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 antplatelet 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, and more than a third of deaths in developed nations annually. Increased use of evidence-based therapies and lifestyle changes have spurred considerable reductions in mortality from coronary heart disease in recent decades. 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.

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. Today, NSTEMI comprises 60–75% of all myocardial infarctions. Further, both in-hospital and 1-year mortalities from STEMI have declined in the past two decades (5–6% and 7–18%, respectively), a testament to advances in pharmacological, reperfusion, and preventive strategies.

Pathophysiology
Acute myocardial infarction is divided into STEMI and NSTEMI. 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 (NSTE-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 I). A severe stenosis (ie, ≥70% diameter) is required to precipitate angina; however, such stenoses less commonly cause type I 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. 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. 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). In each case, the diagnosis of myocardial infarction relies on biomarker evidence of
myocyte necrosis, and either electrocardiographic (ECG) criteria of ischaemia or infarction, or ischaemic symptoms, or both. 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. 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. The 2015 European Society of Cardiology (ESC) NSTE-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%. 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. 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). 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. 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. However, doing PCI after 24 h has been associated with longer hospitalisation, 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). 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.

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 I).

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).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.17 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.14,15 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,16,17 and is advised if it can be completed in 120 min or less (appendix p 3).15

**Balloon angioplasty versus stenting**
Stent placement decreases target vessel revascularisation and subsequent myocardial infarction compared with balloon angioplasty alone.18,19 Several studies and meta-analyses show that drug-eluting stents (DES) reduce target vessel revascularisation compared with bare-metal stents (BMS),20,21 and some studies suggest that DES might also reduce major adverse cardiac events (MACE) in some patients.22–24 Concurrently, the current ESC revascularisation guidelines recommend DES exclusively in patients with acute myocardial infarction.25

**Routine aspiration thrombectomy**
Two recent trials (TOTAL18 and TASTE19) 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.26,27 Two meta-analyses showed that compared with femoral access, radial access for primary PCI is associated with fewer vascular complications and could reduce mortality,28,29 with some studies suggesting reduced MACE and hospitalisation duration.30,31 These findings were reinforced by the recent MATRIX study of 8404 patients with STEMI and NSTEMI, 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).32 Although in subgroup analysis patients with NSTEMI benefited most, neither approach appeared advantageous in STEMI.33 Regardless, ESC guidelines embrace radial access as the preferred approach for primary PCI.14,15

Fibrinolysis
**Role in the triage of STEMI**
Thrombolytic agents promote the conversion of endogenous plasminogen to plasmin, which lyses fibrin and dissolves clots.10,11 Fibrinolysis is estimated to reduce mortality by 29% compared with placebo in STEMI.34,35 That said, several trials indicate that primary PCI with balloon angioplasty or stenting, or both, should be preferred to fibrinolysis because PCI more reliably 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.36

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. An analysis of about 19000 patients from the National Registry of Myocardial Infarction (NRMI) 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. By contrast, a meta-analysis of 25 randomised trials, including NRMI 2, 3, and 4 suggested primary PCI was associated with lower 30-day mortality than fibrinolysis, irrespective of treatment delay. 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). 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. 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 tenecteplase. (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. 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 tenecteplase. (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. 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. 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. 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. 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.

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, 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. 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). 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).

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%; hazard ratio [HR] 1·16, 95% CI 0·92–1·45; p=0·20). Other studies suggest that although PCI might improve arterial patency on angiography, this does not correlate with improved left ventricular ejection fraction or outcomes. 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.

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. This recommendation is supported by data from several studies, summarised in the appendix p 8. Further, staged revascularisation of non-culprit lesions following STEMI is a class IIA recommendation in the ESC guidelines. Additionally, fractional flow reserve-guided complete revascularisation might reduce the need for repeat PCI after STEMI, as shown in DANAMI-3-PRIMULTI. 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).\(^{4,7,44-46}\)

**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.\(^{17}\) 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).\(^{7}\) 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.\(^{66,67}\)

**P2Y\(_{12}\), inhibitors**

Clopidogrel is a second generation thienopyridine that irreversibly antagonises the platelet P2Y\(_{12}\) 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.\(^{76}\) 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.\(^{77}\) 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.\(^{78,79}\) Current ESC and ACC/AHA guidelines recommend the more potent P2Y\(_{12}\), receptor inhibitors prasugrel and ticagrelor over clopidogrel for use in acute myocardial infarction.\(^{80}\)

Prasugrel is a third generation thienopyridine P2Y\(_{12}\), 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), 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. 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).81 In the ATLANTIC study, upstream ticagrelor did reduce procedural bleeding and is considered safe, unlike prasugrel in ACCOAST.82 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; 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.83 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.84,85 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,86,87 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.88 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.89,90,91 Guidelines recommend DAPT for at least 1 year after acute coronary syndrome regardless of whether medially managed or if PCI is done, irrespective of stent type (BMS or DES).1,12 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.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.95

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.96
At 3 years compared with placebo, both doses of ticagrelor reduced myocardial infarction (HR for ticagrelor 90 mg vs placebo 0·81, p=0·01; HR for ticagrelor 60 mg vs placebo 0·84, p=0·03), and MACCE (cardiovascular death, myocardial infarction, and stroke; HR for ticagrelor 90 mg vs placebo 0·85, p=0·008; HR for ticagrelor 60 mg vs placebo 0·84, p=0·004). 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=0·001 for each dose vs placebo).

Derived from the DAPT study, the DAPT score (appendix p 9) appears to be very useful to individualise the duration of antiplatelet therapy. 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, and some studies suggest, might almost completely endothelise by 3 months. Although still considered reasonable in the ACC/AHA guidelines, the use of BMS is discouraged in patients with indications for triple antithrombotic therapy after PCI.

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 0·46, 95% CI, 0·26−0·81; p=0·001), ischaemic events (11·1% vs 17·6%; 0·60, 0·38–0·94; p=0·025), and mortality (2·5% vs 6·3%; 0·39, 0·16–0·93; p=0·027) compared with all three agents after DES. In patients at high risk of bleeding, gastrointestinal protection (ie, proton-pump inhibitor therapy) should be considered.

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

<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Unfractioned heparin</th>
<th>Enoxaparin</th>
<th>Fondaparinux</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Increases AT inhibition of FXa, thrombin (FII), and other coagulation proteases</td>
<td>Increases AT inhibition of FXa more than other proteases</td>
<td>Increases AT inhibition of FXa only</td>
<td>Directly inhibits FII</td>
</tr>
<tr>
<td>Monitoring</td>
<td>aPTT (goal 1·5–2 times normal, or 50–70%)</td>
<td>FXa levels (not routinely measured)</td>
<td>FXa levels (not routinely measured)</td>
<td>aPTT (elevated, not used for titration)</td>
</tr>
<tr>
<td>STEMI</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Can be considered</td>
<td>Not approved</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>Recommended</td>
<td>Can be considered</td>
<td>Caution if used*</td>
<td>Recommended</td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Can be considered</td>
<td>Not approved</td>
</tr>
<tr>
<td>Unstable angina/NSTEMI</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Decrease dose if CrCl ≤30 mL/min, avoid if CrCl &gt;30 mL/min</td>
<td>Recommended</td>
</tr>
<tr>
<td>During PCI</td>
<td>Recommended</td>
<td>Can be considered</td>
<td>Caution if used*</td>
<td>Recommended</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Recommended</td>
<td>Decrease dose if CrCl &lt;20 mL/min, avoid in stage 4 CKD</td>
<td>Decrease dose if CrCl &lt;30 mL/min, avoid in stage 4 CKD</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>Contraindicated</td>
<td>Can be considered</td>
<td>Can be considered</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

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. FII=factor II. FXa=factor Xa. aPTT=activated partial thromboplastin time. GPIs=glycoprotein IIb/IIIa inhibitors. CrCl=creatinine clearance. CKD=chronic kidney disease.

*Given increased risk of catheter thrombosis, if fondaparinux is used, a second anticoagulant is recommended during PCI.
DAPT,102,103 Patients who benefit the most from GPs include patients with high-risk ACS undergoing PCI, inadequate P2Y₁₂ inhibition before PCI, or low bleeding risk.104 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.111,112 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.113 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.114-116 As such, the use of bivalirudin in acute myocardial infarction is
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. 

**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. 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, A to Z, and PROVE-IT TIMI 22 (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). 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. 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, the 2016 ACC consensus statement does note that the above LDL concentrations, termed thresholds for therapy, are appropriate for high-risk patients.

The IMPROVE-IT trial suggests that lower LDL targets could improve outcomes. In IMPROVE-IT, 18 144 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. These results indicate that the use of ezetimibe to further lower

**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 atioventricular 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 or with established coronary artery disease and low bleeding risk (appendix p 10).
Seminar

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.4–10

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.11–13 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
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