Acute myocardial infarction

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Modern management of acute myocardial infarction is built on a clinical evidence base drawn from many studies undertaken over the past three decades. The evolution in clinical practice has substantially reduced mortality and morbidity associated with the condition. Key to this success is the effective integration of antithrombotic therapy combined with timely reperfusion, either primary percutaneous coronary intervention or fibrinolysis for ST-elevation myocardial infarction, and invasive investigation and revascularisation for non-ST-elevation myocardial infarction, underpinned by risk stratification and optimised systems of care. After the development of troponin assays for the detection of myonecrosis, the universal definition and classification of myocardial infarction now indicates the underlying pathophysiology. Additionally, an increasing appreciation of the importance of adverse events, such as bleeding, has emerged. Remaining challenges include the effective translation of this evidence to all patients with myocardial infarction, especially to those not well represented in clinical trials who remain at increased risk of adverse events, such as elderly patients and those with renal failure. On a global level, the epidemic of diabetes and obesity in the developed world and the transition from infectious diseases to cardiovascular disease in the developing world will place an increasing demand on health-care infrastructures required to deliver time-dependent and resource-intensive care. This Seminar discusses the underlying pathophysiology, evolving perspectives on diagnosis, risk stratification, and the invasive and pharmacological management of myocardial infarction.

Introduction

Myocardial infarction is a major cause of morbidity and mortality worldwide. More than 3 million people each year are estimated to have an acute ST-elevation myocardial infarction (STEMI), with more than 4 million having a non-ST-elevation myocardial infarction (NSTEMI). From being an illness seen predominantly in developed countries, myocardial infarction is now becoming increasingly more common in developing countries. Commensurate with the robust evidence base on which the care of acute myocardial infarction[1,2] is now practised, registries have documented a decline in mortality.[3–6]

The epidemiology, basic science, and clinical evidence that inform contemporary management of acute myocardial infarction is extensive. These data span the landmark global studies that have highlighted the contribution of lifestyle factors to its incidence, explored genetic underpinnings, and provided clinical methods and biomarkers for early diagnosis and risk stratification.[7–9] Many clinical trials have also explored therapeutic innovations, and there is an emerging discipline that assesses health-care systems for the optimum delivery of this care.[10]

Search strategy and selection criteria

We searched Medline 2002–08 using the search terms: "myocardial infarction", "acute coronary syndromes", "angioplasty", "coronary stenting", "fibrinolysis", "thrombolysis", "cardiogenic shock", "stem cells", "anti-platelet therapy", "anti-thrombotic therapy", "clinical guidelines", "quality of care", "survival". We also searched the reference lists of articles identified by the search strategy and selected those we judged relevant to contemporary practice.

Improvements in morbidity and mortality need a comprehensive approach incorporating all evidence tailored to the specifics of local health-care structures (figure 1). This need is greater in developing countries, where progressive urbanisation has led to increasing rates of obesity,[11] diabetes, and an emerging epidemic of coronary heart disease, and where health-care services are not as well developed.[12,13] Although several International Guidelines have reviewed this evidence in detail,[1,2,14,15] the focus in our Seminar is on management frameworks that are important for delivering the best outcomes for patients with acute myocardial infarction.

Pathophysiology

Partial or complete epicardial coronary artery occlusion from plaques vulnerable to rupture or erosion is the

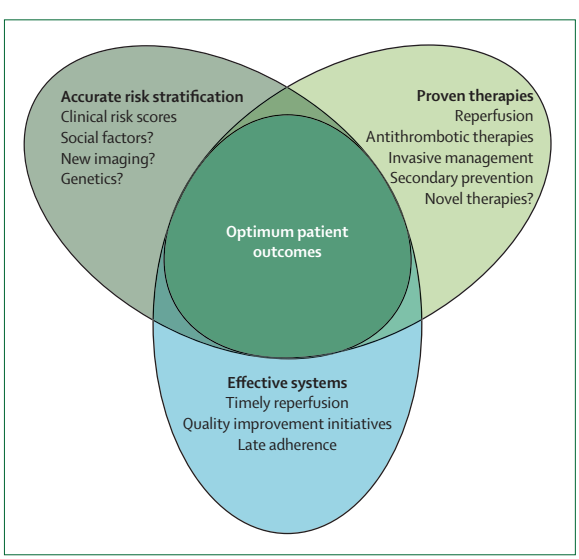

Figure 1: **Framework for optimising patient outcomes in acute myocardial infarction**

commonest cause of myocardial infarction, accounting for around 70% of fatal events.[16,17] This thrombotic process diminishes microcirculatory perfusion by reduced coronary artery flow through epicardial stenoses, as well as by distal embolisation of thrombus. This pathophysiology provides the rationale for fibrinolytic and antithrombotic therapies, whereas residual epicardial stenoses are targets for percutaneous and surgical revascularisation approaches. Vulnerable plaques likely to rupture or erode have evidence of inflammation with monocytes, macrophages, and sometimes T-cell infiltrates, together with thin fibrous caps and large lipid cores. This process involves the entire coronary vasculature, and the true culprit lesion can be difficult to define.[18–20] Platelet hyper-reactivity and pro-coagulant states also contribute to this thrombotic disease and give rise to the idea of so-called vulnerable blood.[21,22] Additionally, coronary spasm, emboli, or dissection of the coronary artery are causes of infarction in the absence of occlusive atherosclerosis, and are reported in 5–10% of patients with STEMI and 10–15% of patients with NSTEMI.[18] Similar proportions of patients with non-ST-elevation acute coronary syndromes (NSTEACS) have angiographically normal coronary arteries despite elevated troponins[23] and myocardial infarctions detected by MRI.[24]

Epidemiological studies have underscored the contribution of lifestyle factors in the development of atherosclerosis and myocardial infarction. In the INTERHEART study[25] of over 15 000 patients, 90% of myocardial infarctions were attributable to modifiable risk factors such as smoking, dyslipidaemia, hypertension, abdominal obesity, and diabetes in men (94% in women). Novel imaging techniques such as MRI and CT scanning might have a future role in refining risk assessment, especially in identifying patients at low risk in whom preventive therapies might not be justified. Similarly, a greater understanding of the genetic foundation could offer more accurate identification of patients at heightened risk, where more aggressive prevention strategies might be warranted.[26] Although several genetic variants delineating important disease pathways have been defined, their translation to effective preventive strategies needs further study.

New definitions

In 2000, the European Society of Cardiology and the American College of Cardiology Consensus group redefined myocardial infarction, with the definition being based on myocyte necrosis as determined by troponins in the clinical setting of ischaemia. Troponin T and I, more sensitive and specific measures of myocyte necrosis than creatine kinase or creatine kinase-MB (panel 1),[27] have been associated with a 60–80% increase in incidence of myocardial infarction in patients presenting with suspected acute coronary syndrome (figure 2). Challenges with implementation of the new definition have included the availability of troponin assays with sufficient diagnostic precision and the interpretation of raised troponin levels in the context of other plausible differential diagnoses.[27] In this regard, although coronary ischaemia is the most common cause

Panel 1: **Universal criteria for acute myocardial infarction**[28]

- Detection of rise and or fall of troponins with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischaemia with at least one of:
  - Symptoms of ischaemia
  - ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block)
  - Development of pathological Q waves
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, new left bundle branch block, evidence of fresh thrombus by coronary angiography or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of troponins in the blood
- For PCI, increases of biomarkers greater than 3×99th percentile upper reference limit. A subtype is related to a stent thrombosis
- For coronary artery bypass grafting increases of biomarkers greater than 5×99th percentile upper reference limit plus either new Q waves or new left bundle branch block, or documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium
- Pathological findings of acute myocardial infarction at post mortem
- Clinical classification of different types of myocardial infarction[28]
  - Type 1: Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque fissuring, erosion or rupture, or dissection
  - Type 2: Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supplies—eg, coronary artery spasm, coronary embolism (thrombus, vegetations, or atrial myxoma), anaemia, arrhythmias, hypertension, or hypotension
  - Type 3: Sudden unexpected cardiac death with symptoms suggestive of myocardial ischaemia, accompanied by new ST elevation, or new left bundle branch block, but dying before blood samples could be obtained, or in the lag phase of cardiac biomarkers in the blood
  - Type 4 A: Myocardial infarction associated with PCI
  - Type 4 B: Stent thrombosis
  - Type 5: Myocardial infarction associated with coronary artery bypass grafting

PCI=percutaneous coronary intervention.

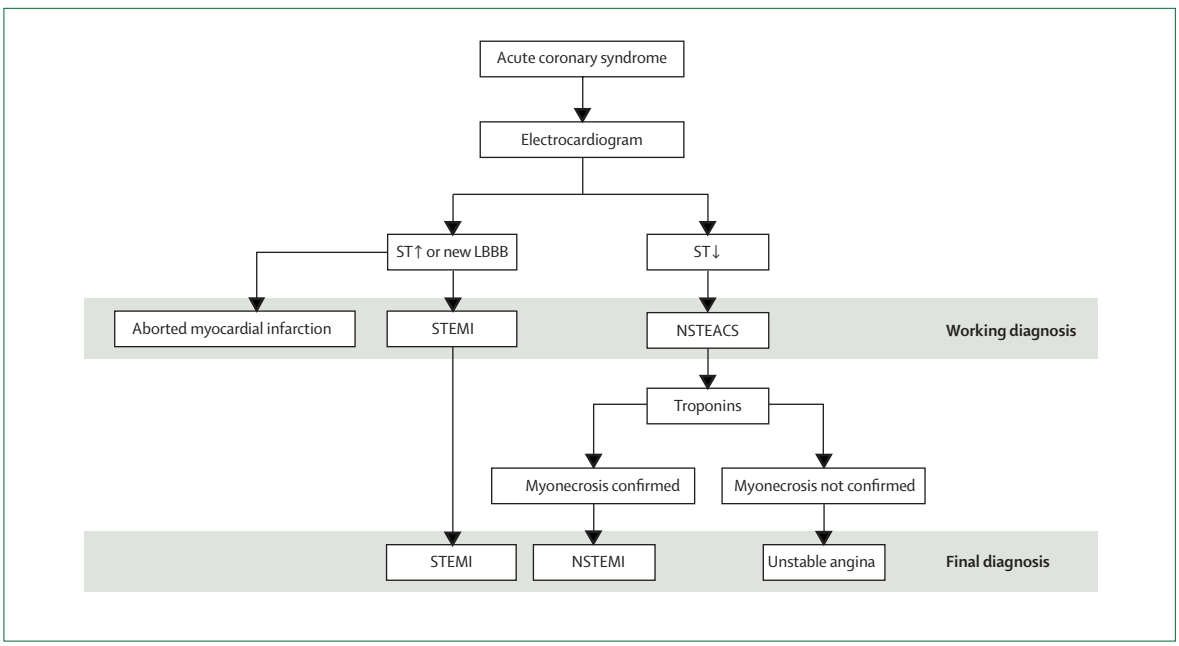

Figure 2: **Classification of acute coronary syndromes**
STEMI=ST-elevation myocardial infarction. NSTEACS=non-ST-elevation acute coronary syndromes. NSTEMI=non-ST-elevation myocardial infarction. LBBB=left bundle branch block.

of troponin elevation, it is one of many causes, and the interpretation of an elevated troponin should be assessed within the entire clinical context (panel 2). All causes of elevated troponin indicate a worse prognosis than if troponin levels are not elevated, and in the absence of a clinical presentation suggestive of coronary ischaemia, a search for other causes is needed.

A universal definition developed by an international task force[28] includes a clinical classification with five different types of myocardial infarction (panel 1). This classification incorporates the underlying pathophysiology, with implications for differing treatment approaches—eg, the treatment of anaemia or hypotension in type II myocardial infarction, as opposed to antithrombotic therapy and reperfusion or revascularisation in type I. Clinical coding will need to follow this classification and clinical trials should report the different types of myocardial infarction in a standard manner so as to assess the effects of various therapies.

The range of normal ST-segment deviation differs between men and women. ST-elevation in the V_2 or V_3 leads of 2·0 mV or less in men and 1·5 mV or less in women, or 1·0 mV or less in other leads, is normal.[28] ST-elevation exceeding these levels should be used for assessing reperfusion eligibility in the appropriate clinical context.

Beyond these definitions is the important idea of aborted myocardial infarction, where early reperfusion therapies can prevent detectable myonecrosis. Aborted myocardial infarction is seen in up to 25% of patients treated within 1 h of symptom onset with fibrinolysis, depending on the sensitivity of measures used.[29]

Risk stratification

The rapid and accurate assessment of risk is important for effective management of patients. The appropriate allocation of time-critical resources—such as systems of transport, invasive management, and the coordinated use of pharmacotherapies—requires accurate risk assessment to optimise patient outcomes and mitigate adverse events and costs. Although several risk scores in patients with STEMI and NSTEMI have been developed, their use lies not only in improved appreciation of risk and communication to patients, but also in identifying patient subsets who warrant a different treatment approach.[8,9,30–32] The best risk score for prediction of death and myocardial infarction seems to be the Global Registry for Acute Coronary Events (GRACE) score that incorporates renal dysfunction (tables 1 and 2).[33] The incorporation of other risk parameters such as biomarkers (eg, B-type natriuretic peptide), extent of disease on imaging, genetic markers, as well as functional and socioeconomic factors into the current risk models, and their ability to guide the use of current and novel therapies needs prospective assessment.[26,34,35]

Management

Management involves a complex interplay between rapid restoration of epicardial and microvascular blood flow by pharmacological and catheter-based means, suppression of recurrent ischaemic events through optimised antithrombotic therapies, and treatments aimed at mitigating the effect of myocardial necrosis and preventing future events. Key ideas and treatment

frameworks necessary for affecting improved clinical outcomes are shown in figure 3.

Reperfusion for STEMI

Fibrinolysis

Emergent pharmacological reperfusion with fibrinolysis remains the principal treatment for improving survival after STEMI.[36] Development of fibrinolytics has changed from non-fibrin specific agents (streptokinase and urokinase) by intravenous infusions, to infusions of fibrin-specific agents (tissue plasminogen activator [tPA])[37] with a mortality advantage over streptokinase, to bolus-only fibrin-specific agents (rPA,[38] TNK-tPA[39]), which achieve greater vessel patency than streptokinase and similar mortality benefit as tPA, less systemic bleeding than tPA (TNK-tPA),[39] and have the advantage

***Panel 2:* Causes of elevated troponin values in clinical settings other than acute myocardial infarction**

Cardiac
- Tachyarrhythmia, bradyarrhythmia, heart block
- Hypertension, hypotension
- Congestive heart failure
- Aortic dissection
- Aortic stenosis or regurgitation
- Hypertrophic cardiomyopathy
- Rhabdomyolysis with cardiac myocyte necrosis
- Apical ballooning syndrome (Takotsubo cardiomyopathy)
- Transplant vasculopathy
- Myopericarditis
- Rheumatic fever
- Rheumatoid arthritis
- Systemic vasculitis
- Post-viral

Infiltrative diseases of the myocardium
- Amyloidosis
- Sarcoidosis
- Haemochromatosis
- Scleroderma

Traumatic
- Atrioventricular ablation
- Defibrillation
- Chest wall trauma
- Cardiac surgery

Miscellaneous
- Renal failure
- Transient ischaemic attack, stroke, or subarachnoid haemorrhage
- Drug toxicity (eg, adriamycin, 5-fluorouracil, daunorubicin, herceptin, etc)
- Hypothyroidism
- Pulmonary embolism
- Severe asthma
- Pulmonary hypertension
- Sepsis (including sepsis occurring with shock)
- Critically ill patients
- Phaeochromocytoma
- Severe burns
- Kawasaki disease
- Extreme exertion
- Snake venom

	Points
Age (years)	
<40	0
40–49	18
50–59	36
60–69	55
70–79	73
≥80	91
Heart rate (beats per min)	
<70	0
70–89	7
90–109	13
110–149	23
150–199	36
>200	46
Systolic blood pressure (mm Hg)	
<80	63
80–99	58
100–119	47
120–139	37
140–159	26
160–199	11
>200	0
Creatinine (μmol/L)	
0–34	2
35–70	5
71–105	8
106–140	11
141–176	14
177–353	23
≥354	31
Killip class	
Class I	0
Class II	21
Class III	43
Class IV	64
Other risk factors	
Cardiac arrest at admission	43
Elevated cardiac markers	15
ST segment deviation	30

***Table 1:* GRACE risk score for acute coronary syndromes (0–258)[8]**

	<96	96–112	113–133	>133
30 day death	3·1%	5·3%	5·9%	11·2%
12 month death	4·2%	9·6%	11·9%	27·2%

***Table 2:* Risk corresponding to total points**

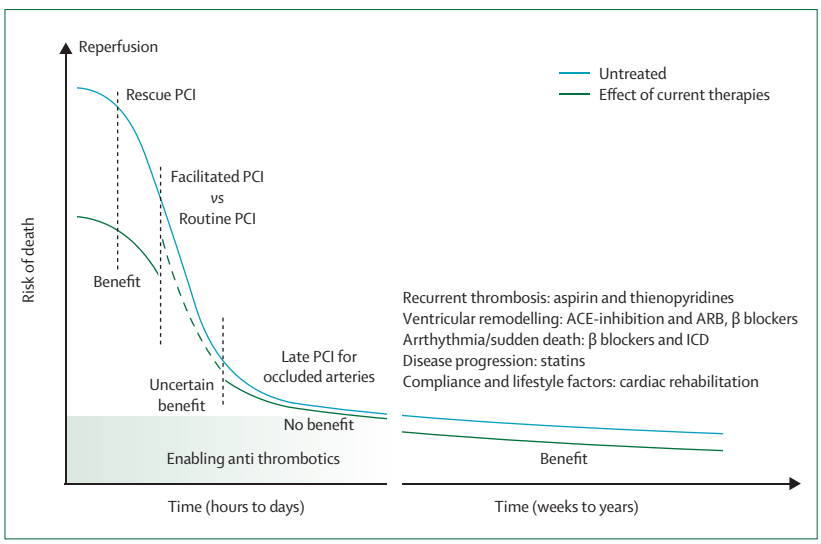

Figure 3: **Schematic integration of therapies and invasive management to effect an early and late mortality reduction in patients with myocardial infarction**
ICD=implantable cardioverter-defibrillator. ARB=angiotensin receptor blockers. ACE=angiotensin converting enzyme. PCI=percutaneous coronary intervention.

of ease of administration. Despite these innovations, further reductions in 30-day or late mortality have not been reported, although simpler regimens should translate to broader application outside hospital, more timely administration, and fewer treatment errors.

The earlier that fibrinolysis is begun, the greater the benefit with respect to preservation of left-ventricular function and reduction in mortality, which suggests an important role for prehospital fibrinolysis.[40–42] In a study of prehospital fibrinolysis with a 26% rate of rescue percutaneous coronary intervention (PCI), fewer patients randomised within 2 h of symptom onset had cardiogenic shock (1·3% *vs* 5·3%, p=0·03) and more survived to 30-days (2·2% *vs* 5·7%) when compared with primary angioplasty, although this finding was not significant (p=0·058).[41] Although studies confirming these observations are needed, the development of clinical networks designed to enable prehospital fibrinolysis could provide further mortality benefits to a broader population of patients presenting with STEMI.

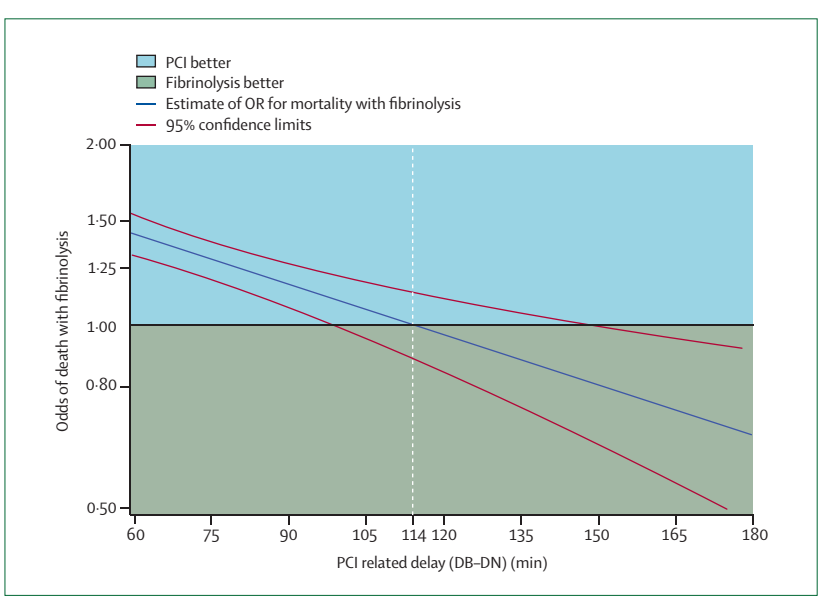

Figure 4: **Time to PCI versus fibrinolysis in STEMI**
Increasing delay in initiating catheter-based reperfusion mitigates the incremental benefits of primary PCI over fibrinolysis. PCI related delay=door to balloon time (DB)–door to needle time (DN). Adapted with permission from Pinto and colleagues.[48]

Catheter-based reperfusion

Although primary PCI is resource-intensive and more difficult to quickly implement than fibrinolysis, when both options are available, primary PCI seems to offer better clinical outcomes. A meta-analysis of 23 randomised trials with 7739 patients showed that primary PCI resulted in a lower rate of early death (7% *vs* 9%, p=0·0002), non-fatal reinfarction (3% *vs* 7%, p<0·0001), and stroke (1% *vs* 2%; p=0·0004) than fibrinolysis.[43] The benefit of PCI over fibrinolysis is evident when patients are treated early after symptom onset and increases with greater delay in presentation.[44] The advent of percutaneously placed emboli protection devices and drug-eluting stents have not provided further reductions in acute (30-day) mortality.[45,46]

The benefit of PCI over fibrinolysis remains dependent on timely implementation, with some analyses suggesting that the incremental benefit is lost with a relative delay (door-to-balloon time[47] *vs* door-to-needle time [PCI]) of between 60 min and 114 min, with less tolerance in high-risk patients.[48,49] There is a complex interplay between patient age, infarct location, and initial delay in presentation, and the tolerable delay for achieving the benefit of primary PCI over fibrinolysis. In general, the improved outcome of primary PCI over fibrinolysis is lost earlier in patients younger than 65 years of age and in those presenting within 120 min of symptom onset (figure 4). Therefore, the advantage of primary PCI over fibrinolysis is dependent on efficient and effective clinical systems that are able to deliver timely and consistent reperfusion.

The key logistical challenge of a primary PCI strategy is the extension of this approach to hospitals without invasive services. Of 4278 patients transferred from other centres for primary PCI drawn from the National Registry of Myocardial Infarction 3 and 4 database in the USA, the median door-to-balloon time was 180 min, with only 4·9% of patients treated within the 90 min recommended in clinical guidelines.[50] The potential value of established health-care networks has been examined in several studies with promising results.[51–53] In the DANAMI-2 study,[52] transfer for PCI was associated with lower rates of stroke, recurrent myocardial infarction, and unplanned revascularisation than was onsite fibrinolysis, but there was no reduction in mortality. The value of such networks needs careful local assessment.

Failed reperfusion

Failure to achieve microvascular flow, as assessed by resolution of ST-segment elevation or contrast flow by angiography, is seen with fibrinolysis (in up to around 40% of patients) and primary PCI (in around 25%).[54,55] Factors associated with failed reperfusion include delay to presentation, infarct location, and concomitant therapies.[56] These suboptimum outcomes have led to pharmacological strategies aimed at improving the efficacy of reperfusion with adjunctive pharmacology before and combined with invasive strategies.

Invasive management after pharmacological reperfusion

In view of the logistical constraints of providing primary PCI to all patients presenting with STEMI, several hybrid pharmacoinvasive strategies have evolved, seeking to take advantage of the ease of fibrinolysis combined with the treatment of the culprit lesion with PCI.[57]

Rescue PCI

In patients who receive fibrinolysis, accumulating evidence supports the role of emergent angiography and rescue PCI for failed reperfusion, defined as ongoing chest-pain, failure of ST-segment resolution by more than 50% at 90 min after fibrinolysis, or both. In a meta-analysis of eight trials with 1117 patients, rescue PCI was associated with lower rates of death, heart failure, and reinfarction by 6 months (29·2% *vs* 41·0%, 11·8% absolute reduction, 95% CI 5–18, p<0·001) than was a conservative strategy with PCI only for recurrent ischaemia after fibrinolysis. A non-significant reduction in mortality (odds ratio [OR] 0·69, 95% CI 0·23–1·05, p=0·09) was observed but rescue PCI was associated with a 3% (95% CI 0–5, p=0·02) absolute increase in the risk of stroke.[47] PCI for reinfarction after fibrinolysis is also better than readministration of fibrinolysis.[58]

Facilitated PCI

Routine emergent PCI after fibrinolysis (ie, very early PCI without ongoing evidence of failed reperfusion) or facilitated PCI has not been associated with benefits. The ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) study[59] of 1667 patients reported an increase in the composite of death, heart failure, and shock compared with primary PCI alone (18·6% *vs* 13·4%, p=0·005). Meta-analysis including the ASSENT-4 PCI study reached the same conclusions.[60] Also the Facilitated Intervention for Enhanced Reperfusion Speed to Stop Events (FINESSE) trial showed no benefit of facilitated PCI following half-dose r-PA and abciximab (a potentially more robust antithrombotic approach) compared with primary PCI in 2653 patients.[61] Whether a facilitated PCI strategy has a role in clinical settings where primary PCI is associated with substantial delays (6–12 h) needs more study.[57]

Routine PCI after fibrinolysis

Early PCI within 24 h could consolidate the benefits of successful reperfusion.[62] Meta-analyses of three trials which compared routine PCI with stenting after fibrinolysis to ischaemia-guided stenting after fibrinolysis showed a reduction in death of 3·8% *vs* 6·7%, OR 0·56; 95% CI 0·29–1·05), p=0.07 and a significant reduction in death and myocardial infarction at 6 months 7·4% *vs* 13·2%, p<0·01.[63] Small studies have also suggested benefits with PCI 3–12 h after fibrinolysis in the context of more robust antithrombotic therapies for improved epicardial flow and tissue perfusion.[61,64] In a small study, early fibrinolysis and PCI within 24 h achieved similar outcomes to primary PCI.[65] A pharmacoinvasive strategy of immediate fibrinolysis and early revascularisation would be practicable in many parts of the developed world, but these results need to be considered carefully in the context of the negative findings associated with facilitated PCI. Collectively, these data seem supportive of very early invasive management after fibrinolysis with reduced composite outcomes of death, recurrent myocardial infarction, and recurrent ischaemia, although these gains are more evident in recurrent myocardial infarction or ischaemia and in patients with ongoing ischaemia (rescue PCI). However, although these questions are the focus of clinical research worldwide, with emerging promising results, firm recommendations regarding early invasive management (2–6 h after fibrinolysis) in patients without ongoing ischaemia cannot be made.

Management of occluded infarct-related arteries

The open artery theory[66,67] postulated that late infarct artery patency would improve left-ventricular remodelling,[68] decrease arrhythmias, and reduce future events through provision of collaterals. This theory was tested in the Occluded Artery Trial,[69] where 2166 patients with an occluded artery within 3–28 days after myocardial infarction were randomised to either PCI or optimum medical management. There was no benefit of PCI for the composite of death, myocardial infarction, or heart failure (17·2% PCI and 15·6% medical therapy [hazard ratio 1·16; 95% CI 0·92–1·45, p=0·20]). Medical management is the recommended treatment for patients with occluded infarct-related arteries 24 h after symptom onset who are free of ongoing ischaemia.

Invasive management of NSTEACS

The rationale for treating the culprit lesion with PCI has been extended to patients without STEMI. Several studies have explored the role of routine invasive management versus a conservative ischaemia-driven strategy in NSTEACS.[70–75] These data have been analysed in two meta-analyses.[76,77] The first included seven trials (n=9212) and recorded a greater rate of in-hospital death or myocardial infarction with an invasive strategy

(conservative 3·8% *vs* invasive 5·2%; OR 1·36; 95% CI 1·12–1·66, p=0·002) but a lower rate of these events after hospital discharge (conservative 11·0% *vs* invasive 7·4%; OR 0·64; 95% CI 0·56–0·75, p<0·001) than with conservative therapy. A greater benefit was seen with troponin elevation.[76] The lack of consistent benefit should be noted and is probably attributable to trial differences in the timing of the invasive approach, the proportion of patients undergoing invasive management in the invasive groups (44%–82%)[70,74] and conservative groups (9%–40%),[71,75] and the antithrombotic therapies used. A subsequent meta-analysis of more contemporary studies with higher rates of glycoprotein IIb/IIIa inhibition, and use of clopidogrel, noted a 17% relative reduction in late mortality (OR 0·83, 95% CI 0·72–0·96, p=0·012) with the routine invasive strategy compared with an ischaemia-driven approach.[77] In the 5 year follow-up of RITA-3,[77] rates of death or myocardial infarction were reduced from 20·0% to 16·6% (OR 0·61; 95% CI 0·61–0·99, p=0·044) and there was a non-significant reduction in death from 15·1% to 12·1% (OR 0·76, 95% CI 0·81–1·00, p=0·054), further supporting the routine early invasive strategy

Clinical evidence suggests that early provision of an invasive strategy (within 48–72 h of presentation) is important in achieving this benefit.[78–80] In a comparison of 410 patients with acute coronary syndrome receiving aspirin, clopidogrel, tirofiban, and heparin randomised to invasive therapy within 6 h of presentation or after a cooling off period of 3–5 days, a benefit with very early invasive management was seen.[79] Although small, this study reported a lower rate of 30-day death or myocardial infarction (5·9% *vs* 11·9%, p=0·04) in patients treated within 6 h, with all the difference accounted for by myocardial infarctions occurring before invasive therapy in the delayed group.[78] Hence, where clinically appropriate, after considering comorbid conditions, early invasive management should be implemented as early as possible.

Acute phase adjunctive pharmacotherapies

Modern management of myocardial infarction has evolved to an increased use of invasive management, but this transition has only been enabled by developments in antithrombotic therapies. Improved appreciation of the role of platelet activation and aggregation in ongoing ischaemic events has led to the use of more effective antiplatelet therapies. Likewise, alternative approaches to antithrombin therapies beyond unfractionated heparin have been developed. The clinical challenge is the optimum combination of these therapies for effective suppression of ischaemic events, while avoiding bleeding events, in the context of invasive management that often includes coronary artery bypass grafting.

Antiplatelet therapies

Since the early fibrinolytic studies,[81] aspirin 150–325 mg has been a mainstay treatment for all patients undergoing either pharmacological or catheter-based reperfusion, and recommendations have been made that all patients with acute coronary syndromes and without contraindications should receive aspirin 150–300 mg.[82,83]

Clopidogrel, a thienopyridine antagonist of ADP, is recommended for acute coronary syndromes in the absence of contraindications. Patients younger than 75 years treated with fibrinolysis randomised to receive clopidogrel (300 mg loading dose and 75 mg daily compared with placebo) achieved improved rates of vessel patency 3–5 days later with a non-significant reduction in myocardial infarction (2·5% *vs* 3·6%: p=0·08).[84] These results are, however, supported by a 7% reduction in hospital mortality with clopidogrel (75 mg a day added to aspirin, without a loading dose) among 45 852 patients with myocardial infarction, irrespective of reperfusion status (7·5% *vs* 8·1%, p=0·03).[85]

In a randomised study[86] of 12 562 NSTEACS patients, comparing clopidogrel 300 mg loading and 75 mg daily to placebo on a background of aspirin, a 20% relative risk reduction in cardiovascular death, non-fatal myocardial infarction, and stroke was observed (clopidogrel 9·3% *vs* placebo 11·4%; relative risk [RR] 0·80, 95% CI 0·72–0·90, p<0·001). A higher loading dose of clopidogrel (600 mg) has been shown to achieve more rapid platelet inhibition[87] and is being tested in trials. There is an increased bleeding risk with coronary artery bypass grafting within 5 days of taking clopidogrel and early initiation needs to be carefully considered in patients where clinical feature could suggest the need for early surgical revascularisation.[88]

Prasugrel irreversibly inhibits the $P2Y_{12}$ receptor at the same site as clopidogrel, and has been shown to be better than clopidogrel in patients with NSTEACS particularly in those with diabetes for reducing a composite of cardiovascular death, myocardial infarction, stroke, and to reduce late stent thrombosis, but to increase major bleeding.[89]

Glycoprotein IIb/IIIa antagonists

In patients undergoing primary PCI, abciximab, a chimeric monoclonal antibody fragment targeting the glycoprotein IIb/IIIa receptor, is associated with a reduction in the composite ischaemic endpoints of death, recurrent myocardial infarction, and urgent revascularisation.[90–92] One meta-analysis also reported a reduction in mortality.[92] Small molecule glycoprotein IIb/IIIa inhibitors (tirofiban and eptifibatide) have not been extensively studied,[92] although mechanistic studies have suggested improved vessel patency.[93,94] Trials of half-dose fibrinolytics and glycoprotein IIb/IIIa inhibition for pharmacological reperfusion have also indicated improved patency and more rapid ST-segment resolution, and less recurrent infarction than with standard fibrinolytic therapy, but no reduction in mortality.[38]

In a meta-analysis of 31402 patients with NSTEACS, glycoprotein IIb/IIIa antagonists initiated early after admission reduced death and myocardial infarction by 9% at 30 days (p=0·015). Major bleeding occurred in 2·4% of patients receiving IIb/IIIa antagonists *vs* 1·4% of patients receiving placebo (p<0·0001).[95] The treatment effect was larger (18% reduction in death and myocardial infarction) in patients who had elevated troponin levels (9·3% *vs* 11·3%, p<0·001).

Antithrombotic therapies

Despite limited data supporting its use, unfractionated heparin remains the most common antithrombotic therapy used for the management of myocardial infarction. In patients receiving fibrin-specific fibrinolytic agents, unfractionated heparin commenced early after fibrinolysis is recommended, although the independent benefit of such treatment has not been fully defined. The use of adjunctive unfractionated heparin with streptokinase has been controversial, although a meta-analysis has shown a reduction in mortality compared with placebo.[96] In a meta-analysis of six randomised studies of patients with NSTEACS, unfractionated heparin added to aspirin was associated with a non-significant reduction in death or myocardial infarction (OR 0·67, 95% CI 0·44–1·02; p=0.06).[97]

Limitations of unfractionated heparin include a variable therapeutic response depending on age, weight, and renal function, and the requirement for monitoring of activated partial thromboplastin time. Low molecular weight heparins have anti-Xa and anti-IIa activity, high bioavailability, provide more consistent anticoagulation avoiding the need for monitoring, and are associated with a lower risk for heparin-induced thrombocytopenia than unfractionated heparin. Most of the current data are with enoxaparin,[98] with some earlier studies assessing dalteparin in NSTEACS.[99] In 20479 patients with STEMI receiving fibrinolysis, enoxaparin administered for 4–7 days compared with unfractionated heparin for 48 h reduced the risk of death and non-fatal myocardial infarction at 30 days (9·9% *vs* 12%, RR 0·83, p<0·001), with an increase in major bleeding (2·1% *vs* 1·4%, RR 1·53, p<0·001).[100] Enoxaparin is a suitable antithrombotic with fibrin and non-fibrin specific fibrinolytics. Dose adjustment is necessary in patients over 75 years of age and patients with renal failure.[101]

In NSTEACS, a meta-analysis of trials comparing enoxaparin to unfractionated heparin reported an overall 9% reduction in death and myocardial infarction at 30 days, with a greater effect of 20% seen in trials using more conservative management and when time to PCI was greater.[102] In studies where most patients had early angiography, an increase in major bleeding was also evident in patients receiving enoxaparin compared with unfractionated heparin, with similar rates of death or myocardial infarction at 30 days and 6 months.[103] Enoxaparin is recommended with conservative management and as an alternative to unfractionated heparin with an early invasive strategy.

Direct thrombin inhibitors

In patients with STEMI, bivalirudin, a short-acting direct thrombin inhibitor used as an adjunct to streptokinase, was not associated with any further reduction in 30-day mortality.[104] In primary PCI, bivalirudin reduced major bleeding from 8·3% to 4·9% (p<0·001), compared with unfractionated heparin with a IIb/IIIa antagonist. 30-day cardiac mortality and total mortality were reduced (2·1% *vs* 3·1%, p=0·047), suggesting this agent might be the antithrombotic agent of choice in primary PCI.[105]

For moderate-risk and high-risk NSTEACS and unstable angina, bivalirudin had similar ischaemic benefit as either unfractionated heparin or enoxaparin with a IIb/IIIa antagonist but a 47% reduction in major bleeding (3·0% *vs* 5·6% p<0·001)[106,107] and is an appropriate choice for these patients.

Factor X inhibition

Fondaparinux, a synthetic factor Xa inhibitor, has been found to reduce 30-day death or myocardial infarction in patients receiving fibrinolysis (10·9% *vs* 13·6%; p<0·05) and in those not receiving fibrinolysis (12·2% *vs* 15·1%; p<0·01) compared with unfractionated heparin or placebo.[108] In patients undergoing primary PCI there was no benefit with fondaparinux, with an excess of catheter thrombosis noted.

In 20078 patients with NSTEACS, fondaparinux was similar to enoxaparin at 9 days for the composite endpoint of death, myocardial infarction, or refractory ischaemia (5·8% fondaparinux *vs* 5·7% enoxaparin), but a 48% reduction in major bleeding (4·1% to 2·2%) was reported (p<0·0001).[109] A reduction in mortality with

	Unfractionated heparin	Enoxaparin	Fondaparinux	Bivalirudin
STEMI				
Fibrinolysis	Can be used	Strong preference	Strong preference	
No fibrinolysis			Strong preference	
Primary PCI	Can be used			Strong preference
NSTEMI				
Early invasive management (<12 h)	Can be used			Strong preference
Early invasive management (12–48 h)	Can be used	Can be used	Strong preference	Strong preference
Conservative management	Can be used	Preference	Strong preference	
Increased bleeding risk			Strong preference	Strong preference
Renal impairment*	Can be used		Can be used	Strong preference
Thrombocytopenia†		Can be used	Can be used	Strong preference

*Fondaparinux and bivalirudin can be used without dose adjustment above a creatinine clearance of 30 mL/min. Enoxaparin should be dose adjusted to 1 mg/kg subcutaneously once a day for creatinine clearance <60 mL/min and not used in patients with creatinine clearance <30 mL/min. †Heparin induced thrombocytopenia is the most common form.

Table 3: **Choice of antithrombotic therapy**

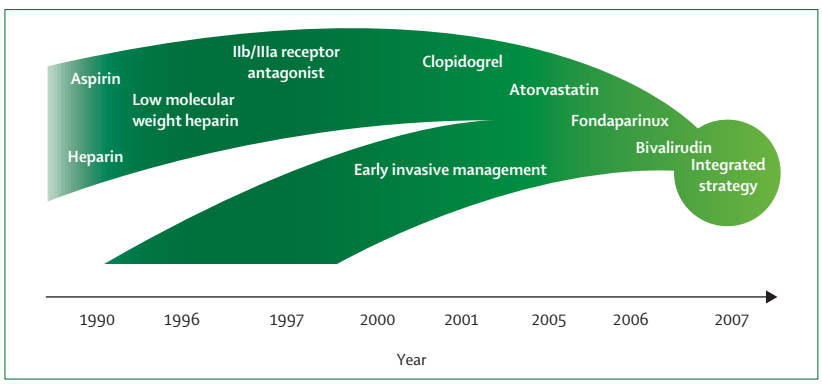

Figure 5: **Evolution of therapies in the management of acute coronary syndromes**

fondaparinux was seen at 6 months (5·8% *vs* 6·5%, p=0·05). Catheter-related thrombus was again seen in patients undergoing PCI, although this finding was mitigated by the addition of unfractionated heparin. Fondaparinux is an appropriate choice in patients with STEMI treated and not treated with fibrinolysis and in patients with NSTEACS, but should not be used with primary PCI.

Combination of antithrombotic therapies

Integration of antithrombotic therapies into a single strategy that optimises ischaemic outcomes, while reducing bleeding risk, remains challenging, particularly in patients at increased risk of bleeding undergoing invasive management. Consideration also needs to be given to the timing of angiography and possible PCI. In general, all patients should receive aspirin and clopidogrel and one antithrombin agent (unfractionated heparin, enoxaparin, bivalirudin, or fondaparinux, but not a combination). Where there is an increased bleeding risk and an invasive strategy is planned, use of bivalirudin is supported by strong data,[106,107] whereas for patients in whom conservative management is planned, fondaparinux is associated with reduced bleeding and mortality.[108,109] Recommended choices of antithrombotic agent according to indications, timing of intervention, bleeding risk, renal failure, and presence of thrombocytopenia are given in table 3.

Evidence supports the additive benefits of combination antiplatelet agents (aspirin, thienopyridines, and glycoprotein IIb/IIIa inhibition). For patients with elevated troponin levels undergoing PCI, abciximab in addition to clopidogrel and aspirin further reduces ischaemic events.[110] Glycoprotein IIb/IIIa inhibition commenced in the catheterisation laboratory rather than soon after admission has been shown to reduce major bleeding (4·9% *vs* 6·1%, p<0·01) with a non-significant increase in ischaemic events (7·9% *vs* 7·1%, p=0·13), although the 95% confidence limits do not exclude a 29% increase.[111] Thus aspirin, clopidogrel, and an antithrombin agent should be commenced soon after admission, whereas initiation of a glycoprotein IIb/IIIa inhibitor can be deferred until assessment with angiography. Ongoing trials will refine this approach.

Complications of myocardial infarction

Mortality from myocardial infarction has been decreasing. Data from GRACE for 1999 and 2006[3] reported a 3·9% (95% CI 1·9–5·3, p<0·001) absolute risk reduction in hospital deaths for patients presenting with STEMI and 0·7% (95% CI –0·3 to 1·7, p=0·02) for those presenting with NSTEACS, with a 2·7% (95% CI 0·5–4·3, p=0·02) absolute reduction in cardiogenic shock and heart failure. Most deaths in hospitalised patients with STEMI or NSTEMI are due to heart failure and mechanical complications including: myocardial rupture; mitral regurgitation due to papillary muscle dysfunction or chordal rupture; and ventricular septal rupture. Despite contemporary therapies including reperfusion, emergent revascularisation, and intra-aortic balloon pumping, half of patients with cardiogenic shock will die.[112] Compared with the pre-reperfusion era, fatal ventricular tachyarrhythmias are now less common, although sudden cardiac death remains a substantial cause of late mortality in those with severe impairment of left ventricular function (ejection fraction <35%).

Bleeding

The importance of iatrogenic bleeding and the relation with mortality is increasingly recognised. These events are the result of an interaction between potent antithrombotic therapy, invasive management, and an increasing prevalence of factors that predispose to bleeding including advanced age, hypertension, and renal impairment.[113–115] Why bleeding is associated with a roughly 5-fold increased late mortality is not known, but possibilities include hypotension resulting in myocardial ischaemia and infarction, transfusion-associated diseases, and cessation of therapies such as aspirin and clopidogrel with loss of their benefits.[114]

Therapeutic approaches to reducing secondary events

Adherence to proven therapies and control of lifestyle factors such as smoking, obesity, lack of exercise, and cardiac rehabilitation are important for improving outcomes. Systematic analysis of 63 randomised secondary prevention studies (21295 patients) has clearly indicated sustained mortality benefits (risk ratio 0·85, 95% CI 0·77–0·94) associated with these programmes, irrespective of the inclusion of structured exercise components. However, the cost-effectiveness implications require further clarification.[116] Beyond the initial phase of management, both aspirin and clopidogrel have been associated with further reductions in ischaemic events and should be continued indefinitely for aspirin and for 3–12 months for clopidogrel. Angiotensin-converting enzyme (ACE) inhibitors are indicated in patients with heart failure, anterior infarction, or a history of previous infarction. These

agents exert some of their effects on reducing left ventricular remodelling (figure 5).[117,118] Angiotensin II receptor blockers have a role when ACE-inhibitors are not tolerated.[119] In the absence of severe renal dysfunction or hyperkalaemia, post-myocardial infarction patients with an ejection fraction of less than 40% or heart failure should receive an aldosterone antagonist.[120]

Much evidence supports the use of statin therapy as secondary prevention after acute coronary syndromes, with these agents providing substantial reductions in mortality as well as in non-fatal ischaemic events.[121] Although data suggest that early initiation of statin therapy might provide further reductions in ischaemic events, a meta-analysis of 12 clinical trials with 13 024 patients enrolled soon after an acute coronary event found no significant reduction in death, recurrent myocardial infarction, and stroke at 30 days compared with placebo, low-dose statins, or usual care.[122]

In another study, metoprolol was associated with no reduction in mortality but with fewer recurrent myocardial infarctions (metoprolol 2·0% *vs* placebo 2·5%; OR 0·82; 0·72–0·92; p=0·001) and episodes of ventricular fibrillation (2·5% *vs* 3·0%; OR 0·83; 0·75–0·93; p=0·001), irrespective of reperfusion status. This benefit was associated with an increase in the risk of cardiogenic shock (5·0% *vs* 3·9%; OR 1·30; 1·19–1·41, p<0·0001).[123] Although the relative benefit of β blockers after myocardial infarction in the context of more aggressive revascularisation is unclear, these agents are recommended. Long-acting agents (carvedilol, bisoprolol, and metoprolol succinate) should be given to those patients with substantial reductions in left ventricular function.

Implantable defibrillators

Robust evidence supports the use of implantable cardioverter-defibrillators in patients with life-threatening ventricular arrhythmias with (and without) an ischaemic basis, especially in the presence of reduced left-ventricular function. This evidence extends to the primary prevention of sudden cardiac death.[124–126] Cardioverter-defibrillators are better than conventional antiarrhythmic therapies in patients with a left-ventricular ejection fraction of 35% or less and inducible ventricular tachycardia on electrophysiologic testing (hazard ratio 0·46; 95% CI 0·26–0·92, p<0·009). They are also preferable after myocardial infarction (>30 days after the event) in patients with left ventricular ejection fraction of 30% or less without any electrophysiological risk criteria (hazard ratio 0·69; 95% CI 0·51–0·93; p=0·02).[125,126] A challenge is the generalisability of these data, including their application to elderly patients and those with significant comorbidities.[127]

Special patient groups

Specific patient subgroups, namely elderly people,[128,129] people with diabetes,[130,131] and those with renal dysfunction,[132–134] endure a disproportionate burden of the morbidity and mortality associated with myocardial infarction. However, proven therapies such as fibrinolysis and early revascularisation remain under-used, despite evidence suggesting a greater absolute benefit.[135–138] For example, in NSTEACS patients with diabetes at presentation, a 1·78-fold (95% CI 1·24–2·56, p<0·001) increase in mortality is evident at 30 days and a 1·65-fold (95% CI 1·30–2·10, p<0·001) increase is evident at 1 year.[130] Similarly, the absolute benefit of a routine invasive approach in terms of death or myocardial infarction at 6 months in NSTEACS was greater in patients older than 65 years than in those aged 65 years and younger within an observational analysis of the TACTICS-TIMI-18 study (invasive 10·8% *vs* conservative 21·6%; p=0·016), although an increased risk of bleeding was also seen in elderly patients.[138]

Many current recommendations rely on subgroup analyses of larger trials, with limited capacity to detect moderate treatment differences among these high-risk groups. To improve the evidence base on which specific recommendations can be made, future clinical trials validating current therapies and exploring new approaches or specific treatment strategies to ameliorate excess risk are required. Dose attenuation by age has been formally studied with enoxaparin in patients receiving fibrinolysis, with reduced bleeding events observed.[101]

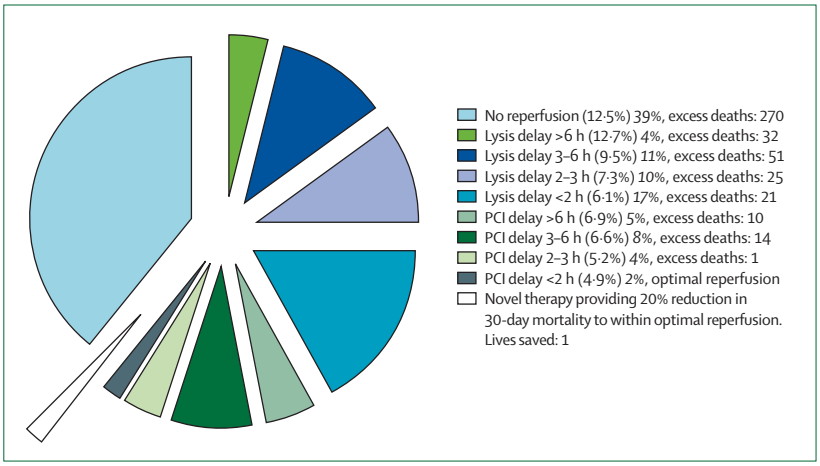

Figure 6: **Missed opportunities in reperfusion for STEMI**
Estimates of the proportion of all STEMI patients receiving either fibrinolysis or catheter-based reperfusion (*italic*) at various degrees of delay, combined with literature-based estimates of mortality observed with the reperfusion modality and associated delay (parentheses). Excess deaths estimated by multiplying the excess mortality rate above primary PCI undertaken within 2 h of onset of symptoms by the proportion of patients at risk in a cohort of 10 000 patients presenting with STEMI.[44,135]

Novel therapies

Results of studies of several novel therapies, including complement inhibitors,[139] glucose-insulin potassium,[140] and peri-infarction cooling, have been disappointing.[141] Pexelizumab, a C5 complement inhibitor was studied

as an adjunctive agent with primary PCI.[139] There was no effect on mortality by 30 days (4·1% *vs* 3·9%, p=0·78). Of 20 201 patients treated with fibrinolytic therapy, infusions of glucose-insulin-potassium irrespective of diabetic status have also shown no additional benefit over standard therapy.[140] Nevertheless, control of acute hyperglycaemia in those with raised glucose levels, and ongoing management of glucose control for patients with newly diagnosed and established diabetes, is strongly recommended. Hypothermia to a temperature of 33°C to decrease myocardial metabolism showed no overall reduction in infarction size, although there was a small reduction for patients with anterior myocardial infarctions.[141]

Whether reparative approaches such as stem cell therapies are able to provide substantial improvements in cardiac morbidity and sudden cardiac death among patients with severe left-ventricular impairment is still being researched.[142]

The last mile

Despite this rich evidence base, large-scale registries have documented missed opportunities in the provision of reperfusion therapy and other proven therapies.[135–137,143] Clinical outcome studies show the strong association between the lack of provision of care and non-adherence, with increased late mortality in patients presenting with acute coronary syndromes.[144–146] Evidence from GRACE indicates that almost 40% of STEMI patients receive no reperfusion therapy.[135] Improving the proportion of patients receiving reperfusion and decreasing the delay in delivering reperfusion would save more lives than changing from the strategy of fibrinolysis to primary PCI or introducing novel adjunctive therapies to current reperfusion practices (figure 6). Increasing the numbers of patients treated with reperfusion therapy would save an estimated 270 lives per 10 000 STEMI patients. Reducing time to lysis or changing to a PCI strategy from lysis would save an estimated 154 lives per 10 000 STEMI patients. The effect of a novel therapy reducing mortality by 20% to patients receiving optimal reperfusion (PCI less than 2 h) would result in one life saved per 10 000 patients with STEMI. Hence, these studies suggest the potential for greater improvements in patient outcome with improved care delivery compared with the potential gains from therapeutic innovations, especially among understudied and underserved groups where adverse outcomes remain high.

Several initiatives have explored the engineering of better health-care systems aimed at improved provision of timely and effective care for patients.[53,147,148] Such programmes have sought to imbed methods aimed at increasing application of proven therapies, used clinical networks with common protocols, and promoted a culture of objective assessment of clinical care. Importantly, substantial 1-year mortality reductions have been reported with such initiatives (OR 0·53; 95% CI 0·36–0·76, p=0·0006).[148] Similarly, focused analysis of the care processes can inform the design of better local clinical systems.[149] Further studies focusing on the determinants of poor adherence, lack of evidence application, systems of care, and their association with patient outcomes are required. The resources required to optimally implement these system changes are unclear, and formal cost-effectiveness evaluation of such initiatives could help prioritise future resource allocation to research and health care.

Conclusion

Therapeutic options for treatment of patients with myocardial infarction have improved substantially over the past 25 years. Our understanding of the pathophysiology has also meant a shift in our focus. Biotechnological innovation, such as gene modulating strategies to favourably affect inflammation, remodelling, oxidated stress, and angiogenesis are being tested in animal studies and might further change the current framework of optimum treatment for patients. However, the largest gains are likely to come from improvements in the effectiveness of our ability to apply these therapies.

In view of the predicted increase and distribution of myocardial infarction mortality in the next 20 years, a crucial task in the global health agenda is to ensure that clinical and system-specific lessons learned from the research largely done in the developed world are effectively translated to the emerging epidemic in the developing world.

Conflict of interest statement

HDW has attended a Scientific Board Meeting funded by Sanofi-Aventis, has given talks at Sanofi-Aventis funded meetings and receives Research Grants from Sanofi-Aventis, Eli Lilly, The Medicines Company, Johnson & Johnson, Proctor and Gamble, and Schering Plough. DPC is on Speaker Bureau for Sanofi-Aventis, and Commonwealth Serum Laboratory Biotherapeutics, Australia.

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