

Acute myocardial infarction

Grant W Reed, Jeffrey E Rossi, Christopher P Cannon



Acute myocardial infarction has traditionally been divided into ST elevation or non-ST elevation myocardial infarction; however, therapies are similar between the two, and the overall management of acute myocardial infarction can be reviewed for simplicity. Acute myocardial infarction remains a leading cause of morbidity and mortality worldwide, despite substantial improvements in prognosis over the past decade. The progress is a result of several major trends, including improvements in risk stratification, more widespread use of an invasive strategy, implementation of care delivery systems prioritising immediate revascularisation through percutaneous coronary intervention (or fibrinolysis), advances in antiplatelet agents and anticoagulants, and greater use of secondary prevention strategies such as statins. This seminar discusses the important topics of the pathophysiology, epidemiological trends, and modern management of acute myocardial infarction, focusing on the recent advances in reperfusion strategies and pharmacological treatment approaches.

Epidemiology

Acute myocardial infarction is the most severe manifestation of coronary artery disease, which causes more than 2·4 million deaths in the USA, more than 4 million deaths in Europe and northern Asia,¹ and more than a third of deaths in developed nations annually.² Increased use of evidence-based therapies and lifestyle changes have spurred considerable reductions in mortality from coronary heart disease in recent decades.¹ However, myocardial infarction retains a substantial footprint on global health, affecting more than 7 million individuals worldwide each year. Concordantly, its economic impact is tremendous; in 2010, more than 1·1 million US hospitalisations were a result of myocardial infarction, with estimated direct costs of at least US\$450 billion.³

Since the mid-1990s there has been a steady decline in the proportion of patients with ST-segment elevation myocardial infarction (STEMI), and a smaller increase in non-STEMI (NSTEMI), leading to an overall decline in myocardial infarction.² Today, NSTEMI comprises 60–75% of all myocardial infarctions.^{2,4} Further, both in-hospital and 1-year mortalities from STEMI have declined in the past two decades (5–6% and 7–18%, respectively),⁴ a testament to advances in pharmacological, reperfusion, and preventive strategies.

Pathophysiology

Acute myocardial infarction is divided into STEMI and NSTEMI.⁵ Unstable angina is also considered an acute coronary syndrome (ACS), because it is an imminent precursor to myocardial infarction. Unstable angina has a similar pathophysiology to NSTEMI, and they are together referred to as non-ST-segment elevation ACS (NSTEMI-ACS). They have traditionally been grouped together for management decisions. In most cases, myocardial infarction is due to disruption of a vulnerable atherosclerotic plaque or erosion of the coronary artery endothelium (type 1).^{5,6} A severe stenosis (ie, $\geq 70\%$ diameter) is required to precipitate angina; however, such stenoses less commonly cause type 1 myocardial infarction, because they tend to have dense fibrotic caps that are less

likely to rupture, and collateral circulation forms over time. By contrast, vulnerable plaques tend to have 30–50% stenosis, thin fibrous caps, and contain more inflammatory cells such as lipid-laden macrophages.^{5,6} Upon rupture, the plaque releases its thrombogenic contents, causing platelet activation, initiation of the coagulation cascade, mural thrombus formation, and embolisation of atherosclerotic debris downstream. This hypercoagulable state could contribute to the rupture of additional vulnerable fibroatheromas, and thus there can be more than one culprit lesion.⁶ The end result is myocyte necrosis, detectable by elevation of cardiac biomarkers in the peripheral blood. The factors influencing severity of ischaemia include whether the vessel was partially or completely occluded, duration of occlusion, amount of myocardium supplied, presence of collaterals, and the adequacy of reperfusion following treatment.

Diagnosis

A combined task force of major professional societies revised the definition of myocardial infarction in 2012 to reflect any event leading to myocardial ischaemia causing cardiac myocyte cell death, and suggested myocardial infarction be classified by its pathological cause into five types (appendix p 5).⁵ In each case, the diagnosis of myocardial infarction relies on biomarker evidence of

Lancet 2017; 389: 197–210

Published Online

August 5, 2016

[http://dx.doi.org/10.1016/S0140-6736\(16\)30677-8](http://dx.doi.org/10.1016/S0140-6736(16)30677-8)

This online publication has been corrected. The corrected version first appeared at the lancet.com on January 12, 2017

Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH, USA (G W Reed MD, J E Rossi MD); and Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Executive Director Cardiometabolic Trials, Harvard Clinical Research Institute, Boston, MA, USA (Prof C P Cannon MD)

Correspondence to: Prof Christopher P Cannon MD, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 930 W Commonwealth Ave, 3rd floor, Boston, MA 02215, USA christopher.cannon@hcr.i.harvard.edu

See Online for appendix

Search strategy and selection criteria

We searched MEDLINE between Jan 1, 2002, and Dec 31, 2015, with the following search terms: "ST segment elevation myocardial infarction", "non-ST segment myocardial infarction", "acute coronary syndrome", "myocardial infarction", "fibrinolysis", "thrombolysis", "angioplasty", "stent", "cardiogenic shock", "anti-platelet therapy", "anti-thrombotic therapy", "clinical guidelines", "quality of care", and "survival". Additionally, we reviewed the reference lists of manuscripts identified by this search strategy and the major guideline texts. We selected sources judged to be most relevant to contemporary practice, and modified our reference list on the basis of comments from peer reviewers.

myocyte necrosis, and either electrocardiographic (ECG) criteria of ischaemia or infarction, or ischaemic symptoms, or both.^{5,7} Although beyond the scope of this Seminar, the appendix (p 1) provides a brief overview of ECG changes consistent with myocardial infarction.

Cardiac troponin (cTn) isoforms I and T have emerged as the preferred diagnostic biomarkers, because they are highly sensitive and specific for myocardial injury, detectable within 2–3 h, and peak within 24–28 h.⁸ The advent of high-sensitivity cardiac troponin T (hs-cTnT) has led to a 20% increase in the diagnosis of NSTEMI and concomitant reduction in the diagnosis of unstable angina.⁹ The 2015 European Society of Cardiology (ESC) NSTEMI-ACS guidelines embrace using the change in hs-cTnT within 1 or 3 h to rule out NSTEMI where applicable. Although beyond the scope of the present review, when used in conjunction with ECG findings and overall clinical presentation, the negative predictive value for myocardial infarction in patients with hs-cTnT below the upper limit of normal on two consecutive checks at least 1 h apart might approach 98%, with a positive predictive value of 75–80%.⁹ Although available in Europe, the hs-cTnT assays have yet to be approved in the USA.

Creatine kinase myocardial band (CK-MB) follows similar kinetics as cTn; although a CK-MB to total CK ratio of 2–5% or more is specific for myocardial injury, it is relatively insensitive for detecting small myocardial infarctions, and both European and US guidelines emphasise the use of cTn as the preferred biomarker for diagnosis of acute myocardial infarction.^{9,10} A limitation of cTn is that it can remain in the circulation up to for 7–10 days, or longer in patients with renal failure. Thus, early ischaemic events might not be detected with serial

cTn unless cTn is falling and subsequently rises again, or stays persistently elevated despite an expected fall. Although CK-MB can be used to detect recurrent myocardial injury, this might miss small repeat infarctions, because it is not as sensitive as cTn.

Risk assessment

Early risk stratification of patients with myocardial infarction allows for prognostication and triage via initiation of one of several vital treatment pathways. Several clinical prediction scores estimate short-term and long-term risks of recurrent ischaemic events and death after myocardial infarction. The TIMI risk score is easiest to use, whereas GRACE is more accurate, comprehensive, and applicable to both NSTEMI and STEMI (appendix p 2).¹¹ Dedicated STEMI risk scores also exist, but they largely predict death and are less used in clinical practice. Additionally, biomarkers such as C-reactive protein and B-type natriuretic peptide could help to further risk-stratify patients at intermediate risk. However, these biomarkers have yet to be incorporated into large, strategy-based studies. There are currently no guideline-approved treatment pathways based on any biomarker other than cTn.

Reperfusion and revascularisation strategies

General principles

In NSTEMI, antithrombotic therapy is thought to stabilise the vulnerable plaque and allow endogenous fibrinolysis to restore patency.¹² Percutaneous coronary intervention (PCI) is usually pursued to improve blood flow and prevent recurrent ischaemia. PCI should be done within 24 h of NSTEMI if possible, but some studies suggest that PCI could be done in low-risk patients up to 48–72 h without clinical consequence.¹³ However, doing PCI after 24 h has been associated with longer hospitalisation,¹⁴ which could increase costs, therefore reducing quality of care. Conversely, in STEMI, priority should be given to immediate reperfusion to limit infarct size, and antithrombotic therapy is used adjunctively (appendix p 3).^{4,15,16} Similarly, patients with NSTEMI and high-risk features or elevated risk scores (figure 1 and appendix p 2) require urgent revascularisation, emphasising the importance of early risk stratification.^{10,16,17}

For STEMI, patients usually have complete arterial occlusion, and as such reperfusion is needed to restore patency as quickly as possible (eg, within 60–90 min; appendix p 3). Patients who undergo fibrinolysis often have residual stenosis, and a reduction in this stenosis with subsequent angioplasty or stenting, or both, improves perfusion and prevents acute reocclusion. For NSTEMI, the artery is usually patent but severely stenosed with a ruptured plaque. The goal is to prevent progression of the thrombus to complete occlusion. The timeframe is broader, measured in hours to days, but more immediate if there is active ongoing ischaemic pain or haemodynamic compromise (figure 1, panel 1).

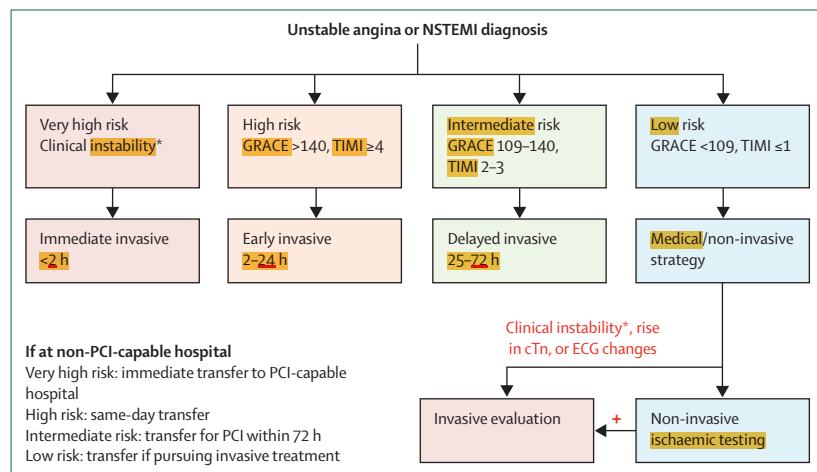


Figure 1: Reperfusion strategies for the triage and treatment of unstable angina or NSTEMI

Simplified reperfusion schematic demonstrating the different reperfusion strategies for unstable angina or NSTEMI. Immediate, early, delayed invasive, or conservative strategies might be appropriate, depending on overall patient risk. Non-invasive testing typically involves nuclear myocardial perfusion imaging or stress echocardiogram, less often cardiac CT or MRI. *Angina refractory to medical therapy, cardiogenic shock, Killip III–IV heart failure, ventricular tachycardia or fibrillation. cTn=cardiac troponin. ECG=electrocardiographic. NSTEMI=non-ST-segment elevation myocardial infarction. PCI=percutaneous coronary intervention.

STEMI

Both US and European guidelines recommend reperfusion therapy be administered as quickly and effectively as possible for STEMI (appendix p 3).^{4,15,16} Several large studies showed that patients who receive reperfusion more rapidly have a smaller infarct size and lower mortality than those who have a delay in treatment.¹⁸ The reperfusion strategy should be chosen balancing which therapy would most likely completely restore arterial patency in the shortest time.

Primary PCI

First medical contact to time of primary PCI

Total ischaemic time should be kept to 120 min or less, and ideally 60 min or less. To achieve this goal, guidelines recommend a first medical contact to time of primary PCI (also known as first medical contact-to-device, or door-to-balloon time) of 90 min or less, because this time correlates with improved morbidity and mortality.^{4,15,18} For patients just outside of the 90-min time window, results of the PRAGUE-2 and DANAMI-2 trials suggest that transfer to a PCI-capable hospital is safe and decreases mortality compared with fibrinolysis,^{19–21} and is advised if it can be completed in 120 min or less (appendix p 3).^{4,15}

Balloon angioplasty versus stenting

Stent placement decreases target vessel revascularisation and subsequent myocardial infarction compared with balloon angioplasty alone.^{22,23} Several studies and meta-analyses show that drug-eluting stents (DES) reduce target vessel revascularisation compared with bare-metal stents (BMS),^{24–26} and some studies suggest that DES might also reduce major adverse cardiac events (MACE) in some patients.^{27–29} Concurrently, the 2014 ESC revascularisation guidelines recommend DES exclusively in patients with acute myocardial infarction.¹⁶

Routine aspiration thrombectomy

Two recent trials (TOTAL³⁰ and TASTE³¹) showed that routine aspiration thrombectomy does not reduce mortality, recurrent myocardial infarction, heart failure, or cardiogenic shock, but might increase the risk of stroke within 30 days. As such, although catheter-based aspiration thrombectomy can be an effective adjunct therapy during primary PCI, it should be reserved for patients with a large thrombus burden and should not be the default strategy.

Operator experience and vascular access

There is evidence that operator inexperience is associated with higher mortality after primary PCI. The appendix (p 6) outlines recommendations regarding minimal operator volume.^{32–34} Two meta-analyses showed that compared with femoral access, radial access for primary PCI is associated with fewer vascular complications and could reduce mortality,^{35,36} with some studies suggesting reduced MACE and hospitalisation duration.^{35,37} These

findings were reinforced by the recent MATRIX study of 8404 patients with STEMI and NSTEMI-ACS, which found that compared with femoral access, the radial approach significantly reduced major bleeding (1.6% vs 2.3%, relative risk [RR] 0.67, 95% CI 0.49–0.92; $p=0.013$) and all-cause mortality (1.6% vs 2.2%, RR 0.72, 95% CI 0.53–0.99; $p=0.045$).³⁸ Although in subgroup analysis patients with NSTEMI-ACS benefited most, neither approach appeared advantageous in STEMI.³⁸ Regardless, ESC guidelines embrace radial access as the preferred approach for primary PCI.^{9,16}

Fibrinolysis**Role in the triage of STEMI**

Thrombolytic agents promote the conversion of endogenous plasminogen to plasmin, which lyses fibrin and dissolves clots.^{39–43} Fibrinolysis is estimated to reduce mortality by 29% compared with placebo in STEMI.^{40,42} That said, several trials indicate that primary PCI with balloon angioplasty or stenting, or both, should be preferred to fibrinolysis,^{20,21,44} because PCI more reliably and completely restores perfusion. In a meta-analysis of 23 trials, primary PCI improved short-term major adverse cardiac and cerebrovascular events (MACCE) compared with fibrinolysis (8% vs 14%; $p<0.0001$), with a persistent long-term reduction.⁴⁴

Panel 1: Clinical features useful for guiding the timing of revascularisation for unstable angina or NSTEMI**Immediate invasive (<2 h)**

- Refractory angina (despite therapies)
- Heart failure—Killip III–IV
- Sustained ventricular tachycardia or fibrillation (or arrest)
- Haemodynamic instability

Early invasive (2–24 h)

- High-risk score (TIMI ≥ 4 , GRACE >140)
- Persistent high-risk or dynamic electrocardiographic changes
- ST elevation not meeting STEMI criteria

Delayed invasive (25–72 h)

- No features requiring an immediate or early invasive strategy
- Intermediate-risk score (TIMI 2–3, GRACE 109–140)
- Recurrent angina or signs of ischaemia despite therapies
- Ejection fraction $<40\%$, diabetes, renal insufficiency (estimated glomerular filtration rate <60 mL/min/1.73 m²), prior coronary artery bypass grafting, or percutaneous coronary intervention within 6 months

Ischaemia-guided strategy

- No features requiring an immediate, early, or delayed strategy
- Low-risk score (TIMI ≤ 1 , GRACE <109)
- Patient preference

NSTEMI=non-STEMI. STEMI=ST elevation myocardial infarction.

Fibrinolysis can play an important role in the treatment of STEMI if primary PCI is not readily available.⁴⁵ An analysis of about 19 000 patients from the National Registry of Myocardial Infarction (NRM1) 2, 3, 4, and 5 studies showed that **when delays in door-to-balloon time are 120 min or more, the survival benefit of PCI over fibrinolysis is lost.**⁴⁵ By contrast, a meta-analysis of 25 randomised trials, including NRM1 2, 3, and 4 suggested **primary PCI was associated with lower 30-day mortality than fibrinolysis, irrespective of treatment delay.**⁴⁶ Regardless, guidelines from both American College of Cardiology (ACC)/American Heart Association (AHA) and **ESC recommend fibrinolysis** for patients with **STEMI who present within 12 h of symptom onset in whom PCI will be delayed by 120 min or more**, if it can be given within 30 min of first medical contact (appendix p 3), and there are no contraindications (appendix p 7).^{4,15} Importantly, **fibrinolysis** should be given only in STEMI; it is **contraindicated in NSTEMI**, because studies have shown that the risks outweigh the benefits.

Choice of thrombolytic agent

The available pharmacological reperfusion agents include streptokinase, tissue plasminogen activator (tPA), and its **recombinant forms (alteplase, reteplase, and tenecteplase)**. tPA and its **recombinant forms** are more **fibrin-specific** and more **effective** at restoring perfusion and reducing mortality than streptokinase.^{39,41} Both **tPA and alteplase must be given as continuous infusions over 90 min**; however, **reteplase** can be given as **two separate boluses 30 min apart**. Reteplase had a trend toward improved mortality over streptokinase and was non-inferior to alteplase in the INJECT and GUSTO-III trials, respectively.^{43,47} Furthermore, ASSENT-2 randomly assigned patients with STEMI to alteplase or tenecteplase given in a single bolus (in addition to aspirin and heparin), and found that adjusted 30-day mortality was equivalent, but there was less non-cerebral bleeding and need for blood transfusion with tenecteplase.⁴⁸ Cost considerations are also a major factor in agent choice.

Very early PCI after fibrinolysis (rescue and facilitated PCI)

Fibrinolysis is only 33–60% successful in restoring arterial patency.⁴⁰ **Emergent rescue PCI** is necessary with **persistent ST elevation of more than 50% early after lysis**, severe heart failure or **cardiogenic shock**, persistent chest pain, haemodynamic or electrical instability, or high-risk features on non-invasive imaging.^{4,15}

Facilitated PCI refers to full-dose or partial-dose **fibrinolysis plus** a combination of **glycoprotein IIb/IIIa inhibitors (GPIs)**, heparin, or other antithrombotic agents **followed by immediate PCI, without evidence of failed reperfusion**. Data have shown **no benefit** and suggest harm (increased ischaemic events, bleeding, and mortality) with facilitated PCI,^{49–52} and it is **not recommended** for these reasons.

Early PCI after fibrinolysis (pharmacoinvasive strategy)

By contrast with facilitated PCI, **early (but not immediate) PCI at 3–24 h after fibrinolysis might improve** outcomes. An apparent component of early PCI is that it is carried out **at least 3 h after lysis to minimise bleeding complications.**⁵³ In TRANSFER-AMI, immediate lysis and transfer for PCI within 6 h (median 2.8 h)—versus standard therapy (transfer and PCI within a median of 21.9 h)—was associated with lower composite death, myocardial infarction, recurrent ischaemia, heart failure, or cardiogenic shock at 30 days (11.0% vs 17.2%; hazard ratio [HR] 0.64, 95% CI 0.47–0.87; $p=0.004$).⁵⁴ Similarly, CARESS-in-AMI found that patients transferred for PCI **within 12 h of half-dose reteplase** and abciximab had lower composite mortality, myocardial infarction, or refractory ischaemia at 30 days than patients in the standard care or rescue PCI group (4.4% vs 10.7%; HR 0.40, 95% CI 0.21–0.76; $p=0.004$).⁵⁵

Late PCI in occluded infarct arteries

The OAT trial of 2166 patients found that **elective PCI for complete occlusion of the infarct artery 3–28 days after myocardial infarction did not improve** composite death, myocardial infarction, or class IV heart failure compared with medical therapy (17.2% vs 15.6%; HR 1.16, 95% CI 0.92–1.45; $p=0.20$).^{56,57} Other studies suggest that although PCI might improve arterial patency on angiography, this does not correlate with improved left ventricular ejection fraction or outcomes.^{58,59} Thus, **PCI of a totally occluded infarct artery is not recommended in stable**, otherwise asymptomatic patients, but is indicated if patients develop signs of recurrent ischaemia, and is reasonable with intermediate-risk or high-risk features on non-invasive testing.⁴

Culprit vessel versus multivessel PCI

Complete revascularisation including severely stenosed non-infarct vessels at the time of primary PCI is a class IIb recommendation in the ACC/AHA primary PCI guidelines.⁶⁰ This recommendation is supported by data from several studies, summarised in the appendix p 8.^{61–63} Further, staged revascularisation of non-culprit lesions following STEMI is a class IIa recommendation in the ESC guidelines.¹⁶ Additionally, fractional flow reserve-guided complete revascularisation might reduce the need for repeat PCI after STEMI, as shown in DANAMI-3-PRIMULTI.⁶³ Although **follow-up stress testing is not routinely indicated after PCI for myocardial infarction, it is reasonable in patients with unrevascularised non-culprit lesions**, or recurrent ischaemic symptoms despite PCI.

Coronary artery bypass grafting (CABG)

Primary **PCI** has **replaced CABG** as the preferred revascularisation strategy for most patients with STEMI. However, CABG could play an important **role** in patients who have **not responded to PCI** or a **mechanical complication** of myocardial infarction (ie, ventricular septal

rupture). Further, CABG can be considered in stable NSTEMI patients with diabetes, reduced left ventricular ejection fraction, left main or proximal left anterior descending coronary artery (LAD) stenosis, multivessel disease, inability to tolerate extended dual antiplatelet therapy (DAPT), or a high SYNTAX score (ie, ≥ 34).^{4,15,17,64–66}

NSTEMI

Invasive versus conservative strategies

In NSTEMI, the decision to pursue an initial invasive strategy of catheterisation with intent to do PCI or CABG within approximately 48 h versus an early conservative strategy with medical management followed by catheterisation and revascularisation if the patient has recurrent or provoked ischaemia should be guided by each patient's risk (panel 1 and figure 1).^{9,17} In TACTICS-TIMI-18, patients with unstable angina or NSTEMI given a GPI were randomly assigned to early angiography with or without PCI within 4–48 h, or a selective invasive strategy. The early invasive strategy had fewer composite deaths, non-fatal myocardial infarctions, and hospitalisations within 6 months (15.9% vs 19.4%; odds ratio [OR] 0.78, 95% CI 0.62–0.97; $p=0.025$).¹³ The TIMACS trial subsequently compared early PCI (median 12 h) versus a delayed invasive strategy of PCI (median 50 h) after unstable angina or NSTEMI. In a prespecified analysis stratified by GRACE risk score, the highest GRACE tertile (>140) had a reduction in the primary endpoint (death, new myocardial infarction, or stroke) at 6 months with early intervention (13.9% vs 21.0%; HR 0.65, 95% CI 0.48–0.89; $p=0.006$), but there was no difference with lower risk.⁶⁷ The ABOARD trial further randomised patients with unstable angina or NSTEMI to immediate intervention (median 70 min) versus PCI on the subsequent working day (median 31 h). Immediate PCI offered no benefit with regard to peak cTn or composite death, new myocardial infarction, or urgent target vessel revascularisation within 1 month, but the early invasive strategy did lead to shorter hospital stays (55 vs 77 h; $p<0.01$).¹⁴ The results of these and several earlier studies provide support to angiography with intent to pursue revascularisation as soon as possible in patients with NSTEMI who are clinically unstable and in those with elevated risk for clinical events, whereas a delayed invasive strategy is acceptable in lower-intermediate-risk patients.

Antithrombotic therapies for acute myocardial infarction

Antiplatelet agents

Aspirin

Randomised trials have shown a reduction in death or myocardial infarction of greater than 50% with aspirin compared with placebo in patients with ACS.^{68,69} Guidelines recommend a loading dose of aspirin (162–325 mg) as soon as possible following myocardial infarction, whereas indefinite low-dose aspirin (75–100 mg) is advised for secondary prevention, because

it is as effective as higher doses at preventing ischaemic events but causes less bleeding.^{4,15,17}

P2Y₁₂ inhibitors

Clopidogrel is a second generation thienopyridine that irreversibly antagonises the platelet P2Y₁₂ ADP receptor, and is effective at inhibiting platelet activation and aggregation. Several trials support its routine use in ACS, regardless of whether PCI is done. The CURE trial randomly assigned 12 562 patients with unstable angina or NSTEMI to aspirin alone or aspirin plus clopidogrel (300 mg loading followed by 75 mg daily), and showed a 20% reduction in the risk of cardiovascular death, non-fatal myocardial infarction, and stroke with clopidogrel (9.3% vs 11.4%; relative risk [RR] 0.80, 95% CI 0.72–0.90; $p<0.001$), at the expense of increased major bleeding.⁷⁰ A prespecified subgroup analysis, PCI-CURE, showed an especially pronounced reduction in cardiac events of 31% at 30 days and 1 year in patients undergoing PCI.⁷¹ Similar results were observed in the COMMIT/CCS-2 and CLARITY-TIMI 28 trials of patients with STEMI given fibrinolysis, in which long-term addition of clopidogrel 75 mg significantly reduced recurrent cardiovascular events and mortality compared with aspirin alone.^{72,73} A loading dose of clopidogrel 300 mg is advised in patients undergoing fibrinolysis (unless older than 75 years, in which case clopidogrel 75 mg should be given). A dose of 600 mg should be given to patients undergoing PCI or medical management alone, because it is able to achieve adequate platelet inhibition within 2–6 h of administration, and could improve outcomes.^{71,74} Current ESC and ACC/AHA guidelines recommend the more potent P2Y₁₂ receptor inhibitors prasugrel and ticagrelor over clopidogrel for use in acute myocardial infarction.^{9,17}

Prasugrel is a third generation thienopyridine P2Y₁₂ inhibitor, which is metabolised to its active form more quickly and fully than clopidogrel, and thus has a more potent and consistent effect.⁷⁵ The pivotal trial of prasugrel, TRITON-TIMI 38, randomly assigned 13 608 patients with ACS to aspirin plus prasugrel (60 mg loading, followed by 10 mg daily) or clopidogrel (300 mg loading, followed by 75 mg daily). There was a reduction in composite cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke with prasugrel (9.9% vs 12.1%; HR 0.81, 95% CI 0.73–0.90; $p<0.001$),⁷⁶ largely driven by non-fatal myocardial infarction. Further, prasugrel also decreased occurrence of target vessel revascularisation and stent thrombosis. The improvement in ischaemic outcomes came at a cost, because prasugrel increased major bleeding (HR 1.32; 95% CI 1.03–1.68; $p=0.03$), and life-threatening bleeding (1.4% vs 0.9%; $p=0.01$). It should be noted that apart from STEMI, most patients were randomly assigned after diagnostic angiography.

However, prasugrel does not appear superior to clopidogrel when administered in medically managed patients or before coronary angiography. TRILOGY-ACS

randomly assigned 7243 patients with unstable angina or NSTEMI treated conservatively (without PCI) to prasugrel versus clopidogrel, and found no difference in ischaemic outcomes.⁷⁷ Further, the ACCOAST trial randomly assigned 4033 patients with unstable angina or NSTEMI treated invasively to prasugrel 30 mg upstream, followed by an additional 30 mg at the time of PCI (60 mg total), compared with 60 mg at the time of PCI in the control group. Ischaemic outcomes did not differ, but major bleeding increased with prasugrel pretreatment (HR 1.90, 95% CI 1.19–3.02; $p=0.006$).^{78,79}

Ticagrelor is a novel P2Y₁₂ inhibitor, which unlike clopidogrel or prasugrel is not a thienopyridine, is direct-acting, and is reversible. Ticagrelor is faster acting than either clopidogrel or prasugrel, with a half-life of 12 h, and inhibits platelets almost twice as potently as clopidogrel at tested doses.⁸⁰ The PLATO trial randomly assigned 18642 patients with acute coronary syndromes (STEMI or NSTEMI or unstable angina), to ticagrelor (180 mg loading followed by 90 mg twice daily), or clopidogrel (300–600 mg loading followed by 75 mg daily), on a background of aspirin and other standard therapy. At 30 days, ticagrelor lowered composite cardiovascular death, myocardial infarction, or stroke, and led to a reduction of 16% in the primary endpoint by 12 months (9.8% vs 11.7%; HR 0.84, 95% CI 0.77–0.92; $p<0.001$), with a slight increase in non-procedure-related bleeding (4.5% vs 3.8%, $p=0.03$).⁸⁰ In the ATLANTIC study, upstream ticagrelor did reduce procedural bleeding and is considered safe, unlike prasugrel in ACCOAST.⁸¹ Similar to prasugrel, ticagrelor has not been studied in fibrinolysis, and is not recommended in this context.

Practical considerations with oral P2Y₁₂ inhibitors

Prasugrel, unlike clopidogrel or ticagrelor, is contraindicated with a history of previous transient ischaemic attack or stroke, and should be used with caution in individuals with a bodyweight less than 60 kg or in those aged 75 years or older. There is variability among guidelines as to how long surgery (including CABG) should be delayed after P2Y₁₂ therapy administration to reduce bleeding risk. The ACC/AHA guidelines recommend delaying surgery for 7 days after prasugrel, and for 5 days following clopidogrel or ticagrelor. However, the ESC guidelines recommend a 3–5-day waiting period following ticagrelor administration; this recommendation is supported by a 2016 study demonstrating an increased risk of perioperative bleeding in patients given ticagrelor less than 24 h before surgery, but no difference comparing 3 days with 5 days.⁸² Studies have demonstrated that crushing prasugrel or ticagrelor rather than taking integral pills might lead to faster gastrointestinal absorption and faster platelet inhibition before PCI.^{83,84} Although clopidogrel or ticagrelor can be given upstream to PCI, guidelines advise delaying prasugrel loading until after coronary anatomy is defined.

Cangrelor

Cangrelor is an intravenous, reversible ADP receptor antagonist, with rapid and intense P2Y₁₂ inhibition within 2 min. Although early trials of cangrelor versus placebo in patients adequately treated with clopidogrel before PCI yielded mixed results,^{85,86} the recent CHAMPION PHOENIX compared cangrelor with a 300 or 600 mg loading dose of clopidogrel before PCI, and found that cangrelor was superior to clopidogrel in reducing composite death and ischaemic events, including stent thrombosis within 48 h after PCI (4.7% vs 5.9%; OR 0.78; 95% CI 0.66–0.93; $p=0.005$), without an increase in bleeding.⁸⁷ The exact place of cangrelor in clinical practice is still being defined; it might be most useful in patients not adequately loaded with a P2Y₁₂ inhibitor undergoing PCI, although it has not yet been well studied in this context.

Duration of dual antiplatelet therapy

DAPT with aspirin and a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor) is essential to mitigate the risk of ischaemic events such as stent thrombosis after PCI.^{76,80,88}

Guidelines recommend DAPT for at least 1 year after acute coronary syndrome regardless of whether medically managed or if PCI is done, irrespective of stent type (BMS or DES).^{4,15–17} The optimal duration of DAPT beyond 1 year following DES is unclear, with some studies showing reduced myocardial infarction and death, and others no difference in ischaemic outcomes but an increased bleeding with prolonged DAPT.^{89–92}

Two trials suggest that a longer duration of DAPT might reduce ischaemic events. In the DAPT study, 9961 patients with either acute coronary syndrome or stable angina were randomly assigned to 12 or 30 months of DAPT after DES. 30 months of DAPT reduced the risk of stent thrombosis (0.4% vs 1.4%; HR 0.29; $p<0.001$), myocardial infarction (2.1% vs 4.1%; HR 0.47; $p<0.001$), and MACCE (composite death, myocardial infarction, and stroke; 4.3% vs 5.9%; HR 0.71; $p<0.001$), at the cost of increased moderate or severe bleeding (2.5% vs 1.6%, $p=0.001$).⁹³ The reduction in ischaemic events was greater for patients with myocardial infarction than for those without myocardial infarction.⁹⁴ The risk of stent thrombosis and myocardial infarction increased in the DAPT group after discontinuation of thienopyridine, which suggests that the risk of very late stent thrombosis might rise after DAPT discontinuation.⁹³

Importantly, the magnitude of the reduction in myocardial infarction in the DAPT study was larger than the reduction in stent thrombosis, suggesting that long-term DAPT might be effective at secondary prevention of myocardial infarction beyond stent-related infarcts. This premise is supported by the PEGASUS trial, which randomly assigned 21162 patients who had had a myocardial infarction in the past 1–3 years to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo on a background of low-dose aspirin for 33 months.⁹⁵

At 3 years compared with placebo, both doses of ticagrelor reduced myocardial infarction (HR for ticagrelor 90 mg vs placebo 0·81, $p=0\cdot01$; HR for ticagrelor 60 mg vs placebo 0·84, $p=0\cdot03$), and MACCE (cardiovascular death, myocardial infarction, and stroke; HR for ticagrelor 90 mg vs placebo 0·85, $p=0\cdot008$; HR for ticagrelor 60 mg vs placebo 0·84, $p=0\cdot004$). Although both doses increased bleeding, ticagrelor 60 mg had a more favourable bleeding profile (major bleeding 2·6% for 90 mg, 2·3% for 60 mg, 1·1% for placebo; $p<0\cdot001$ for each dose vs placebo).⁹⁵

Derived from the DAPT study, the DAPT score (appendix p 9) appears to be very useful to individualise the duration of antiplatelet therapy.⁹⁶ The DAPT score identifies the 50% of individuals who derive a large benefit from prolonged DAPT with minimal bleeding risk, while the other 50% has a greater increase in bleeding and mortality with minimal reduction in MACE.

Although 1 year of DAPT is recommended following ACS regardless of whether medically managed or whether PCI is done, in patients with concerns for bleeding or medication non-compliance, it might be reasonable to consider use of the latest generation DES, which have been shown to have a very low incidence of late stent thrombosis.^{97,98} And some studies suggest, might almost completely endothelialise by 3 months.⁹⁹ Although still considered reasonable in the ACC/AHA guidelines, the use of BMS is discouraged in patients with elevated bleeding risk in recent ESC guidelines.¹⁶ If bleeding risk prohibits the continued use of DAPT during follow-up, aspirin should be discontinued and the

P2Y₁₂ inhibitor continued if possible, because ischaemic risk is highest when P2Y₁₂ inhibitor therapy is stopped.

Triple antithrombotic therapy after PCI

Patients with indications for triple antithrombotic therapy with warfarin and DAPT represent an especially challenging population given the increased risk of bleeding with all three agents. The ideal duration and combination of aspirin, P2Y₁₂ inhibitor therapy, or oral anticoagulant in this population has yet to be defined, and studies in this area are ongoing. One trial suggests that double therapy with clopidogrel and warfarin after 1 month could reduce major or minor bleeding (19·4% vs 44·4%; HR 0·36, 95% CI, 0·26–0·50; $p<0\cdot0001$), ischaemic events (11·1% vs 17·6%; 0·60, 0·38–0·94; $p=0\cdot025$), and mortality (2·5% vs 6·3%; 0·39, 0·16–0·93; $p=0\cdot027$) compared with all three agents after DES.¹⁰⁰ In patients at high risk of bleeding, gastrointestinal protection (ie, proton-pump inhibitor therapy) should be considered.¹⁰¹

Glycoprotein IIb/IIIa inhibitors

GPIs (abciximab, tirofiban, and eptifibatide) provide potent inhibition of platelet aggregation, limiting thrombus propagation at the expense of increased bleeding risk. Once widely used, the role of GPIs has diminished. The bulk of evidence supporting GPI use was established before the DAPT era, and contemporary trials have shown no benefit to routine GPI use in patients with STEMI treated with PCI also given

	Unfractionated heparin	Enoxaparin	Fondaparinux	Bivalirudin
Class of agent	Long-chain heparin	Low-molecular-weight heparin	Heparin derivative; essential pentasaccharide	Direct thrombin inhibitor
Mechanism	Increases AT inhibition of FXa, thrombin (FII), and other coagulation proteases	Increases AT inhibition of FXa more than other proteases	Increases AT inhibition of FXa only	Directly inhibits FII
Monitoring	aPTT (goal 1·5–2 times normal, or 50–70)	FXa levels (not routinely measured)	FXa levels (not routinely measured)	aPTT (elevated; not used for titration)
STEMI				
Fibrinolysis	Recommended	Recommended	Can be considered	Not approved
Primary PCI	Recommended	Can be considered	Caution if used*	Recommended
Unstable angina/NSTEMI				
Conservative management	Recommended	Recommended	Recommended	Not approved
During PCI	Recommended	Recommended	Caution if used*	Recommended
Special populations				
Renal dysfunction	Recommended	Decrease dose if CrCl 30–60 mL/min; avoid if CrCl <30 mL/min	Decrease dose if CrCl <30 mL/min; avoid in stage 4 CKD	Decrease dose if CrCl <30 mL/min; avoid in stage 4 CKD
Heparin-induced thrombocytopenia	Contraindicated	Can be considered	Can be considered	Recommended

Patients taking the novel anticoagulants (direct thrombin inhibitor dabigatran, FXa inhibitors rivaroxaban and apixaban) are often encountered; there are no guidelines to direct anticoagulation for acute coronary syndrome or during PCI in these patients. AT=antithrombin III. FXa=factor Xa. aPTT=activated partial thromboplastin time. PCI=percutaneous coronary intervention. STEMI=ST elevation myocardial infarction. NSTEMI=non-STEMI. CrCl=creatinine clearance. CKD=chronic kidney disease.

*Given increased risk of catheter thrombosis, if fondaparinux is used, a second anticoagulant is recommended during PCI.

Table: Comparison of anticoagulants used to treat acute coronary syndrome

DAPT.^{102,103} Patients who benefit the most from GPIs include patients with high-risk ACS undergoing PCI, inadequate P2Y₁₂ inhibition before PCI, or low bleeding risk.³⁴ The most common reason for GPI administration is for bailout during PCI with a high-thrombus burden, although data for its use in this setting are scarce.

Anticoagulant agents

In initial management, inhibition of the coagulation cascade is **essential** to limit thrombus propagation in patients with acute myocardial infarction, whether managed invasively or conservatively. The table provides a comparison of the common anticoagulant agents, and the appendix (p 4) shows their therapeutic targets.

Unfractionated heparin

The use of unfractionated heparin in acute coronary syndrome and during PCI has been ubiquitous for more than 20 years. Several small randomised trials from the 1990s and a meta-analysis showed that the **addition** of unfractionated **heparin** to **aspirin** during the acute phase

of ACS **reduces subsequent myocardial infarction and mortality as much as 33%**.^{68,104}

Low-molecular-weight heparin

In early trials, enoxaparin (a low-molecular-weight heparin) reduced myocardial infarction and mortality compared with unfractionated heparin among high-risk patients with unstable angina or NSTEMI (ie, TIMI risk score ≥ 3) managed medically,^{105,106} whereas nadroparin and dalteparin were equivalent to unfractionated heparin. However, in the ATOLL trial of patients with STEMI given unfractionated heparin versus enoxaparin, the primary endpoint of composite death, myocardial infarction, procedural failure, or major bleeding at 30 days was not met, although composite death, myocardial infarction, or major bleeding was significant ($p=0.03$), as was death or myocardial infarction ($p=0.02$).¹⁰⁷ As such, as a part of an early-invasive strategy, **enoxaparin appears as effective in secondary prevention of myocardial infarction and death as does unfractionated heparin**. Enoxaparin could be considered as an **alternative** to unfractionated **heparin** in patients with ACS; patients who benefit most include those with high-risk acute coronary syndrome given PCI.^{105,106,108}

Fondaparinux

On the basis of the OASIS-5 and OASIS-6 trials, another anticoagulant—fondaparinux—appears **non-inferior to unfractionated heparin or enoxaparin** in the reduction of death and ischaemic outcomes when used during ACS, and might reduce bleeding. However, this **benefit** (reduction of death, ischaemic outcome, and bleeding) appears **limited** to patients **managed medically**, because fondaparinux **increases catheter-related thrombosis** during PCI.^{109,110} Thus, fondaparinux carries a class III recommendation as the sole anticoagulant agent during PCI;^{4,15,17} **unfractionated heparin should also be given during PCI to any patient given fondaparinux**.

Direct thrombin inhibitors

Bivalirudin is the most widely studied and commonly used direct thrombin inhibitor during PCI. A meta-analysis showed that bivalirudin monotherapy reduces major bleeding compared with unfractionated heparin or enoxaparin-based regimens (RR 0.62, 95% CI 0.49–0.78; $p<0.0001$), but the effect varies depending on whether a GPI is given.¹¹¹ The effect of bivalirudin on ischaemic outcomes compared with unfractionated heparin monotherapy is less clear, because most trials have compared bivalirudin with unfractionated heparin plus a GPI rather than unfractionated heparin alone. Pooled data suggest that bivalirudin monotherapy increases the risk of acute stent thrombosis (RR 1.38, 95% CI 1.09–1.74; $p=0.0074$), and trials have reported variable effects on myocardial infarction, MACE, and mortality, depending on whether radial or femoral access is used.^{112–118} As such, the **use of bivalirudin in acute myocardial infarction** is

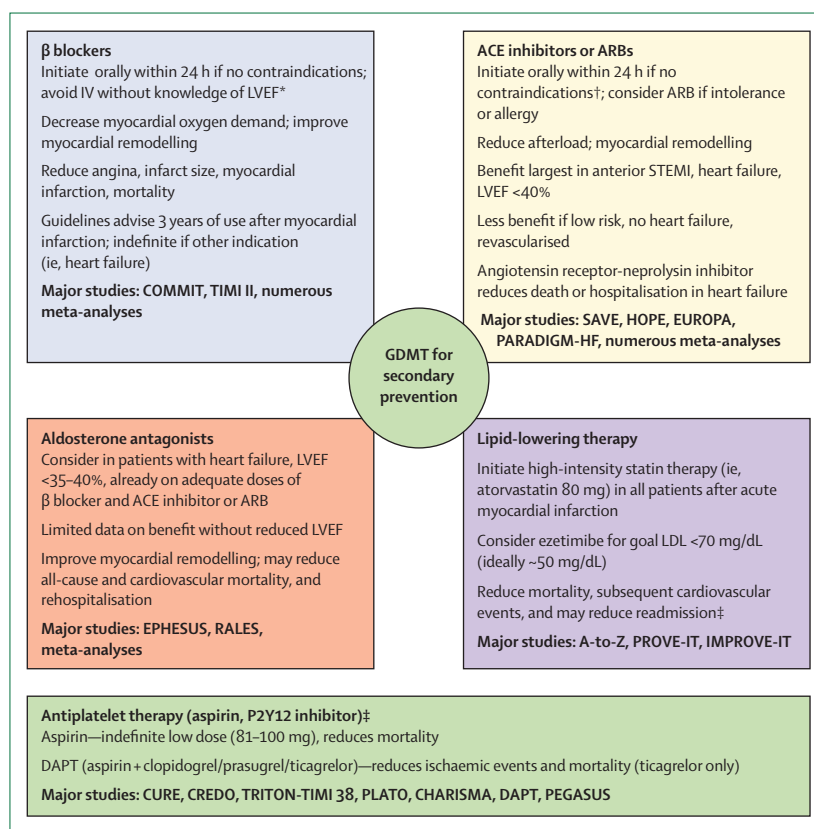


Figure 2: GDMT for secondary prevention of cardiovascular events after acute myocardial infarction

Clopidogrel is no longer recommended in ESC guidelines; prasugrel or ticagrelor are preferred instead. ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. GDMT=guideline directed medical therapy. LVEF=left ventricular ejection fraction. STEMI=ST segment elevation myocardial infarction.^{119–128}

*Contraindications to β blockade include decompensated heart failure, cardiogenic shock, prolonged first degree atrioventricular block (PR >240 ms), or reactive airway disease. †Contraindications to ACE inhibitors or ARBs include worsening renal failure, advanced kidney disease, bilateral renal artery stenosis, or hyperkalaemia, or hypotension. ‡Indicates topic was discussed elsewhere in the Seminar.

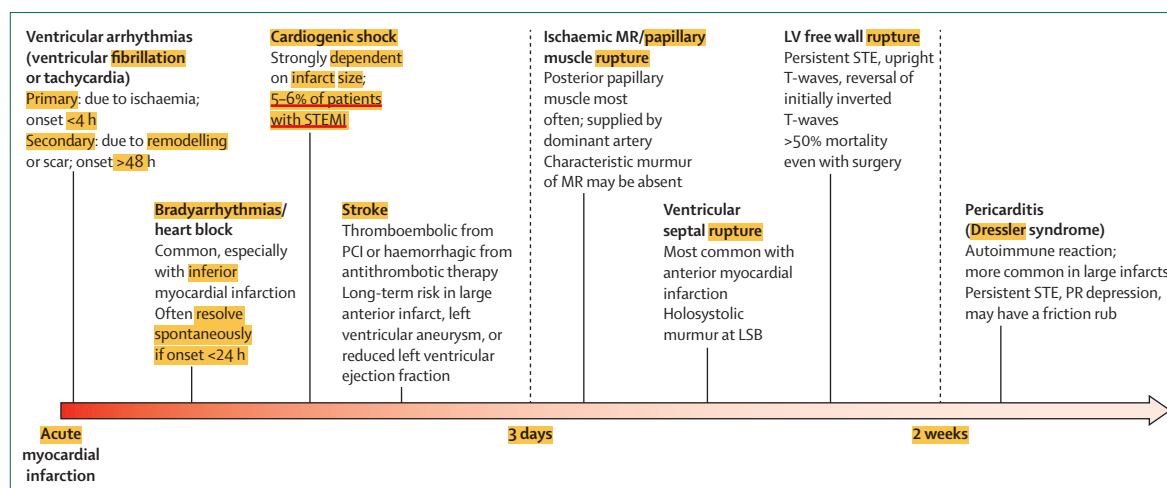


Figure 3: Complications of acute myocardial infarction

Common complications following acute myocardial infarction and their approximate timing. Approximately 50% of bradyarrhythmias are Mobitz I, 50% are Mobitz II or third degree atrioventricular block. Posterior papillary muscle rupture is the most common mechanical complication of acute myocardial infarction, most often because of infarction of the right communicating artery (which is dominant in 85% of patients). Not listed above, atrial fibrillation could be seen any time after acute myocardial infarction, most often in patients with left atrial enlargement. LSB=left sternal border. LV=left ventricle. MR=mitral regurgitation. PCI=percutaneous coronary intervention. STEMI=ST segment elevation myocardial infarction.

controversial, with most physicians preferring a heparin-based regimen unless allergic or at high risk of bleeding. Furthermore, most studies of bivalirudin have been done in patients with STEMI, and the evidence base for bivalirudin use in NSTEMI is weaker.

Long-term medical therapies

In addition to the antithrombotic therapies discussed above, β blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists have been shown to improve long-term outcomes in selected patients after myocardial infarction (figure 2). Physicians, nurses, and all health-care providers should work with patients to improve compliance with medications.¹²⁹

Complications from acute myocardial infarction

Knowledge of the cardinal features and timing of the complications of myocardial infarction is essential to recognise and properly treat these potentially fatal events (figure 3).

Secondary prevention

New antithrombotic therapies

When added to DAPT, both rivaroxaban and vorapaxar improve the secondary prevention of cardiovascular events, at the expense of increased bleeding.^{130,131} Either therapy could be useful in high-risk patients following myocardial infarction or with established coronary artery disease and low bleeding risk (appendix p 10).

Lipid-lowering therapy

Aggressive control of LDL cholesterol with high-intensity statin therapy (eg, atorvastatin 80 mg) is advised in all patients after myocardial infarction on the basis of results

of several trials, including MIRACL,¹³² A to Z,¹¹⁹ and PROVE-IT TIMI 22¹²⁰ (figure 2). Previously, the US National Cholesterol Education Program's Adult Treatment Panel III called for the treatment of all patients with coronary heart disease to an LDL goal of less than 2.6 mmol/L (100 mg/dL), and in a 2004 update recommended an ideal LDL goal of less than 1.8 mmol/L (70 mg/dL).¹³³ The most recent ESC cholesterol management guidelines released in 2011 follow a similar approach to ATP III, incorporating LDL concentrations and patient risk factors in treatment recommendations.¹³⁴ Although in 2013 the ACC/AHA released new, somewhat controversial guidelines that recommend high-intensity statin therapy after myocardial infarction, and not specific LDL targets,⁷ the 2016 ACC consensus statement does note that the above LDL concentrations, termed thresholds for therapy, are appropriate for high-risk patients.¹³⁵

The IMPROVE-IT trial¹²¹ suggests that lower LDL targets could improve outcomes. In IMPROVE-IT, 18144 patients with ACS were randomly assigned to 40 mg simvastatin plus 10 mg ezetimibe versus 40 mg simvastatin alone. In the simvastatin plus ezetimibe group, LDL was 1.4 mmol/L (53.7 mg/dL) versus 1.8 mmol/L (69.5 mg/dL) in the simvastatin alone group ($p<0.001$). The primary endpoint of composite cardiovascular death, non-fatal myocardial infarction, unstable angina requiring hospitalisation, coronary revascularisation, or non-fatal stroke was significantly lower with simvastatin plus ezetimibe than with simvastatin alone (32.7% vs 34.7%, absolute risk difference 2.0%; HR 0.936, 95% CI 0.89–0.99; $p=0.016$), with the benefit emerging after 1 year.¹²¹ These results indicate that the use of ezetimibe to further lower

Panel 2: Lifestyle and activity recommendations after acute myocardial infarction

Recommendations in all patients

- Referral to cardiac rehabilitation (improves mortality)
- Smoking cessation (if applicable)
- Counselling on the severity of their condition and warning signs of depression
- Counselling on medication adherence (especially dual antiplatelet therapy after percutaneous coronary intervention)
- Heart-healthy diet (low saturated fat and cholesterol)

Activity recommendations

- Avoid exertion but gradually increase activity over 1–2 weeks
- Begin exercise and sexual activity after 2 weeks
- Avoid concomitant nitrate and sildenafil or tadalafil use
- Return to work within 2–4 weeks

LDL will reduce cardiovascular events, and that lowering LDL closer to 1.3–1.4 mmol/L (~50 mg/dL) might have improved long-term outcomes after ACS. Further, these results support the use of LDL targets in future guidelines.

Implantable cardioverter-defibrillators

The risk of sudden cardiac death is highest in patients who have ventricular tachycardia or fibrillation at least 48 h after the myocardial infarction. This risk persists indefinitely, and is greatest in some high-risk populations, which have been identified in several clinical trials (MUSTT, MADIT, MADIT II, and SCD-HeFT). On the basis of these studies, an implantable cardioverter-defibrillator is indicated for the prevention of sudden cardiac death in patients with a persistently decreased left ventricular ejection fraction lower than 35% and NYHA class II or III symptoms (or left ventricular ejection fraction <30% and NYHA class I symptoms) despite optimal medical therapy at least 40 days after myocardial infarction and suspected survival for at least 1 year.^{136–140}

Activity and lifestyle recommendations

A full discussion of activity and lifestyle recommendations after acute myocardial infarction is beyond the scope of this Seminar, but panel 2 provides essential recommendations.^{4,141} Although cardiac rehabilitation is strongly recommended following myocardial infarction, which components of rehabilitation are most beneficial is unclear.

Future directions

Continued progress in improving outcomes following acute myocardial infarction will be made only with a commitment to research targeted at improving the systems in which care is delivered. The largest gains might be from research into increasing adherence to guideline-directed medical therapies and spreading

established systems-based advances to developing countries. Additionally, it is hopeful that emerging technologies and translational science (including novel applications of gene and stem-cell therapy) could further revolutionise care after myocardial infarction.

The reduction in mortality following acute myocardial infarction is one of the success stories of modern medicine. Despite this progress, there is still a need to streamline reperfusion strategies, refine antithrombotic therapies, and find innovative ways to maximise secondary prevention. With an unwavering commitment to research in this field of myocardial infarction treatment therapies, the future is bright, and patient outcomes following acute myocardial infarction will continue to improve.

Contributors

The first draft was written by GWR; JER and CPC made additional edits and wrote sections. All authors did the literature search, and interpreted data and evidence.

Declaration of interests

CPC has grants from Arisaph, AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, GlaxoSmithKline, Merck, and Takeda; and consulting fees from Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Kowa, Merck, Takeda, Lipimedix, Pfizer, Regeneron, and Sanofi. GWR and JER declare no competing interests.

References

- 1 Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *Eur Heart J* 2014; **35**: 2950–59.
- 2 Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med* 2010; **362**: 2155–65.
- 3 Weintraub WS, Daniels SR, Burke LE, et al, and the American Heart Association Advocacy Coordinating Committee, and the Council on Cardiovascular Disease in the Young, and the Council on the Kidney in Cardiovascular Disease, and the Council on Epidemiology and Prevention, and the Council on Cardiovascular Nursing, and the Council on Arteriosclerosis, and the Thrombosis and Vascular Biology, and the Council on Clinical Cardiology, and Stroke Council. Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. *Circulation* 2011; **124**: 967–90.
- 4 O'Gara PT, Kushner FG, Ascheim DD, et al, and the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; **127**: e362–425.
- 5 Thygesen K, Alpert JS, Jaffe AS, et al, and the Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction, and the Authors/Task Force Members Chairpersons, and the Biomarker Subcommittee, and the ECG Subcommittee, and the Imaging Subcommittee, and the Classification Subcommittee, and the Intervention Subcommittee, and the Trials & Registries Subcommittee, and the Trials & Registries Subcommittee, and the Trials & Registries Subcommittee, and the ESC Committee for Practice Guidelines (CPG), and the Document Reviewers. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; **60**: 1581–98.
- 6 Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med* 2013; **368**: 2004–13.
- 7 Stone NJ, Robinson JG, Lichtenstein AH, et al, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **129** (suppl 2): S1–45.

- 8 Morrow DA, Cannon CP, Jesse RL, et al, and the National Academy of Clinical Biochemistry. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation* 2007; **115**: e356–75.
- 9 Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37**: 267–315.
- 10 Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2012; **60**: 645–81.
- 11 de Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTEMI-ACS. *Eur Heart J* 2005; **26**: 865–72.
- 12 Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. *Mayo Clin Proc* 2009; **84**: 917–38.
- 13 Cannon CP, Weintraub WS, Demopoulos LA, et al, and the TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)—Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001; **344**: 1879–87.
- 14 Montalescot G, Cayla G, Collet JP, et al, and the ABOARD Investigators. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. *JAMA* 2009; **302**: 947–54.
- 15 Steg PG, James SK, Atar D, et al, and the Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33**: 2569–619.
- 16 Windecker S, Kolh P, Alfonso F, et al, and the Authors/Task Force members. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; **35**: 2541–619.
- 17 Amsterdam EA, Wenger NK, Brindis RG, et al, and the American College of Cardiology, and the American Heart Association Task Force on Practice Guidelines, and the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons, and the American Association for Clinical Chemistry. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **64**: e139–228.
- 18 Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000; **283**: 2941–47.
- 19 Widimský P, Budesínský T, Vorác D, et al, and the 'PRAGUE' Study Group Investigators. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial—PRAGUE-2. *Eur Heart J* 2003; **24**: 94–104.
- 20 Andersen HR, Nielsen TT, Rasmussen K, et al, and the DANAMI-2 Investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003; **349**: 733–42.
- 21 Busk M, Maeng M, Rasmussen K, et al, and the DANAMI-2 Investigators. The Danish multicentre randomized study of fibrinolytic therapy vs. primary angioplasty in acute myocardial infarction (the DANAMI-2 trial): outcome after 3 years follow-up. *Eur Heart J* 2008; **29**: 1259–66.
- 22 Nordmann AJ, Hengstler P, Harr T, Young J, Bucher HC. Clinical outcomes of primary stenting versus balloon angioplasty in patients with myocardial infarction: a meta-analysis of randomized controlled trials. *Am J Med* 2004; **116**: 253–62.
- 23 Zhu MM, Feit A, Chadow H, Alam M, Kwan T, Clark LT. Primary stent implantation compared with primary balloon angioplasty for acute myocardial infarction: a meta-analysis of randomized clinical trials. *Am J Cardiol* 2001; **88**: 297–301.
- 24 Pasceri V, Patti G, Speciale G, Pristipino C, Richichi G, Di Sciascio G. Meta-analysis of clinical trials on use of drug-eluting stents for treatment of acute myocardial infarction. *Am Heart J* 2007; **153**: 749–54.
- 25 Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J* 2007; **28**: 2706–13.
- 26 De Luca G, Stone GW, Suryapranata H, et al. Efficacy and safety of drug-eluting stents in ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *Int J Cardiol* 2009; **133**: 213–22.
- 27 Menichelli M, Parma A, Pucci E, et al. Randomized trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). *J Am Coll Cardiol* 2007; **49**: 1924–30.
- 28 Moses JW, Leon MB, Popma JJ, et al, and the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349**: 1315–23.
- 29 Spaulding C, Henry P, Teiger E, et al, and the TYPHOON Investigators. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med* 2006; **355**: 1093–104.
- 30 Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med* 2015; **372**: 1389–98.
- 31 Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013; **369**: 1587–97.
- 32 Kumbhani DJ, Cannon CP, Fonarow GC, et al, and the Get With the Guidelines Steering Committee and Investigators. Association of hospital primary angioplasty volume in ST-segment elevation myocardial infarction with quality and outcomes. *JAMA* 2009; **302**: 2207–13.
- 33 Badheka AO, Patel NJ, Grover P, et al. Impact of annual operator and institutional volume on percutaneous coronary intervention outcomes: a 5-year United States experience (2005–2009). *Circulation* 2014; **130**: 1392–406.
- 34 Levine GN, Bates ER, Blankenship JC, et al, and the American College of Cardiology Foundation, and the American Heart Association Task Force on Practice Guidelines, and the Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011; **58**: e44–122.
- 35 Jang JS, Jin HY, Seo JS, et al. The transradial versus the transfemoral approach for primary percutaneous coronary intervention in patients with acute myocardial infarction: a systematic review and meta-analysis. *EuroIntervention* 2012; **8**: 501–10.
- 36 Joyal D, Bertrand OF, Rinfret S, Shimony A, Eisenberg MJ. Meta-analysis of ten trials on the effectiveness of the radial versus the femoral approach in primary percutaneous coronary intervention. *Am J Cardiol* 2012; **109**: 813–18.
- 37 Mamas MA, Ratib K, Routledge H, et al. Influence of access site selection on PCI-related adverse events in patients with STEMI: meta-analysis of randomised controlled trials. *Heart* 2012; **98**: 303–11.
- 38 Valgimigli M, Gagnor A, Calabró P, et al, and the MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015; **385**: 2465–76.
- 39 The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; **329**: 673–82.

- 40 Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994; **343**: 311–22.
- 41 TIMI Study Group. The Thrombolysis in Myocardial Infarction: Phase I findings. *N Engl J Med* 1985; **312**: 932–36.
- 42 French JK, Hyde TA, Patel H, et al. Survival 12 years after randomization to streptokinase: the influence of thrombolysis in myocardial infarction flow at three to four weeks. *J Am Coll Cardiol* 1999; **34**: 62–69.
- 43 Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. International Joint Efficacy Comparison of Thrombolytics. *Lancet* 1995; **346**: 329–36.
- 44 Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **361**: 13–20.
- 45 Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation* 2006; **114**: 2019–25.
- 46 Boersma E, and the Primary Coronary Angioplasty vs. Thrombolysis Group. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 2006; **27**: 779–88.
- 47 The Global Use of Strategies to Open Occluded Coronary Arteries: A comparison of reteplase with alteplase for acute myocardial infarction. (GUSTO III) Investigators. *N Engl J Med* 1997; **337**: 1118–23.
- 48 Van De Werf F, Adgey J, Ardissino D, et al, and the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; **354**: 716–22.
- 49 Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006; **367**: 569–78.
- 50 Zalewski J, Bogaerts K, Desmet W, et al. Intraluminal thrombus in facilitated versus primary percutaneous coronary intervention: an angiographic substudy of the ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) trial. *J Am Coll Cardiol* 2011; **57**: 1867–73.
- 51 Ellis SG, Tendera M, de Belder MA, et al, and the FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008; **358**: 2205–17.
- 52 Armstrong PW, Gershlick AH, Goldstein P, et al, and the STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013; **368**: 1379–87.
- 53 Collet JP, Montalescot G, Le May M, Borentain M, Gershlick A. Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol* 2006; **48**: 1326–35.
- 54 Cantor WJ, Fitchett D, Borgundvaag B, et al, and the TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med* 2009; **360**: 2705–18.
- 55 Di Mario C, Dudek D, Piscione F, et al, and the CARESS-in-AMI (Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction) Investigators. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet* 2008; **371**: 559–68.
- 56 Hochman JS, Lamas GA, Buller CE, et al, and the Occluded Artery Trial Investigators. Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 2006; **355**: 2395–407.
- 57 Menon V, Ruzyllo W, Carvalho AC, et al. Infarct artery distribution and clinical outcomes in occluded artery trial subjects presenting with non-ST-segment elevation myocardial infarction (from the long-term follow-up of Occluded Artery Trial [OAT]). *Am J Cardiol* 2013; **111**: 930–35.
- 58 Steg PG, Thuaire C, Himbert D, et al, and the DECOPI Investigators. DECOPI (DESobstruction CORonaire en Post-Infarctus): a randomized multi-centre trial of occluded artery angioplasty after acute myocardial infarction. *Eur Heart J* 2004; **25**: 2187–94.
- 59 Dzavik V, Buller CE, Lamas GA, et al, and the TOSCA-2 Investigators. Randomized trial of percutaneous coronary intervention for subacute infarct-related coronary artery occlusion to achieve long-term patency and improve ventricular function: the Total Occlusion Study of Canada (TOSCA)-2 trial. *Circulation* 2006; **114**: 2449–57.
- 60 Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol* 2016; **67**: 1235–50.
- 61 Wald DS, Morris JK, Wald NJ, et al, and the PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013; **369**: 1115–23.
- 62 Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2015; **65**: 963–72.
- 63 Engström T, Kelbæk H, Helqvist S, et al, and the DANAMI-3—PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet* 2015; **386**: 665–71.
- 64 Farkouh ME, Domanski M, Sleeper LA, et al, and the FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012; **367**: 2375–84.
- 65 Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013; **381**: 629–38.
- 66 Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; **124**: 2610–42.
- 67 Mehta SR, Granger CB, Boden WE, et al, and the TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009; **360**: 2165–75.
- 68 The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990; **336**: 827–30.
- 69 Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. *N Engl J Med* 1985; **313**: 1369–75.
- 70 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, and the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**: 494–502.
- 71 Mehta SR, Bassand JP, Chrolavicius S, et al, and the CURRENT-OASIS 7 Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010; **363**: 930–42.
- 72 Chen ZM, Jiang LX, Chen YP, et al, and the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366**: 1607–21.
- 73 Sabatine MS, Cannon CP, Gibson CM, et al, and the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; **352**: 1179–89.
- 74 Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 2005; **111**: 2099–106.

- 75 Gurbel PA, Erlinge D, Ohman EM, et al, and the TRILOGY ACS Platelet Function Substudy Investigators. Platelet function during extended prasugrel and clopidogrel therapy for patients with ACS treated without revascularization: the TRILOGY ACS platelet function substudy. *JAMA* 2012; **308**: 1785–94.
- 76 Wiviott SD, Braunwald E, McCabe CH, et al, and the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**: 2001–15.
- 77 Roe MT, Armstrong PW, Fox KA, et al, and the TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012; **367**: 1297–309.
- 78 Montalescot G, Bolognese L, Dudek D, et al, and the ACCOAST Investigators. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med* 2013; **369**: 999–1010.
- 79 Montalescot G, Collet JP, Ecollan P, et al, and the ACCOAST Investigators. Effect of prasugrel pre-treatment strategy in patients undergoing percutaneous coronary intervention for NSTEMI: the ACCOAST-PCI study. *J Am Coll Cardiol* 2014; **64**: 2563–71.
- 80 Wallentin L, Becker RC, Budaj A, et al, and the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361**: 1045–57.
- 81 Montalescot G, van 't Hof AW, Lapostolle F, et al, and the ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med* 2014; **371**: 1016–27.
- 82 Hansson EC, Jidéus L, Åberg B, et al. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. *Eur Heart J* 2016; **37**: 189–97.
- 83 Parodi G, Xanthopoulos I, Bellandi B, et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. *J Am Coll Cardiol* 2015; **65**: 511–12.
- 84 Rollini F, Franchi F, Hu J, et al. Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: the CRUSH study. *J Am Coll Cardiol* 2016; **67**: 1994–2004.
- 85 Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 2009; **361**: 2318–29.
- 86 Bhatt DL, Lincoff AM, Gibson CM, et al, and the CHAMPION PLATFORM Investigators. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 2009; **361**: 2330–41.
- 87 Bhatt DL, Stone GW, Mahaffey KW, et al, and the CHAMPION PHOENIX Investigators. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013; **368**: 1303–13.
- 88 Steinhubl SR, Berger PB, Mann JT 3rd, et al, and the CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **288**: 2411–20.
- 89 Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *N Engl J Med* 2010; **362**: 1374–82.
- 90 Collet JP, Silvain J, Barthélémy O, et al, and the ARCTIC investigators. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. *Lancet* 2014; **384**: 1577–85.
- 91 Feres F, Costa RA, Abizaid A, et al, and the OPTIMIZE Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 2013; **310**: 2510–22.
- 92 Valgimigli M, Campo G, Monti M, et al, and the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012; **125**: 2015–26.
- 93 Mauri L, Kereiakes DJ, Yeh RW, et al, and the DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014; **371**: 2155–66.
- 94 Yeh RW, Kereiakes DJ, Steg PG, et al, and the DAPT Study Investigators. Benefits and risks of extended duration dual antiplatelet therapy After PCI in patients with and without acute myocardial infarction. *J Am Coll Cardiol* 2015; **65**: 2211–21.
- 95 Bonaca MP, Bhatt DL, Cohen M, et al, and the PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015; **372**: 1791–800.
- 96 Yeh RW, Secemsky EA, Kereiakes DJ, et al, and the DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 2016; **315**: 1735–49.
- 97 Sabate M, Cequier A, Iñiguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 2012; **380**: 1482–90.
- 98 Sarno G, Lagerqvist B, Nilsson J, et al. Stent thrombosis in new-generation drug-eluting stents in patients with STEMI undergoing primary PCI: a report from SCAAR. *J Am Coll Cardiol* 2014; **64**: 16–24.
- 99 de la Torre Hernández JM, Tejedor P, Camarero TG, et al. Early healing assessment with optical coherence tomography of everolimus-eluting stents with bioabsorbable polymer (synergy™) at 3 and 6 months after implantation. *Catheter Cardiovasc Interv* 2015; published online Nov. 3. <http://dx.doi.org/10.1002/ccd.26299>.
- 100 Dewilde WJ, Oirbans T, Verheugt FW, et al, and the WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013; **381**: 1107–15.
- 101 Bhatt DL, Cryer BL, Contant CF, et al, and the COGENT Investigators. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010; **363**: 1909–17.
- 102 Van't Hof AW, Ten Berg J, Heestermans T, et al, and the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008; **372**: 537–46.
- 103 Mehilli J, Kastrati A, Schulz S, et al, and the Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) Study Investigators. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 2009; **119**: 1933–40.
- 104 Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA* 1996; **276**: 811–15.
- 105 Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999; **100**: 1593–601.
- 106 Goodman SG, Cohen M, Bigonzi F, et al. Randomized trial of low molecular weight heparin (enoxaparin) versus unfractionated heparin for unstable coronary artery disease: one-year results of the ESSENCE Study. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events. *J Am Coll Cardiol* 2000; **36**: 693–98.
- 107 Montalescot G, Zeymer U, Silvain J, et al, and the ATOLL Investigators. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. *Lancet* 2011; **378**: 693–703.
- 108 Gibson CM, Murphy SA, Montalescot G, et al, and the ExTRACT-TIMI 25 Investigators. Percutaneous coronary intervention in patients receiving enoxaparin or unfractionated heparin after fibrinolytic therapy for ST-segment elevation myocardial infarction in the ExTRACT-TIMI 25 trial. *J Am Coll Cardiol* 2007; **49**: 2238–46.
- 109 Yusuf S, Mehta SR, Chrolavicius S, et al, and the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; **354**: 1464–76.
- 110 Yusuf S, Mehta SR, Chrolavicius S, et al, and the OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006; **295**: 1519–30.
- 111 Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. *Lancet* 2014; **384**: 599–606.

- 112 Stone GW, McLaurin BT, Cox DA, et al, and the ACUTY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; **355**: 2203–16.
- 113 Kastrati A, Neumann FJ, Schulz S, et al, and the ISAR-REACT 4 Trial Investigators. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. *N Engl J Med* 2011; **365**: 1980–89.
- 114 Stone GW, Mehran R, Goldstein P, et al. Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary percutaneous coronary intervention: pooled patient-level analysis from the HORIZONS-AMI and EUROMAX trials. *J Am Coll Cardiol* 2015; **65**: 27–38.
- 115 Steg PG, van 't Hof A, Hamm CW, et al, and the EUROMAX Investigators. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 2013; **369**: 2207–17.
- 116 Shahzad A, Kemp I, Mars C, et al, and the HEAT-PPCI trial investigators. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014; **384**: 1849–58.
- 117 Han Y, Guo J, Zheng Y, et al, and the BRIGHT Investigators. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *JAMA* 2015; **313**: 1336–46.
- 118 Valgimigli M, Frigoli E, Leonardi S, et al, and the MATRIX Investigators. Bivalirudin or unfractionated heparin in acute coronary syndromes. *N Engl J Med* 2015; **373**: 997–1009.
- 119 Cutlip DE, Kereiakes DJ, Mauri L, Stoler R, Dauerman HL, and the EDUCATE Investigators. Thrombotic complications associated with early and late nonadherence to dual antiplatelet therapy. *JACC Cardiovasc Interv* 2015; **8**: 404–10.
- 120 Mega JL, Braunwald E, Wiviott SD, et al, and the ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; **366**: 9–19.
- 121 Morrow DA, Braunwald E, Bonaca MP, et al, and the TRA 2P–TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012; **366**: 1404–13.
- 122 Schwartz GG, Olsson AG, Ezekowitz MD, et al, and the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001; **285**: 1711–18.
- 123 de Lemos JA, Blazing MA, Wiviott SD, et al, and the Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004; **292**: 1307–16.
- 124 Cannon CP, Braunwald E, McCabe CH, et al, and the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**: 1495–504.
- 125 Grundy SM, Cleeman JJ, Merz CN, et al, and the National Heart, Lung, and Blood Institute, and the American College of Cardiology Foundation, and the American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **110**: 227–39.
- 126 Reiner Z, Catapano AL, De Backer G, et al, and the European Association for Cardiovascular Prevention & Rehabilitation, and the ESC Committee for Practice Guidelines (CPG) 2008–2010 and 2010–2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011; **32**: 1769–818.
- 127 Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology task force on clinical expert consensus documents. *J Am Coll Cardiol* 2016; **68**: 92–125.
- 128 Cannon CP, Blazing MA, Giugliano RP, et al, and the IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; **372**: 2387–97.
- 129 Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G, and the Multicenter Unsustained Tachycardia Trial Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999; **341**: 1882–90.
- 130 Moss AJ, Hall WJ, Cannom DS, et al, and the Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996; **335**: 1933–40.
- 131 Moss AJ, Zareba W, Hall WJ, et al, and the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**: 877–83.
- 132 Bardy GH, Lee KL, Mark DB, et al, and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352**: 225–37.
- 133 Epstein AE, DiMarco JP, Ellenbogen KA, et al, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices), and the American Association for Thoracic Surgery, and the Society of Thoracic Surgeons. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation* 2008; **117**: e350–408.
- 134 Perk J, De Backer G, Gohlke H, et al, and the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), and the ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012; **33**: 1635–701.
- 135 Chen ZM, Pan HC, Chen YP, et al, and the COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366**: 1622–32.
- 136 Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. *Circulation* 1991; **83**: 422–37.
- 137 Pfeffer MA, Braunwald E, Moyé LA, et al, and the The SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. *N Engl J Med* 1992; **327**: 669–77.
- 138 Fox KM, and the EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; **362**: 782–88.
- 139 McMurray JJ, Packer M, Desai AS, et al, and the PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**: 993–1004.
- 140 Pitt B, Remme W, Zannad F, et al, and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348**: 1309–21.
- 141 Pitt B, Zannad F, Remme WJ, et al, and the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; **341**: 709–17.

THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.
We post it as supplied by the authors.

Supplement to: Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *Lancet* 2016; published online Aug 5. [http://dx.doi.org/10.1016/S0140-6736\(16\)30677-8](http://dx.doi.org/10.1016/S0140-6736(16)30677-8).

Seminar: Acute Myocardial Infarction
Appendix

I	aVR	V1	V4
II	aVL	V2	V5
III	aVF	V3	V6

Appendix Figure 1: Overview of ECG leads and criteria for diagnosis of myocardial infarction

For STEMI, at least 1 mm of ST segment elevation is necessary in contiguous leads (in V1–V2, 2 mm if male, 1.5 mm if female). Presence of ST segment elevation alone indicates myocardial injury and impending infarction; presence of Q-waves indicates progression to infarction. For non-STEMI, ST segment depression and/or T-wave inversion indicate ischaemic changes and might not be specific to a given coronary artery distribution. Pink = lateral (might see reciprocal changes in aVR). Green=inferior. Blue=septal (if anteroseptal, might extend to V3, V4). Orange=anterior (might also see changes in V2, V5). Grey=right (might see reciprocal ST-depressions laterally; obtain dedicated right-sided electrocardiogram). Posterior=might see ST-depressions in V1–V4 (obtain dedicated posterior electrocardiogram). STEMI=ST segment elevation myocardial infarction.

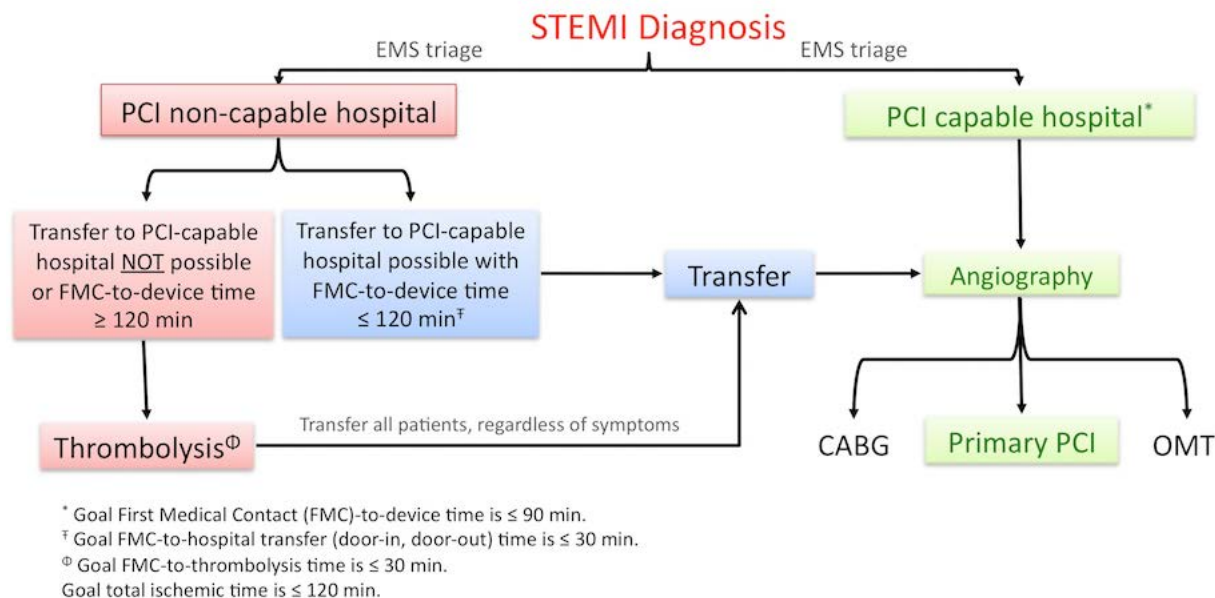
GRACE Risk Score			TIMI Risk Score		
Feature		Points	Feature		Points
Age	< 40	0	Age ≥ 65		1
	40-49	18	≥ 3 Risk factors for CAD		1
	50-59	36	≥ 2 episodes of angina in < 24 hours		1
	60-69	55	Use of aspirin in last 7 days		1
	70-79	73	Known coronary stenosis ≥ 50%		1
	≥ 80	91	ST-segment depression ≥ 0.5 mm in ≥ 2 leads		1
Heart rate (bpm)	< 70	0	Elevated cardiac markers		1
	70-89	7			
	90-109	13			
	110-149	23			
	150-199	36			
	≥ 200	46			
Systolic BP (mmHg)	< 80	63			
	80-99	58			
	100-119	47			
	120-139	37			
	140-159	26			
	160-199	11			
Creatinine (mg/dL)	≥ 200	0			
	0-0.39	2			
	0.4-0.79	5			
	0.8-1.19	8			
	1.2-1.59	11			
	1.6-1.99	14			
Killip class	2-3.99	23			
	≥ 4	31			
	I	0			
	II	21			
	III	43			
	IV	64			
Cardiac arrest at admission		43			
Elevated cardiac markers		15			
ST-segment deviation		30			

Outcomes		
TIMI Risk Score		Outcome (%)*
Low (0-2)		5.4 (8.1)
Intermediate (3-4)		7.3 (15.7)
High (5-7)		8.1 (19.5)
<i>C-statistic</i>	30-days:	0.55 (0.50-0.60)
	1-year:	0.59 (0.54-0.63)
GRACE Risk Score		Outcome (%)*
< 96		3.1 (4.2)
96-112		5.3 (9.6)
113-133		5.9 (11.9)
>133		11.2 (27.2)
<i>C-statistic</i>	30-days:	0.67(0.63-0.71)
	1-year:	0.72 (0.67-0.76)

Appendix Figure 2: Comparison of risk scores for NSTEMI or unstable angina

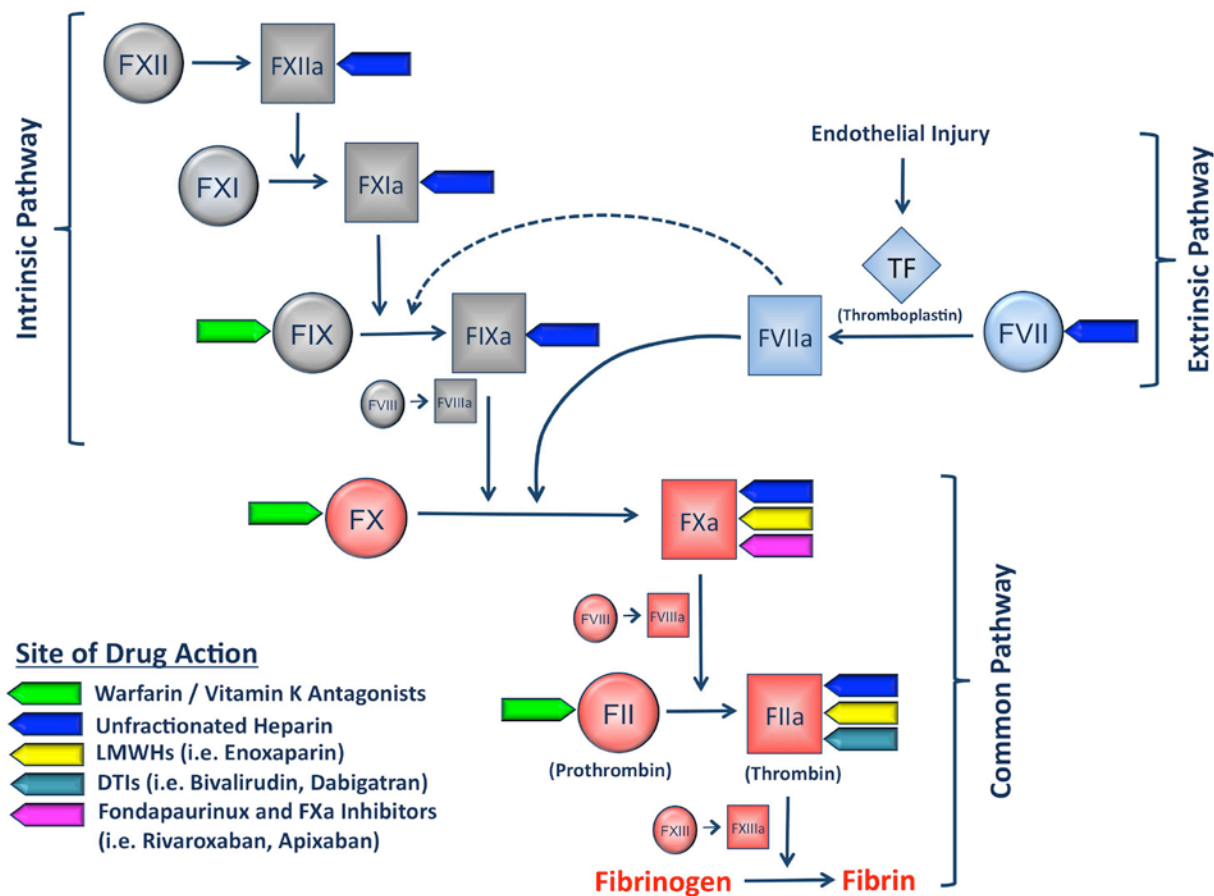
Comparing the most commonly used risk scores for NSTEMI or unstable angina, the GRACE risk score has a greater predictive value, while the TIMI risk score is easiest to use.

*Outcome of death or non-fatal myocardial infarction at 30 days and 1 year in a validation cohort. CAD=coronary artery disease. NSTEMI=non-ST segment elevation myocardial infarction.



Appendix Figure 3: Reperfusion strategies for the triage and treatment of STEMI

Simplified reperfusion schematic demonstrating that the preferred pathway is immediate angiography with first medical contact to device time within 90 min in all patients with STEMI. The goal total ischaemic time is ≤ 120 min. *Goal first medical contact to device time is ≤ 90 min. †Goal first medical contact to hospital transfer (door-in, door-out) time is ≤ 30 min. ‡Goal first medical contact to thrombolysis time is ≤ 30 min. CABG=coronary artery bypass grafting. OMT=optimal medical therapy. PCI=percutaneous coronary intervention. STEMI=ST segment elevation myocardial infarction.



Appendix Figure 4: Coagulation cascade and targets of anticoagulant medications

Simplified schematic of the coagulation cascade and the therapeutic targets the most commonly used anticoagulant agents. DTI=direct thrombin inhibitor. F=factor. LMWH=low-molecular-weight heparin.

Type 1	Spontaneous MI due to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection leading to intramural thrombus
Type 2	MI due to increased oxygen demand or decreased supply (e.g. coronary artery spasm, coronary artery embolus, arrhythmias, anemia, hypertension, hypotension, hypothyroidism, etc.)
Type 3	MI related to sudden unexpected cardiac death
Type 4a	MI associated with percutaneous coronary intervention (PCI)*
Type 4b	MI associated with stent thrombosis
Type 4c	MI associated with $\geq 50\%$ restenosis of prior angioplasty and/or stenting
Type 5	MI associated with coronary artery bypass graft surgery

MI, myocardial infarction. * Thresholds for the definition of MI post-PCI differ by professional societies.

Appendix Table 1. Classification of myocardial infarction, defined by the cause of myocardial injury.

Minimum Volume Criteria for Primary PCI:
Physician must do at least 75 interventions/year, and
Lab must perform at least 200 interventions/year, and
Lab must perform at least 36 STEMI (primary PCI) interventions/year

Appendix Table 2. Current US guideline recommended primary PCI volume criteria.

<u>Absolute Contraindications*</u>
Active bleeding or predisposition to bleeding
Prior intracerebral hemorrhage
Ischemic stroke <u>within 3 months</u> (excluding acute within 4.5 hours)
Closed-head or facial trauma <u>within 3 months</u>
Intracranial or spinal surgery <u>within 2 months</u>
Structural cerebral vascular lesion (e.g. Arteriovenous malformation)
Malignant intracranial neoplasm
Aortic dissection (or suspected dissection)
Severe, uncontrolled hypertension
<u>Relative Contraindications*</u>
Acute hypertensive episode (BP >180/110)
Chronic uncontrolled hypertension
Ischemic stroke <u>> 3 months ago</u>
Surgery or CPR (>10 min) <u>within past 3-weeks</u>
Recent internal or serious bleeding <u>within 2-4 weeks</u>
Serious injury (egg. Non-compressible puncture wounds)
Active gastrointestinal ulcer disease, history of serious GI bleed
Anticoagulant use (especially novel anticoagulant agents)
Any other intracranial pathology
Pregnancy
Dementia

* Not all-inclusive. Modified from the 2013 AHA/ACC STEMI Guidelines.

Appendix Table 3. Contraindications to fibrinolytic therapy.

	PRAMI	CvLPRIT	DANAMI-3-PRIMULTI
Sample size	465 patients	296 patients	627 patients
Randomization	Infarct-artery PCI (n=234) vs “Preventative” PCI of stenoses $\geq 50\%$ (n=231)	Infarct-artery PCI (n=146) vs “Complete” PCI (n=150) of severe stenoses ($>70\%$ in 1 plane, $>50\%$ stenosis in 2 planes)	Infarct-artery PCI (n=313) vs FFR-guided complete revascularization (n=314) prior to discharge
Primary Outcome	Composite cardiac death, recurrent MI, angina	Composite all-cause death, recurrent MI, heart failure, ischemia-driven revascularization	Composite all-cause death, recurrent MI, ischemia-driven revascularization
Follow-up	23 months	12 months	12 months (minimum)
Trial Results	Primary outcome reduced with complete PCI (HR 0.35, 95% CI 0.21-0.58; $P<0.001$) All components of composite significantly reduced	Primary outcome reduced with complete PCI (HR 0.45, 95% CI 0.24-0.84; $P=0.009$); no reduction in individual components of composite when analyzed separately	Primary outcome reduced with FFR-guided PCI (HR 0.56, 95% CI 0.38-0.83; $P=0.004$); driven by fewer repeat revascularizations (no difference in all-cause mortality or recurrent MI when analyzed separately)

Abbreviations: STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; FFR, fractional flow reserve; HR, hazard ratio; CI, confidence interval.

Appendix Table 4. Recent trials of infarct-artery only vs complete revascularization for STEMI.

<u>Characteristic</u>	<u>Points</u>
Age	
≥ 75 years	-2
65 to under 75 years	-1
< 65 years	0
Diabetes	1
Cigarette smoking within last 2 years	1
Prior MI or PCI	1
MI at presentation	1
Stent diameter < 3 mm	1
Vein graft PCI	2
Heart failure or LVEF $< 30\%$	2
<u>Risk Stratification</u>	<u>Patients</u>
Score ≥ 2	
NNT to prevent an ischemic event	34
NNH with a bleeding event	272
Score < 2	
NNT to prevent an ischemic event	153
NNH with a bleeding event	64

Calculator available at: http://daptstudy.org/for-clinicians/score_calculator.htm

Abbreviations: DAPT, dual antiplatelet therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; NNT, number needed to treat; NNH, number needed to harm.

Appendix Table 5. DAPT Trial score by characteristic.

For scores of 2 or more, number needed to treat to prevent an ischaemic event was 34; number needed to harm with a bleeding event was 272. For scores less than 2, number needed to treat to prevent an ischaemic event was 153; number needed to harm with a bleeding event was 64.

Calculator available at: http://daptstudy.org/for-clinicians/score_calculator.htm

PCI=percutaneous coronary intervention.

	Rivaroxaban	Vorapaxar
Class	Anticoagulant	Antiplatelet agent
Mechanism	FXa inhibitor	Antagonises the PAR-1 _R , inhibiting thrombin-induced platelet activation
Dose	2·5 mg or 5·0 mg taken orally twice a day	2·5 mg taken orally daily
Pivotal trial	ATLAS ACS 2-TIMI 51 ¹¹⁸	TRA 2P-TIMI 50 ¹¹⁹
Trial patients	Following acute coronary syndrome	History of myocardial infarction (not active acute coronary syndrome)
Trial results	Combined 2·5 or 5·0 mg dose twice a day. Reduced primary endpoint* (HR 0·84; 95% CI 0·74–0·96) versus placebo, but increased major bleeding, including ICH	Reduced primary endpoint* (HR 0·87; 95% CI 0·80–0·94) versus placebo, but increased moderate to severe bleeding, including ICH
Current use	2·5 mg twice a day (low) dose class IIb recommendation in Europe; not approved in USA	2·5 mg daily approved in both Europe and USA; contraindicated if history of stroke, transient ischaemic attack, or ICH

Appendix Table 6: Comparison of novel oral antithrombotics for secondary prevention after myocardial infarction

*Death from cardiovascular causes, myocardial infarction, or stroke. FXa=factor Xa.

PAR=protease-activated receptor. HR=hazard ratio. ICH=intracranial haemorrhage.