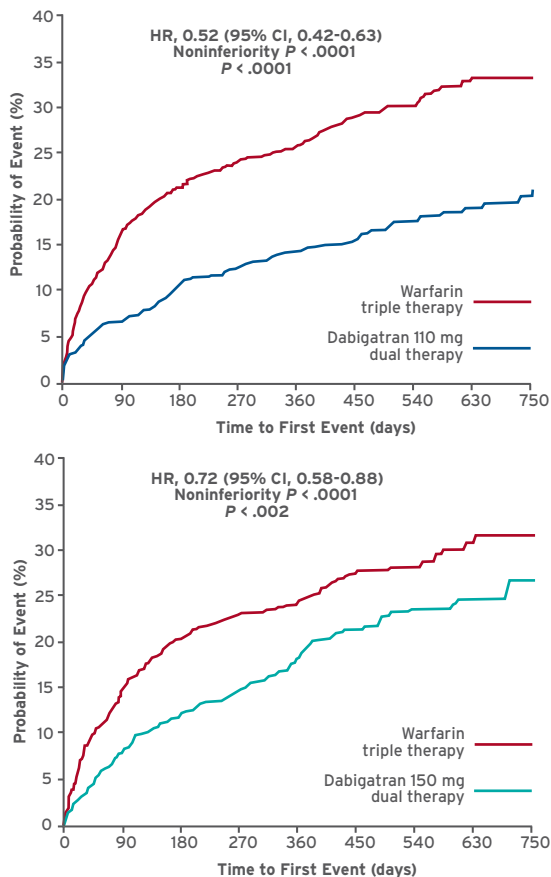
From *The New England Journal of Medicine,* Cannon CP et al, Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. EPub 28 August 2017. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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.

Beta-Blocker Therapy Before Primary PCI Did Not Improve Outcomes in STEMI Patients

Written by **Toni Rizzo**

The METOCARD-CNIC trial is the only randomised study of early β-blockers in the primary percutaneous coronary intervention (PCI) era, but it was not placebo controlled and only studied early β-blockers in patients with anterior infarcts [Ibanez B et al. *Circulation*. 2013; Pizarro G et al. *J Am Coll Cardiol*. 2014]. Vincent Roolvink, MD, Isala Hospital, Zwolle, The Netherlands, presented the 1-year results from the EARLY-BAMI trial, which assessed the long-term clinical effect of early (pre-primary PCI) intravenous β-blockers in patients with ST-segment elevation myocardial infarction (STEMI).

Patients > 18 years aged with > 30 minutes and < 12 hours since symptom onset and electrocardiogram (ECG) showing > 2 mm to > 1 mV ST-elevation or new left bundle branch block were included in the EARLY-BAMI trial, if systolic blood pressure was > 100 mm Hg and heart rate > 60 bpm. The patients (n = 683) were randomised to treatment with intravenous metoprolol (one 5 mg bolus given in the ambulance, and a second 5 mg bolus in the catheterisation laboratory if blood pressure and heart rate permitted) versus placebo before primary PCI. All patients were planned to receive oral metoprolol < 12 hours after PCI, according to current guidelines.

All infarct locations were included in this 1-year planned secondary analysis. Magnetic resonance imaging (MRI) was performed at 1 month and clinical follow-up at 1 year. The 1-year clinical outcomes were major cardiac adverse events (MACE), defined as the composite of cardiac death, nonfatal reinfarction, or target vessel revascularisation.

A total of 336 patients were randomised to metoprolol, 312 of whom participated in the 1-year follow-up. Of the 347 patients randomised to placebo, 317 participated in the 1-year follow-up. The median time from first study dose to reperfusion was 54 minutes.

At 1 year, MACE occurred in 7.7% of patients in the metoprolol group compared with 7.3% in the placebo group (*P* = .835). No significant difference was observed between the metoprolol and placebo groups in the rate of MACE or any of the other outcomes.

A prespecified subgroup analysis at 1 year found no significant difference between the metoprolol and

placebo groups in any of the subgroups comparisons, including patients with anterior infarct versus non-anterior infarct and those with previous β-blocker therapy versus those without (Figure 1).

Figure 1. Prespecified Subgroup Analysis

	Metoprolol	Placebo		Odds Ratio (95% CI)
All patients	24/312 (7.7%)	23/317 (7.3%)		1.07 (0.59-1.93)
Gender				
Female	5/77 (6.5%)	4/74 (5.4%)		1.22 (0.31-4.71)
Male	19/235 (8.1%)	19/243 (7.8%)		1.04 (0.53-2.01)
Interacton *P* value .84				
Location of MI				
Anterior infarct	11/145 (7,6%)	9/153 (5.9%)		1.31 (0.53-3.27)
Non anterior infarct	12/147 (8.2%)	12/139 (8.6%)		0.94 (0.41-2.17)
Interacton *P* value .60				
β-blocker use before inclusion				
β-blocker	6/52 (12%)	9/49 (18%)		0.58 (0.19-1.77)
No β-blocker	17/256 (6.6%)	14/265 (5.3%)		1.28 (0.62-2.64)
Interacton *P* value .25				
Time between first bolus study medication and start PCI				
Time ≤ = median	9/121 (7.4%)	10/142 (7.0%)		1.06 (0.42-2.70)
Time < median	12/142 (8.5%)	11/119 (9.2%)		0.91 (0.38-2.14)
Interacton *P* value .81				

0.1   1   10

Favours Metoprolol   **Favours Placebo**

MI, myocardial infarction.

Reproduced with permission from V Roolvink, MD.

The EARLY-BAMI trial was the largest β-blocker trial in STEMI patients treated with primary PCI. According to Dr Roolvink, the results did not confirm the effect observed in the smaller METOCARD-CNIC trial. Comparing the results of the 2 trials, a trend in MACE reduction was observed at 6 months in METOCARD-CNIC versus no difference at 1 year in EARLY-BAMI. Significant reductions in hospitalisation for heart failure (HF) and implantable cardioverter defibrillator (ICD) implantation were found in the METOCARD-CNIC trial at 6 months versus no difference at 1 year in EARLY-BAMI.

There were several differences in the METOCARD-CNIC trial that might account for the different results. METOCARD-CNIC only included anterior infarctions, had a higher dose of metoprolol (15 mg vs 10 mg in EARLY-BAMI), excluded patients on long-term β-blockers therapy before admission, and had a longer time from β-blocker treatment to primary PCI.

In conclusion, the EARLY-BAMI secondary analysis found no difference at 1 year in MACE, re-admission for HF, or ICD implantation between STEMI patients treated with early pre-hospital IV metoprolol versus placebo. These findings reinforce that there remains no indication for routine early intravenous of β-blocker therapy in acute MI, which remains limited to use in patients with refractory angina or hypertension. In contrast, oral β-blocker therapy remains recommended within 24 hours of presentation.

Empagliflozin Cuts Risk of Death in T2D Patients After CABG

Written by **Nicola Parry**

Empagliflozin is a selective sodium–glucose cotransporter 2 inhibitor that reduces hyperglycemia in patients with type 2 diabetes (T2D) by reducing renal glucose reabsorption, and thereby increasing urinary glucose excretion.

Subodh Verma, MD, PhD, FRCSC, University of Toronto, Canada, reported data from an analysis of the EMPA-REG OUTCOME trial, demonstrating that empagliflozin given in addition to standard of care markedly reduced the rates of cardiovascular (CV) death, all-cause mortality, and hospitalisation for HF (HHF) in patients with T2D with a history of coronary artery bypass graft (CABG) surgery. The analysis compared data from the pooled empagliflozin dose groups (10 mg and 25 mg) with data from the placebo group, in patients who received ≥ 1 dose of the study drug.

The EMPA-REG OUTCOME trial had shown that empagliflozin treatment in addition to standard care led to substantial reductions in the risk of CV death (38%), all-cause mortality (32%), and HHF (35%) compared with placebo 6,314 patients with T2D and established CV disease [Zinman B et al. *N Engl J Med*. 2015].

Overall, 25% of patients treated with empagliflozin and 24% of those treated with placebo had a history of CABG at baseline.

The investigators compared study outcomes between the two treatment groups including: the 3-point major adverse CV event (MACE) composite outcome of CV death, non-fatal myocardial infarction (MI), and stroke; CV death; all-cause mortality; HHF; stroke; MI; and incident or worsening nephropathy. They used a time-to-first-event approach and performed the analyses on the pooled empagliflozin dose groups versus the placebo group.

Among 1,738 patients with a history of CABG (1,175 patients receiving empagliflozin), the 3-point MACE outcome was 10.6% in the pooled empagliflozin group compared with 13.3% in the placebo group.

Compared with placebo, empagliflozin treatment substantially decreased the incidence of CV death (3.0% vs 5.7%; HR, 0.52; 95% CI, 0.32 to 0.84), all-cause mortality (5.1% vs 8.9%; HR, 0.57; 95% CI, 0.39 to 0.83), and HHF (3.3% vs 6.7%; HR, 0.50; 95% CI, 0.32 to 0.77). Empagliflozin treatment was also associated with a decreased incidence of stroke (3.3% vs 2.7%), and MI (5.7% vs 7.1%).

According to Dr Verma, the size of the benefits in the CABG subgroup was at least as large as what was found in the main trial. These findings have important translational implications for secondary prevention after CABG, he concluded.

Pharmacotherapy After STEMI

Written by **Brian Hoyle**

Beta-blockers

Early trials indicated the value of intravenous or oral β-blocker therapy in reducing mortality associated with acute myocardial infarction (AMI). This was quickly updated by other trials in the ensuing decades leading to the recommendation of only oral therapy. As such, oral therapy is now considered the norm, while intravenous β-blockers can be considered for ischaemic patients with no haemodynamic instability or heart failure. In the era of percutaneous coronary intervention (PCI), the value of β-blockers was questioned because of the improved outcome resulting from revascularisation, explained Joseph Alpert, MD, University of Arizona College of Medicine, Tucson, Arizona, USA, at the Pharmacotherapy after STEMI: Current Concepts session on 28 August 2017.

The issue remains contentious in the absence of randomised trials of long-term β-blocker therapy in patients treated with primary PCI. Still, for post-MI patients with normal or near-normal left ventricular ejection fraction, it seems reasonable to begin oral β-blockers therapy and continue the therapy for up to 3 years. The consensus is that for most STEMI patients, β-blockers probably reduce short-term complications and improve long-term survival. The general recommendation from various guidelines is that for patients with no contraindications, oral β-blocker begun within 24 hours of diagnosis is acceptable.

There is much less evidence to support longer term use of β-blockers after STEMI however, for high-risk patients, longer treatment may be better. Conversely, β-blocker therapy might be discontinued for lower risk patients or in select scenarios (Table 1).

Table 1. Discontinuing β-Blocker Therapy

Is it reasonable to discontinue β-blocker therapy at some point?
YES
• Patients with unacceptable side effects
• Financial burden – rare
• Polypharmacy
• Absence of compelling indications such as systolic CHF (LVEF < 40%); ventricular arrhythmias

CHF, chronic heart failure; LVEF, left ventricular ejection fraction.

Lipid-Lowering Agents

Lowering cholesterol levels is associated with significant clinical benefit after STEMI. The various strategies were discussed by François Mach, MD, Geneva University Hospital, Geneva, Switzerland.

LDL-C elevation that occurs in dyslipidaemia should be lowered in patients with a very high cardiovascular (CV) risk with a statin used at the highest recommended or tolerable dose [Catapano AL et al. *Eur Heart J*. 2016; Collins R et al. *Lancet*. 2016]. In cases of statin intolerance, ezetimibe and/or bile acid sequestering agents can be used. If the target LDL-C level is not reached, a statin in combination with a cholesterol absorption inhibitor can be used.

While target levels are provided in the guidelines, the evidence from various analyses of over 170,000 patients [Cholesterol Treatment Trialists' Collaboration. *Lancet*. 2010] and the IMPROVE-IT trial [Cannon CP et al. *N Engl J Med*. 2015] indicate that lower levels of LDL-C are associated with reductions in CV risk. However, the reality is that relatively few patients achieve the target LDL-C goal. In the SPUM-ACS trial [Gencer B et al. *Atherosclerosis*. 2015] the success rate was only 30%.

For these patients, treatment with an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) may be warranted. The efficacy and safety of the human monoclonal antibody to PCSK9 evolocumab, in plaque regression [Nicholls SJ et al. *JAMA*. 2016] and risk reduction of CV events have been impressively demonstrated [Giugliano RP et al. *Lancet*. 2017; Sabatine MS et al. *N Engl J Med*. 2017], with no detriment of evolocumab on cognitive function [Giugliano RP et al. *N Engl J Med*. 2017].

Targeting PCSK9 may in addition have merit in the treatment of acute coronary syndrome (ACS) [Navarese EP et al. *Ann Intern Med*. 2016]. The EVOPACS trial comparing evolocumab plus rosuvastatin with placebo plus rosuvastatin will hopefully clarify this issue.

The timing of the reduction of LDL-C is also clinically relevant, with a more rapid reduction delaying the onset of coronary heart disease [Nordestgaard BG et al. *Eur Heart J*. 2013].

Dual Antiplatelet Therapy (DAPT)

The issue of extending dual antiplatelet therapy (DAPT) beyond 1 year in acute coronary syndrome (ACS) patients was discussed by Deepak Bhatt, MD, MPH, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA. The benefits of DAPT with aspirin along with clopidogrel or ticagrelor in ACS are clear [Wallentin L et al. *N Engl J Med*. 2009; Bhatt DL et al. *J Am Coll Cardiol*. 2007; Bhatt DL et al. *N Engl J Med*. 2006]. However, the duration of therapy remains uncertain. The longer-term protection from atherothrombotic events might be counterbalanced by an increased risk of major bleeding.

The results of the PEGASUS-TIMI 54 trial provided evidence of the longer-term accrual of benefits from DAPT using 60 mg ticagrelor twice daily [Bonaca MP et al. *N Engl J Med*. 2015], with comparable relative risk benefit for diabetic and nondiabetic patients [Bhatt DL et al. *J Am Coll Cardiol*. 2016]. The results from the ongoing THEMIS trial [NCT01991795] will specifically address the effects of long-term DAPT involving ticagrelor in 19,000 patients with diabetes at high risk for CV events.

In patients who have experienced an MI, long-term DAPT appears beneficial in terms of reduced CV death, MI, or stroke, with an increase in major bleeding [Udell JA et al. *Eur Heart J*. 2016. The 2017 ESC Focused Update on DAPT in Coronary Artery Disease [Valgimigli M et al. *Eur Heart J*. 2017] provides the following recommendations concerning the duration of therapy (Table 1).

Table 1. DAPT Duration in ACS Patients Treated With PCI

Recommendations	Class	Level
In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.	IIb	A
In patients with MI and high ischaemic risk who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg BID for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.	IIb	B

ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; MI, myocardial infarction.

Adapted from Valgimigli M et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J*. 2017.

The main considerations regarding the optimal duration of DAPT is summarised in Table 2 [Eisen A, Bhatt DL. *Nat Rev Cardiol*. 2015].

Table2. Factors Regarding the Optimal Duration of DAPT

	≤ 12 Months DAPT	≥ 12 Months DAPT
Patient-related factors	Patients with stable CAD	Patients with ACS
	Patients with bleeding history Patients with high risk of bleeding	Patients with diabetes Patients with renal dysfunction Patients with CHF Patents with previous ST Patients with PAD
Anatomy-related factors	Short lesion Single vessel disease	Long lesion Small vessel Bifurcation lesion Complex anatomy Left main coronary artery
Stent-related factors	Second generation DES	First generation DES Long stent Multiple stents

ACS, acute coronary syndrome; CAD, coronary artery disease; CHF, chronic heart failure; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; PAD, peripheral artery disease.

Non–vitamin K Antagonist Oral Coagulation Post STEMI

Dan Atar, MD, Oslo University Hospital Ullevål, Oslo, Norway, discussed non–vitamin K antagonist oral coagulation (NOAC) therapy following STEMI. The persistent elevation of thrombin up to a year following an ACS event creates an environment favouring formation of coronary artery thrombi [Ardissino D et al. *Blood*. 2003]. Warfarin- and aspirin-mediated anticoagulation have long been known to be protective following MI [Hurlen M et al. *N Engl J Med*. 2002; Andreotti F et al. *Eur Heart J*. 2006].

More recent studies have explored the efficacy of NOACs. The APPRAISE-2 randomised controlled trial of twice-daily apixaban plus antiplatelet therapy documented increased major bleeds compared with antiplatelet therapy alone without a significant reduction in recurrent ischaemic events in high-risk patients following an ACS [Alexander JH et al. *N Engl J Med*. 2011]. Likewise, increased bleeding and other complications were also observed with dabigatran in the RE-DEEM randomised controlled trial [Oldgren J et al. *Eur Heart J*. 2011] and with rivaroxaban in ATLAS ACS-TIMI 46 [Mega JL et al. *Lancet*. 2009]. However, a breakthrough was reached when using very low doses of Rivaroxaban in the Phase 3 ATLAS-TIMI 51 study [Mega JL et al. *N Engl J Med*. 2012]. In this population post ACS, rivaroxaban 2.5 mg BID on top of antiplatelet therapy (mostly aspirin and clopidogrel) led to a reduction in stent thrombosis, CV death, MI, or stroke as well as, notably, in all-cause mortality during the 24-month study period. This strong evidence has given rise to a recommendation in the 2012 ESC STEMI guideline, reinforced in the 2017 ESC STEMI guideline (Table 3) [Ibanez B et al. *Eur Heart J*. 2017].

Interestingly, at the same time of the ATLAS-II trial, strong evidence from the TRITON-TIMI 38 study using prasugrel instead of clopidogrel and the PLATO trial using ticagrelor instead of clopidogrel emerged supporting a more aggressive platelet inhibition. As discussed earlier in this article, the pertinent recommendations in the STEMI guidelines are strongly in favour of ticagrelor and prasugrel, diminishing the utility of low-dose rivaroxaban, since the ATLAS-II trial did not test these two newer antiplatelet agents. Hence, for now, according to Dr Atar, there has been limited clinical utility of oral anticoagulation following STEMI. The just-released findings of the COMPASS trial [Eikelboom JW et al. *N Engl J Med*. 2017] could inform treatment recommendations post STEMI, but are valid only in patients with stable CAD and hence not in the acute phase.

Table 3. Maintenance Antithrombotic Strategy After STEMI

Recommendations	Class	Level
Antiplatelet therapy with low-dose aspirin (75-100 mg) is indicated.	I	A
DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding.	I	A
A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding.	I	B
In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy.	I	C
In patients who are high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.	IIa	B
In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy should be considered for 1-6 months (according to a balance between the estimated risk of recurrent coronary events and bleeding).	IIa	C
DAPT for 12 months in patients who did not undergo PCI should be considered unless there are contraindications such as excessive risk of bleeding.	IIa	C
In patients with LV thrombus, anticoagulation should be administered for up to 6 months guided by repeated imaging.	IIa	C
In high ischaemic-risk patients who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg BID on top of aspirin for longer than 12 months may be considered for up to 3 years.	IIb	B
In low-bleeding-risk patients who receive aspirin and clopidogrel low-dose rivaroxaban (2.5 mg BID) may be considered.	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombtic therapy with aspirin and oral anticoagulation.	III	C

DAPT, dual antiplatelet therapy; LV, left ventricular; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.

Reprinted from Ibanez B, James S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017; doi:10.1093/eurheartj/ehx419. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Use of P2Y$_{12}$ Inhibitors for Treatment of Acute Coronary Syndromes

Written by **Nicola Parry**

Deepak L. Bhatt, MD, MPH, Harvard Medical School, Boston, Massachusetts, USA, opened the State of the Art: P2Y$_{12}$ Inhibitors in Acute Coronary Syndromes session on 29 August 2017 with a review of some of the landmark studies of P2Y$_{12}$ inhibitors, beginning with the CURE trial. CURE evaluated the efficacy and safety of clopidogrel plus aspirin in patients with acute coronary syndromes (ACS) without ST-segment elevation (NSTE-ACS). Results showed a significant benefit for clopidogrel on the composite endpoint of death from cardiovascular (CV) causes, nonfatal myocardial infarction (MI), or stroke (RR vs placebo 0.80; 95% CI, 0.72 to 0.90; *P* < .001) but at the risk of increased major (but not life-threatening) bleeding (3.7% vs 2.7%; RR, 1.38; *P* = .001) [Yusuf S et al. *N Engl J Med*. 2001].

Similarly, increased bleeding was noted in the TRITON trial, which compared prasugrel with clopidogrel in patients with moderate- to high-risk ACS scheduled for percutaneous coronary intervention (PCI). Prasugrel significantly reduced ischaemic risk versus clopidogrel, but prasugrel increased the risk of major bleeding (HR, 1.32; 95% CI, 1.03 to 1.68; *P* = .03) and life-threatening bleeding (1.4% vs 0.9%; *P* = .01) [Wiviott SD et al. *N Engl J Med*. 2007].

For the PLATO trial which compared ticagrelor and clopidogrel for the prevention of CV events in patients with ACS with or without ST-segment elevation, Dr Bhatt noted that ticagrelor significantly reduced the rate of death from CV causes, MI, or stroke. There was no significant difference in the rates of major bleeding but ticagrelor was associated with a higher rate of major bleeding not related to coronary artery bypass grafting (CABG; 4.5% vs 3.8%, *P* = .03), including more instances of fatal intracranial bleeding [Wallentin L et al. *N Engl J Med*. 2009].

Patients With NSTE-ACS

Dual therapy with aspirin and a P2Y$_{12}$ inhibitor has become standard of care for patients with NSTE-ACS, said Patrick Riedmaier, MD, Clinic of the City of Ludwigshafen, Germany. Randomised head-to-head trials comparing the new P2Y$_{12}$ inhibitors are lacking, however, and the guidelines do not specify which agent clinicians should choose. Prof Riedmaier conducted a study to compare the intrahospital efficacy and safety of ticagrelor versus prasugrel in patients with NSTE-ACS who underwent PCI. The study was based on data from the German ALKK-PCI registry, which includes > 16,000 consecutive patients treated with ticagrelor, prasugrel, or clopidogrel at 40 hospitals in Germany. Patients treated with clopidogrel were excluded from the analysis. A subanalysis was performed for patients for whom prasugrel is not recommended (ie, those with a history of transient ischaemic attack or stroke, aged ≥75 years, and/or body weight < 60 kg; Core Population).

The study comprised 6,183 patients (ticagrelor, n = 4,269; prasugrel, n = 1,914. In clinical practice ticagrelor was used more often than prasugrel. Patients treated with ticagrelor were older (68.7 vs 61.1 years; P < .001) than those who received prasugrel, and were more likely to be women (28.9% vs 21.7%; P < .001). They also had more comorbidities, including peripheral artery disease (9.5% vs 6.0%; P < .001) and renal insufficiency (19.2% vs 11.2%; P < .001), and were also more likely to have undergone prior coronary artery bypass grafting (10.0% vs 5.8%; P < .001). Prasugrel patients in the Core Population (ticagrelor, n = 2,716; prasugrel, n = 1,656) were also older and sicker compared with those who received ticagrelor.

The rates for nonfatal stroke and bleeding complications (defined as severe bleeding requiring transfusion) were similar between the 2 treatments, despite numerically more bleeds in the prasugrel group overall and in the Core Population. In-hospital mortality and the short-term safety profile were also comparable. The highest rates of in-hospital mortality and major adverse cardiovascular and cerebrovascular events (MACCE) were in ticagrelor patients both overall and in the Core Population (1.6% and 1.9% vs 1.0% and 1.2%; in-hospital mortality and MACCE, ticagrelor vs prasugrel, respectively). In-hospital outcomes for the Core Population are shown in Table 1. This study is limited in that no long-term follow-up is available.

Table 1. Propensity Score Analysis: Core Population In-hospital Outcome

Outcome	OR (95% CI)	P value
Nonfatal stroke	1.93 (0.17 – 21.34)	.6
Bleeding	0.57 (0.22 – 1.42)	.2
In-hospital mortality	1.06 (0.49 – 2.29)	.9
MACCE	1.17 (0.58 – 2.39)	.7

MACCE, major adverse cardiovascular and cerebrovascular event.

Patients With ACS and CKD

Among patients in the PLATO trial who had both ACS and CKD, ticagrelor was a more effective than clopidogrel in reducing ischaemic end points (HR, 0.77; 95% CI, 0.65 to 0.90) and mortality (HR, 0.72; 95% CI, 0.58 to 0.89) without a significant increase in major bleeding regardless of renal function. The benefits were larger with worse poor renal function and without the need for dose reduction to prevent major bleeding [James S et al. *Circulation*. 2010].

However, according to Robert Edfors, MD, Karolinska Institute, Stockholm, Sweden, clinical data are lacking on the comparative efficacy of these drugs in MI patients with renal dysfunction. He reported findings from a recent study that used data from the Swedish MI registry (SWEDEHEART). The study included 45,206 MI patients 36,392 of whom underwent PCI. Patients were stratified by creatinine based estimated glomerular filtration rate (eGFR) > 60 (n = 33,668), 30-60 (n = 9,803), and < 30 mL/min/m^2 (n = 1,735) based on using the Chronic Kidney Disease Epidemiology Collaboration [Levey AS et al. *Ann Intern Med*. 2009].

At 1 year, patients on ticagrelor had a lower risk for the combined primary endpoint of death, MI, or stroke and for the secondary endpoint of death in patients with eGFR 30-60 and eGFR > 60 compared with those who received clopidogrel. The benefit of ticagrelor in patients with eGFR < 30 mL/min/m^2 was unclear, concluded Dr Edfors, and additional studies in this patient subgroup are needed.

Future Perspectives

Based on current and emerging evidence, Robert F. Storey, MD, University of Sheffield, United Kingdom, believes that DAPT will remain the mainstay of antithrombotic therapy following PCI and ACS, because of its effectiveness in preventing broad ischaemic events and acute stent thrombosis, despite an increased risk of nonfatal major bleeding. He highlighted some recommendations from the recently published expert consensus paper of the European Society of Cardiology Working Group on Thrombosis [Halvorsen S et al. *Eur Heart J*. 2017], which recommends that clinicians resume oral antithrombotic therapy after a bleeding event in all cases with a clear indication for therapy, provided that the bleeding is not life-threatening. The guidelines also indicate that prolonged discontinuation of antithrombotic therapy following bleeding events, should be avoided, whenever feasible. Dr Storey also highlighted data from PLATO and PEGASUS-TIMI 54 demonstrating that GDF-15 concentration differentiated patients with low and high bleeding risk.

Discussing new clinical trials in P2Y$_{12}$ inhibitors, Dr Storey noted the GLOBAL LEADERS trial [NCT01813435] that is currently ongoing in all-comer patients undergoing PCI with bivalirudin and BioMatrix drug-eluting stents. This trial will evaluate effectiveness of ticagrelor alone for 23 months after 1 month of DAPT versus 12-month standard DAPT, for long-term prevention of adverse cardiac events. The TWILIGHT study [Baber U et al. *Am Heart J*. 2016] is also enrolling, he added, and will compare use of ticagrelor alone adverse standard therapy with ticagrelor and aspirin in high-risk PCI patients.

Considering all available and emerging data, future studies should aim to identify optimal individualised antithrombotic regimens, Dr Storey concluded.