Evidence-based treatments for STEMI: are we doing enough?

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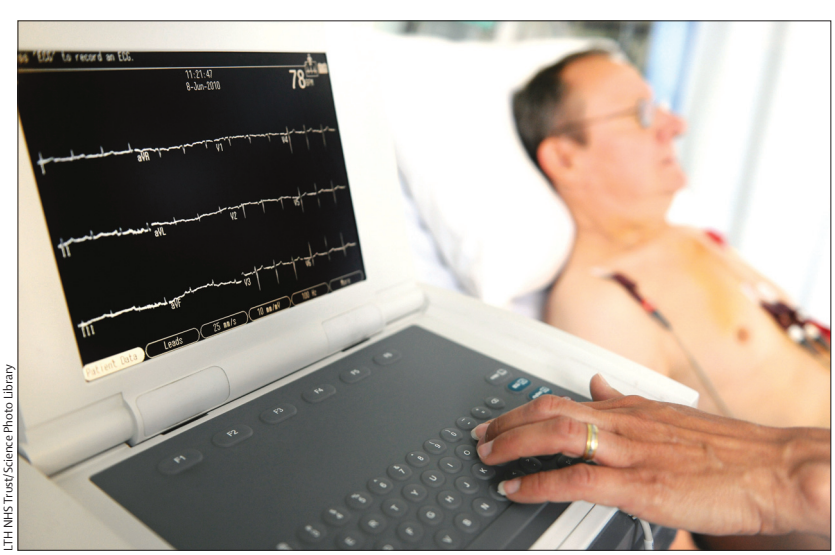
See Series pages 624, 633, and 644

The entire medical profession strives to deliver care that is safe, timely, evidence-based, efficient, equitable, and patient-centred.[1] Towards this goal, cardiology probably enjoys the greatest evidence base of any medical specialty; within cardiology, the treatment of patients with ST-segment elevation myocardial infarction (STEMI) could be the best-studied disorder for which guidelines can be created.[2–4] In fact, the availability of evidence and the creation of guidelines and performance measures[5,6] has led to substantial improvements in the survival of patients with myocardial infarction. Findings from a study by Krumholz and colleagues[7] showed both a substantial reduction in 30-day mortality rates among elderly patients in the USA, and perhaps more importantly, a reduction in the variability of survival across hospitals from 1995 to 2006.[7] Similarly, Jernberg and colleagues[8] reported that implementation of new treatment strategies over 12 years in patients with STEMI in Sweden was associated with an increased use of evidence-based treatments, improved adherence to treatment guidelines, and reduced variation across hospitals. These changes were associated with a large and sustained reduction in mortality, and a mean gain of at least 2·7 years of life per patient.

A Series of three papers in *The Lancet* describes the best evidence-based practices for acute reperfusion,[9] adjunctive therapies for primary percutaneous coronary intervention (PCI),[10] and emerging efforts to improve care for patients with STEMI in the future.[11] This Series, which discusses care up to definitive reperfusion, peri-reperfusion treatment, and emerging innovations in the specialty, provides an excellent conceptual basis for the delivery of optimum treatment for STEMI.



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Anthony Gershlick and colleagues[9] describe the need for patients to recognise the symptoms of myocardial infarction early and for rapid activation of the emergency medical system. They discuss optimum strategies for reperfusion, including the use of prehospital thrombolytic therapy if primary PCI will be delayed by more than 120 min from first medical contact or more than 60 min from the time of thrombolytic administration. These thresholds are more ambitious than the NICE guidelines (which state that primary PCI should be delivered within 120 min of the time when fibrinolysis could have been given),[4] but are in line with recent guidelines from the European Society of Cardiology stating that "PCI-related delay of 120 min is useful in selecting primary PCI over immediate thrombolysis as the preferred mode of reperfusion."[2] These guidelines also encourage monitoring and reporting of performance to achieve quality targets, and state that if the reperfusion therapy is primary PCI, the goal for quality improvement should be to reduce the time from first medical contact (ie, first diagnostic electrocardiogram [ECG]) to wire passage into the culprit artery to less than 90 min (and an even shorter time of 60 min if the patient presents early with a large infarct, or if the patient presents directly to an interventional centre).[2] Experiences from the Swedeheart registry, in which 73% of patients received reperfusion within the recommended time of 90 min from first diagnostic ECG, with a mean delay from the first diagnostic ECG to PCI of 60 min when thrombolysis was used in selected remote areas, show that the recommended time limits are possible to achieve in a sparsely populated country but that reperfusion strategies might still be suboptimal for many.[12] The implications for health-care systems of general deployment of an aggressive thrombolytic strategy by first responders are substantial. Ultimately, evidence of improved survival in systems that accomplish aggressive thrombolytic treatment when transfer delays are likely, compared with those that do not, will lend support to the widespread adoption of these best practices.[13,14]

Organisation of optimum infrastructure within large health-care systems can be difficult. In the USA, for

example, the free market is the main determinant of where and how many PCI-capable catheterisation laboratories are built. A study by Concannon and colleagues[15] compared the growth of PCI-capable laboratories in 2001–06 with improvements in access for patients living within 60 min of a laboratory. Despite a 44% relative increase in the number of primary-PCI-capable hospitals, the proportion of the US population living within 60 min of such a facility increased from 79·0% to only 79·9%, a relative increase of 1%. Despite the efforts of the American Heart Association's Mission: Lifeline[16] to define transferring and receiving hospitals in an effort to improve the coordination of care, allowing market forces to govern the creation of advanced care centres will probably not improve access for the 20% of US residents living more than an hour from a primary-PCI-capable hospital and adjunctive thrombolytic therapy will be important for such patients to have an optimum chance for survival. Moreover, national efforts are needed to allow emergency medical systems to rapidly assess, diagnose, and initiate thrombolytic treatment for acute STEMI. The European Stent for Life initiative is such an example, and improved the implementation of timely primary PCI in several target countries.[17]

Nicholas Curzen and colleagues[10] summarise how best to treat patients once they have received primary PCI, with a focus on optimum management of the thrombotic processes associated with STEMI. Although many clinical trials have investigated various strategies, challenges remain in selection of the best treatment; these challenges show the difficulties in application of evidence-based medicine to individual patients. For example, new thienopyridine drugs offer more rapid and effective inhibition of platelet aggregation than does clopidogrel, but at a cost of increased bleeding accruing over time. The TRITON-TIMI 38 trial[18] explicitly examined heterogeneities in treatment benefit with prasugrel by comparison with clopidogrel, whereby some patients had ischaemic benefits far in excess of their increased bleeding risk, while other patients did not. Because the goal of personalised medicine is to tailor treatments to individual patients, new efforts to support the integration of personal risk estimates into routine clinical care are needed.

This Series paper also shows at least two challenges in assessment of the outcomes of a clinical trial. For example, Curzen and colleagues review the scientific literature regarding reduction in periprocedural myocardial infarctions with intravenous glycoprotein IIb/IIIa inhibitors. However, at the time of those studies, even minor elevations of creatine kinase were regarded as myocardial infarctions, despite evolving knowledge that only larger periprocedural leaks of creatine kinase are prognostically important.[19] Another concern raised by Curzen and colleagues about increased risks of stent thrombosis with bivalirudin seems to be a distraction, in view of the primary results of the HORIZONS-AMI trial,[20] which showed that cardiovascular mortality was reduced with bivalirudin, despite the increased risk of stent thrombosis. As future studies work to improve the periprocedural management of primary PCI, careful design and interpretation of clinical trials—with a focus on outcomes that are most meaningful to patients—is needed. These trials need to be large enough to assess low-frequency events such as death, but need to be feasible to conduct from a financial and practical perspective, which is a challenge.[21]

Despite past successes in management of STEMI, the future is exciting. Stephan Windecker and colleagues[11] provide a good summary of new and future developments in STEMI therapy. The evolution of stent technology from bare-metal stents to first-generation, second-generation, and third-generation drug-eluting stents, and the emergence of drug-eluting bioabsorbable scaffolds, is fascinating and shows the innovation occurring in cardiology. Similarly, conditioning of the ischaemic myocardium by complex or simple devices or drugs, and medical efforts to control inflammation, are imaginative topics of research. Activation of resting stem cells in the myocardium, and delivery of bone-marrow stem cells via different routes, provide opportunities to regenerate injured myocardium. However, with all of these innovations, rigorous assessment of treatment outcomes is needed so that their incremental benefits as compared with present therapies can be readily appreciated.

Measurement of outcomes in cardiology is complex, as imaging techniques such as cardiac MRI provide new ways to examine physiological components of the heart. However, the challenges in use of surrogate outcomes as a means to define benefit should be kept in mind.[22] Many examples, such as new therapies for heart failure to improve ejection fraction and antiarrhythmic drugs to reduce premature ventricular contractions that were later shown to increase mortality, serve as warnings that new therapies should not be adopted until clinically

meaningful outcomes are shown to improve. The most relevant outcomes are clearly mortality and health status,[23] yet many of the clinical trials in STEMI care do not include measures of patients' symptoms, function, and quality of life. As new treatments such as stem-cell therapies are introduced, broadening of assessments of benefit to include these patient-centred outcomes will be crucial to define how best to tailor treatments to the goals and preferences of individual patients.

This Series presents an excellent summary of state-of-the-art and future therapies for STEMI. The remaining challenge is to ensure the consistent and reproducible delivery of optimum treatment in routine care. Although guidelines and performance measures are an important strategy, a culture shift within cardiology is needed to embrace these measures as a means to redesign local delivery systems for health care to optimise outcomes for patients.[24] Additionally, this Series focuses on cross-sectional delivery of health care at the time of a STEMI. However, a STEMI is one point along the continuum of coronary artery disease. Our profession needs to recognise the importance of a STEMI, a turning point in a patient's life, to aggressively promote secondary prevention. Cardiac rehabilitation referral has recently been endorsed as a performance measure for care of patients with acute myocardial infarction,[25] but access is limited in many centres. New strategies need to be investigated to establish how to consistently deliver treatment after myocardial infarction, so that the short-term benefits of improved STEMI care can be translated into years of productive life.

Stefan K James, John A Spertus
Department of Medical Sciences, Cardiology, Uppsala Clinical Research Center, Uppsala University Hospita, 751 85 Uppsala, Sweden (SKJ); and Saint Luke's Mid America Heart Institute, University of Missouri–Kansas City, Kansas City, MI, USA (JAS)
stefan.james@ucr.uu.se

SKJ has received research grants from AstraZeneca, Eli Lilly, Bristol-Myers Squibb, Terumo Inc, Medtronic, and Vascular Solutions; has received honoraria from The Medicines Company, AstraZeneca, Eli Lilly, Bristol-Myers Squibb, and IROKO; and has served as consultant or on advisory boards for AstraZeneca, Eli Lilly, Merck, Medtronic, and Sanofi. JAS has received grants from NIH and NHLBI, AHA, Lilly, Genentech, Gilead, EvaHeart, and Amorcyte, and has developed and owns the copyrights to the Seattle Angina Questionnaire, the Kansas City Cardiomyopathy Questionnaire, and the Peripheral Artery Questionnaire. These questionnaires are all disease-specific quality-of-life measures, and the Seattle Angina Questionnaire is used in some studies to describe the health status of patients recovering from a STEMI. JAS has an equity interest in Health Outcomes Sciences, which provides an IT solution to execute multivariable risk prediction models within the flow of clinical care.

1 Institute of Medicine. Crossing the quality chasm: a new health system for the twenty-first century. Washington, DC: National Academy Press, 2001.
2 Steg PG, James SK, Atar D, et al, for the Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33:** 2569–619.
3 O'Gara PT, Kushner FG, Ascheim DD, et al, for the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College Of Cardiology Foundation/American Heart Association Task Force On Practice Guidelines. *Circulation* 2013; **127:** e362–425.
4 NICE. Myocardial infarction with ST-segment elevation: the acute management of myocardial infarction with ST-segment elevation. NICE clinical guideline 167. July, 2013. http://www.nice.org.uk/nicemedia/live/14208/64410/64410.pdf (accessed Aug 5, 2013).
5 Krumholz HM, Anderson JL, Brooks NH, et al, for the American College of Cardiology, the American Heart Association Task Force on Performance Measures, and the Writing Committee to Develop Performance Measures on ST-Elevation and Non-ST-Elevation Myocardial Infarction. ACC/AHA clinical performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures on ST-Elevation and Non-ST-Elevation Myocardial Infarction). *J Am Coll Cardiol* 2006; **47:** 236–65.
6 Sanfelix-Gimeno G, Peiro S, Ferreros I, et al. Adherence to evidence-based therapies after acute coronary syndrome: a retrospective population-based cohort study linking hospital, outpatient, and pharmacy health information systems in Valencia, Spain. *J Manag Care Pharm* 2013; **19:** 247–57.
7 Krumholz HM, Wang Y, Chen J, et al. Reduction in acute myocardial infarction mortality in the United States: risk-standardized mortality rates from 1995–2006. *JAMA* 2009; **302:** 767–73.
8 Jernberg T, Johanson P, Held C, Svennblad B, Lindback J, Wallentin L, for the Swedeheart/Riks HIA. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. *JAMA* 2011; **305:** 1677–84.
9 Gershlick AH, Banning AP, Myat A, Verheugt FWA, Gersh BJ. Reperfusion therapy for STEMI: is there still a role for thrombolysis in the era of primary percutaneous coronary intervention? *Lancet* 2013; **382:** 624–32.
10 Curzen N, Gurbel PA, Myat A, Bhatt DL, Redwood SR. What is the optimum adjunctive reperfusion strategy for primary percutaneous coronary intervention? *Lancet* 2013; **382:** 633–43.
11 Windecker S, Bax JJ, Myat A, Stone GW, Marber MS. Future treatment strategies in ST-segment elevation myocardial infarction. *Lancet* 2013; **382:** 644–53.
12 Jan Harnek JN, Örjan Friberg, James S, et al. The 2011 outcome from the Swedish health care registry on heart disease (Swedeheart). *Scand Cardiovasc J* 2013; **47** (suppl 62)**:** 1–10.
13 Bjorklund E, Stenestrand U, Lindback J, Svensson L, Wallentin L, Lindahl B. Pre-hospital thrombolysis delivered by paramedics is associated with reduced time delay and mortality in ambulance-transported real-life patients with ST-elevation myocardial infarction. *Eur Heart J* 2006; **27:** 1146–52.
14 Danchin N, Coste P, Ferrieres J, et al, for the FAST-MI Investigators. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the French registry on acute ST-elevation myocardial infarction (FAST-MI). *Circulation* 2008; **118:** 268–76.
15 Concannon TW, Nelson J, Goetz J, Griffith JL. A percutaneous coronary intervention lab in every hospital? *Circ Cardiovasc Qual Outcomes* 2012; **5:** 14–20.
16 Bagai A, Jollis JG, Dauerman HL, et al. Emergency department bypass for ST-segment-elevation myocardial infarction patients identified with a prehospital electrocardiogram: a report from the American Heart Association Mission: Lifeline program. *Circulation* 2013; **128:** 352–59.
17 Kristensen SD, Fajadet J, Di Mario C, et al. Implementation of primary angioplasty in Europe: Stent for Life initiative progress report. *EuroIntervention* 2012; **8:** 35–42.
18 Salisbury AC, Wang K, Cohen DJ, Li Y, Jones PG, Spertus JA. Selecting antiplatelet therapy at the time of percutaneous intervention for an acute coronary syndrome: weighing the benefits and risks of prasugrel versus clopidogrel. *Circ Cardiovasc Qual Outcomes* 2013; **6:** 27–34.
19 Lindsey JB, Kennedy KF, Stolker JM, et al. Prognostic implications of creatine kinase-MB elevation after percutaneous coronary intervention: results from the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry. *Circ Cardiovasc Interv* 2011; **4:** 474–80.

20 Stone GW, Witzenbichler B, Guagliumi G, et al, for the HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; **358:** 2218–30.

21 Frobert O, Lagerqvist B, Gudnason T, et al. Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform: study design and rationale. *Am Heart J* 2010; **160:** 1042–48.

22 Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med* 1996; **125:** 605–13.

23 Spertus JA. Evolving applications for patient-centered health status measures. *Circulation* 2008; **118:** 2103–10.

24 Larsson S, Lawyer P, Garellick G, Lindahl B, Lundstrom M. Use of 13 disease registries in 5 countries demonstrates the potential to use outcome data to improve health care's value. *Health Aff (Millwood)* 2012; **31:** 220–27.

25 Thomas RJ, King M, Lui K, et al, for the AACVPR, ACC, AHA, American College of Chest Physicians, American College of Sports Medicine, American Physical Therapy Association, Canadian Association of Cardiac Rehabilitation, European Association for Cardiovascular Prevention and Rehabilitation, Inter-American Heart Foundation, National Association of Clinical Nurse Specialists, Preventive Cardiovascular Nurses Association, and Society of Thoracic Surgeons. AACVPR/ACC/AHA 2007 performance measures on cardiac rehabilitation for referral to and delivery of cardiac rehabilitation/secondary prevention services endorsed by the American College of Chest Physicians, American College of Sports Medicine, American Physical Therapy Association, Canadian Association of Cardiac Rehabilitation, European Association for Cardiovascular Prevention and Rehabilitation, Inter-American Heart Foundation, National Association of Clinical Nurse Specialists, Preventive Cardiovascular Nurses Association, and the Society of Thoracic Surgeons. *Circulation* 2007; **116:** 1611–42.

Remote preconditioning and all-cause mortality

During the past three decades, experimental cardiology studies have shown that ischaemic conditioning interventions can lessen the risk of fatal reperfusion injury and reduce infarct size. Murry and colleagues[1] noted that repeated brief episodes of myocardial ischaemia induced before a sustained ischaemic insult preconditioned the heart. Zhao and colleagues[2] reported that a similar intervention applied immediately after (but not before) sustained ischaemic insult could postcondition the heart. Przyklenk and colleagues[3] found that the application of short cycles of non-fatal ischaemia at a remote site (eg, the arm) before, during, or immediately after sustained occlusion of a coronary artery improved resistance to reperfusion injury to the heart compared with unconditioned hearts.

Initially, despite substantial progress in reperfusion therapy, no approaches were proposed to lower the risk of fatal reperfusion injury, be it after focal or global ischaemia reperfusion. The discovery and development of conditioning interventions presented an opportunity to protect various organs affected by ischaemia (eg, the heart, brain, and kidneys) during emergencies (eg, acute myocardial infarction, stroke, cardiac arrest) and scheduled therapeutic interventions (eg, cardiac surgery).[4]

Staat and colleagues[5] showed in a proof-of concept study in patients with ST-segment-elevation myocardial infarction that four cycles of 1 min inflation and 1 min deflation of the angioplasty balloon immediately after reperfusion postconditioned the heart and significantly lessened infarct size, by nearly 40%. Hausenloy and co-workers[6] reported remote conditioning by three cycles of 5 min inflation and 5 min deflation of a blood-pressure cuff on the upper arm, which significantly reduced release of troponin T in patients undergoing elective coronary artery bypass graft (CABG) surgery. Although it could be argued that protective therapies are not needed in low-risk patients undergoing CABG, among whom mortality is already low, more than 40% release cardiac enzymes after surgery that are known to be associated with worsening of short-term and long-term outcomes.[7]

In *The Lancet*, Matthias Thielmann and colleagues[8] report a prospective, randomised, controlled trial into which they enrolled 329 consecutive adults with multivessel coronary artery disease. Patients underwent remote ischaemic preconditioning with a blood-pressure cuff around the upper arm (three cycles of inflation for 5 min and reperfusion for 5 min) or no ischaemic preconditioning before elective isolated first-time CABG. In the remote ischaemic conditioning group the area under the curve for release of cardiac troponin I in the first 72 h after revascularisation was significantly lower than that in the control group (266 ng/mL, 95% CI 237–298 *vs* 321 ng/mL, 287–360; difference 17%, 3–30%). The most important finding of this work, however, is the significant improvement in clinical outcomes induced by remote ischaemic conditioning. In this low-risk population, remote ischaemic preconditioning was associated with reduced incidence of all-cause death (hazard ratio 0·27, 95%CI 0·08–0·98) and myocardial infarction (0·35, 0·15–0·78) at 1 year. We congratulate the researchers on providing the evidence that a conditioning intervention can improve clinical outcomes after CABG, although a limited number of serious adverse events were noted in the study population.

Apart from myocardial protective effects, Thielmann and colleagues noted that reduced release of cardiac

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ST-segment Elevation Myocardial Infarction 1

Reperfusion therapy for STEMI: is there still a role for thrombolysis in the era of primary percutaneous coronary intervention?

Anthony H Gershlick, Adrian P Banning, Aung Myat, Freek W A Verheugt, Bernard J Gersh

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This is the first in a **Series** of three papers about ST-segment elevation myocardial infarction

Leicester Cardiovascular Biomedical Research Unit, University of Leicester, University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, UK (Prof A H Gershlick FRCP); **Department of Cardiology, Oxford Radcliffe Hospitals NHS Trust, Oxford, UK** (Prof A P Banning MD); **King's College London BHF Centre of Research Excellence, Cardiovascular Division, The Rayne Institute, St Thomas' Hospital, London, UK** (A Myat MRCP); **Department of Cardiology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands** (Prof F W A Verheugt MD); **and Division of Cardiovascular Sciences, Mayo Clinic, Rochester, MN, USA** (Prof B J Gersh FRCP)

Correspondence to: Prof Anthony H Gershlick, Glenfield Hospital, Leicester LE3 9QP, UK **agershlick@aol.com**

In the past ten years, primary percutaneous coronary intervention (PCI) has replaced thrombolysis as the revascularisation strategy for many patients presenting with ST-segment elevation myocardial infarction (STEMI). However, delivery of primary PCI within evidence-based timeframes is challenging, and health-care provision varies substantially worldwide. Consequently, even with the ideal circumstances of rapid initial diagnosis, long transfer delays to the catheter laboratory can occur. These delays are detrimental to outcomes for patients and can be exaggerated by variations in timing of patients' presentation and diagnosis. In this Series paper we summarise the value of immediate out-of-hospital thrombolysis for STEMI, and reconsider the potential therapeutic interface with a contemporary service for primary PCI. We review recent trial data, and explore opportunities for optimisation of STEMI outcomes with a pharmacoinvasive approach.

Introduction

Optimum management of ST-segment elevation myocardial infarction (STEMI) is the theme of this Series, and in this paper we address whether fibrinolytic drugs add to the contemporary therapeutic armoury. Many people suggest that fibrinolytics have no place in the era of primary PCI, whereas others believe fibrinolytics are needed because primary PCI cannot be delivered to all patients with STEMI within the evidence-based timeframes needed for full effectiveness. In this context, we explore the barriers to full implementation of primary PCI and discuss whether fibrinolytic drugs still have a role in the management of patients with STEMI.

For patients in rural or semirural areas who delay contacting emergency services, achievement of the total time from symptom onset to balloon deployment recommended by guidelines (180 min) can be difficult (panel).[1,2] Often, in areas with challenging geography, the time from first medical contact to balloon deployment is outside guideline mandated times, along with the total ischaemic time (which is dependent on the patient calling for help). Any opportunity to reduce overall ischaemic times in patients with long transport times to the receiving cardiac centre could improve myocardial function. Any further delay that increases time from first medical contact to balloon deployment to more than 120 min has been clearly shown to affect mortality.[3]

Alternatively, paramedics could give patients a fibrinolytic drug before setting off for hospital, allowing reperfusion therapy to occur during transfer. In most patients, reperfusion will be complete by arrival at the hospital door, at which point a clinical and electrocardiogram (ECG) assessment of reperfusion success will be made. A decision can then be taken on whether to proceed with rescue PCI as soon as possible in patients with evidence of failed reperfusion, with all others undergoing angiography as early as possible in their admission. The time saving of early reperfusion therapy in such a scenario is clear, although reperfusion with a fibrinolytic might not be complete for up to 60 min. The question is, does this time saving overcome the reported benefits of primary PCI compared with thrombolysis when primary PCI cannot be delivered within guideline-mandated times?

Search strategy and selection criteria

We searched the Cochrane Library, Medline, PubMed, Embase, and references from relevant articles using a combination of the search terms "STEMI network", "fibrinolysis", "thrombolysis", "primary PCI", "facilitated PCI", "pharmacoinvasive therapy", "first medical contact", and "door to balloon time". We largely selected publications from the past ten years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy, and selected those we judged relevant. All articles published in English between Jan 1, 1980, and May 31, 2013, were included.

Reperfusion and the importance of time

In patients with STEMI, the earlier the patient presents, and the earlier the artery can be recanalised, the better. As early as 1979, Reimer and colleagues[4] noted that the degree of reversibility and extent of myocardial necrosis were both time dependent. Furthermore, the earlier the patient presents, the greater the effect of treatment delays on clinical outcomes in relative terms.[5]

The open artery hypothesis is generally well accepted; in its simplest form it states that an open artery is better than a closed artery. However, the notion has evolved from a simple binary metric to a time-dependent

spectrum in which the sooner the artery is opened, the better. This hypothesis is lent support by findings from the GISSI-1 clinical trial[6,7] of fibrinolysis, in which benefit seemed to be time dependent, with little advantage of fibrinolytic agents compared with control after 6 h. Results of subsequent studies such as the LATE trial[8] suggested that this time window could be extended to 12 h but no longer. Thus, foundations were laid for reperfusion to be given as early as possible, and subsequent clinical trials (including those of primary PCI) have supported guidelines for time-dependent standards to achieve reperfusion.[1,2] Emphasis is also placed on the degree of blood flow through coronary arteries, defined as thrombolysis in myocardial infarction (TIMI) flow, ranging from flow grade 0 (no flow) to TIMI flow grade 3 (that of any reference vessel without obstruction—ie, non-infarct-related vessel). Blood flow to the microvasculature at the myocardial cell level is also important, and robust data have shown an association between high TIMI flow grades and microvascular flow.[9] Intuitively, therefore, the two basic principles underlying optimum outcomes in patients with STEMI are early reperfusion therapy and the restoration of as normal a flow as possible.

When thrombolysis was the dominant reperfusion therapy, outcomes were better after provision of early, prehospital thrombolysis than after inhospital thrombolysis.[10,11] Before prehospital fibrinolysis could be accepted as standard therapy, trial data were reported suggesting that primary PCI was a better option than was fibrinolysis alone.[12,13] These findings and a subsequent meta-analysis by Keeley and colleagues[14] showed that primary PCI produced better outcomes in terms of major adverse cardiac events than did inhospital thrombolysis alone. Some thought the meta-analysis was flawed because the postulated benefit of primary PCI was confined to those patients who received fibrinolysis in the hospital setting. Moreover, when patients with cardiogenic shock were omitted from the analysis and the comparison was made with just tissue plasminogen activator, as opposed to all fibrinolytic drugs such as urokinase and streptokinase, the proportion of patients with major adverse cardiovascular events was similar to that of primary PCI. Despite these misgivings, primary PCI became the preferred reperfusion option, not least since it offered important potential advantages compared with pharmacological reperfusion, such as establishment of TIMI flow grade 3 in 70–90% of patients, and substantial reduction in the risk of intracranial haemorrhage when compared with fibrinolysis. It was definitely preferable in high-risk patients—eg, those with cardiogenic shock, severe congestive heart failure, or haemodynamic or electrical instability. However, primary PCI has to be delivered by a specialist team in a hospital setting, therefore, systems for network delivery must be established to ensure timely delivery.

***Panel:* The importance of time**

A hypothetical patient develops chest pain at 1000 h. As commonly happens, the patient does not call for help immediately, and phones the emergency number only because of persistent pain at 1130 h. Paramedics arrive at 1145 h—the first medical contact. They do a full assessment and record an electrocardiogram, which shows obvious anterior ST-segment elevation. This assessment takes 25 min. The patient lives in a semirural setting, and the time to hospital is about 55 min. If the paramedics radio ahead the patient could be on the catheterisation laboratory table with a vascular sheath deployed within 40 min of arrival at the hospital door. This chain of fairly commonplace events equates to a total ischaemic time of 225 min, compared with the guideline-recommended total time from symptom onset to balloon deployment of 180 min.[1,2]

What is timely delivery of reperfusion therapy?

The time intervals in the period from onset of symptoms to reperfusion are well defined (figure 1), and delivery of primary PCI within these timelines has become the basis of audit standards and European and US guideline recommendations.[1,2] These time periods are: symptom onset to call for help, symptom onset to first medical contact, symptom onset to initiation of fibrinolysis or first balloon or device, and hospital door to either onset of fibrinolytic therapy (door-to-needle time) or to first balloon or device (door-to-balloon time).

Findings from many studies have shown the importance of these timelines. In a study[15] of 29 222 patients with STEMI in the US National Registry of Myocardial Infarction databases 3 and 4, protracted door-to-balloon times were increasingly associated with higher inhospital mortality, ranging from 3% mortality for times of less than 90 min to 7·4% mortality for times of more than 150 min. Although this type of analysis might be confounded, because delays are also more likely in sicker patients, it supports the general consensus (and audit metric) to aim for ever-shorter door-to-balloon times.[16,17] However, not all studies have shown such an association. Thus, although Flynn and colleagues[18] reported that the median door-to-balloon time had decreased yearly from 113 min in 2003 to 76 min in 2008 ($p<0·001$), and that the percentage of patients revascularised with a door-to-balloon time of less than 90 min increased from 28·5% to 67·2% over the same period ($p<0·001$), inhospital mortality did not change significantly (4·1% in 2003 *vs* 3·6% in 2008).

Rapid door-to-balloon times are accepted as an important primary objective, but these and other studies show that door-to-balloon times do not correspond to total duration of ischaemia; shortening of this time metric alone might not affect overall mortality.[18] An important determinant of the optimum therapeutic strategy is total ischaemic time, and the duration of ischaemia before and at the time of

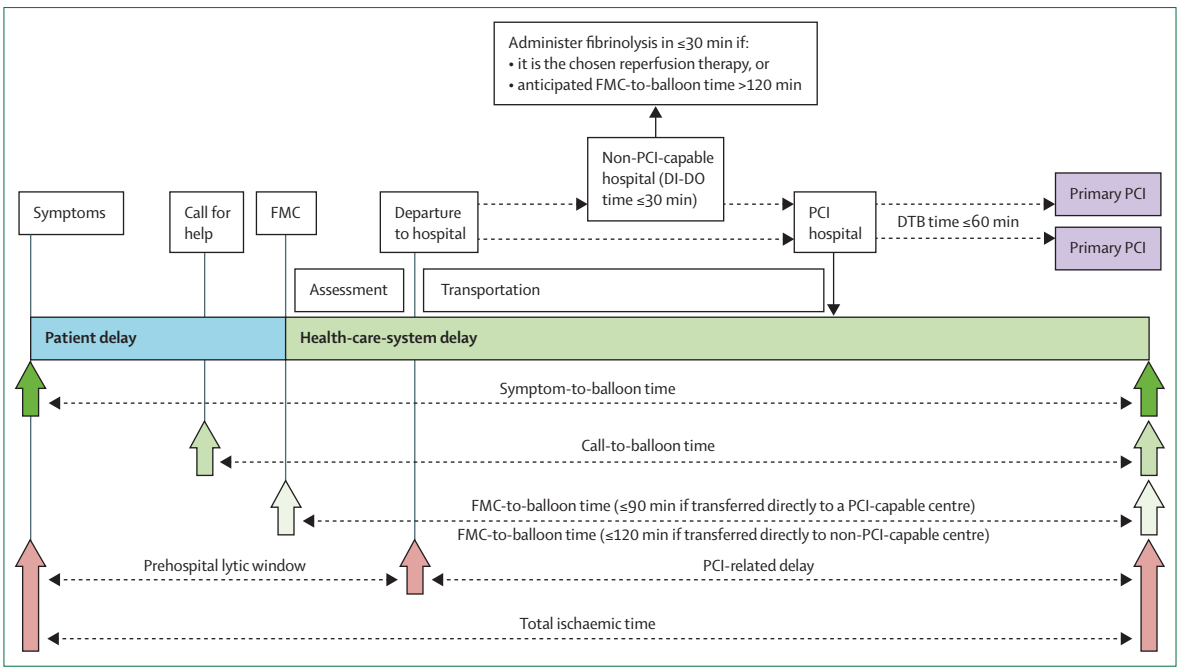

Figure 1: **Important timeline metrics in management of STEMI**
Obstacles to reperfusion can be divided into delays related to patients and to the health-care system. PCI-related delay is the extra time needed to do primary angioplasty rather than give on-scene prehospital thrombolysis. Delay can also occur if the nearest hospital is not PCI capable. Depending on STEMI network infrastructure, the non-PCI hospital is either bypassed or the patient is taken there first before interhospital transfer to a primary-PCI centre. In addition, a fibrinolytic agent can be given at the non-PCI-capable hospital. Delay intervals mandated by European and US guidelines are superimposed.[1,2] Figure not drawn to scale. Patient-related delays can vary substantially in length. STEMI=ST-segment elevation myocardial infarction. PCI=percutaneous coronary intervention. FMC=first medical contact. DI-DO=door-in to door-out. DTB=door to balloon.

first medical contact (figure 2).[5,19,20] Achievement of short total ischaemic time forms the basis of guideline recommendations, and although reperfusion works better in patients with short presentation times, all benefit when the artery can be opened as expeditiously as possible. Thus, when a paramedic arrives at a patient with STEMI, if primary PCI is thought deliverable within 2 h the patient should be transported to the nearest PCI-capable hospital and mechanical reperfusion done as quickly as possible—certainly within 60 min of arrival at the door. Overall ischaemic time in these ideal circumstances should be less than 180 min.

Both European and US guidelines on STEMI management emphasise the need to set up regional networks to deliver reperfusion therapy quickly, effectively, and within mandated timelines.[1,2] Ambulance teams should be trained and equipped to identify patients with STEMI and give initial treatment, including fibrinolysis if applicable. Centres with the ability to perform primary PCI should deliver care on a 24 h, 7 day basis within 90 min of the initial call for help. To achieve these objectives, many countries have established networks for delivery. A report by the UK National Infarct Angioplasty Project emphasised the need for network approaches to the delivery of timely reperfusion.[21] The report concluded that "the key to successful outcomes in treating heart attack is short times to treatment. The longer the time to treatment, the more damage occurs to the heart muscle."

Timely delivery of reperfusion therapy, with attenuated overall ischaemic time, is ideal. However, such a strategy could be difficult to achieve if based solely on primary PCI. In the UK, for example, the percentage of patients who have access to timely primary PCI might vary between 80% to more than 95%, depending on the definition of timely PCI and geographical location.

Delivery of timely primary PCI remains very difficult in many parts of the world. In a review of access to reperfusion in Australia, Ranasinghe and colleagues[22] reported that only 40·2% of the population had timely access to primary PCI (defined as the proportion of the population capable of reaching a fibrinolysis facility ≤60 min or a primary PCI facility ≤120 min from activation of emergency medical services); access was particularly poor in regional areas and "non-existent" in remote areas. They also noted that optimised responses of emergency medical services or increased primary-PCI services resulted in only marginal improvement to timely access (1·8% and 3·7%, respectively), but that direct transport and interhospital transfer for primary PCI improved timely access for 19·4% and 23·5% of the population, respectively. The investigators suggested that an alternative to primary PCI was to encourage prehospital fibrinolysis. This conclusion could well be transposed to many similar regions of the world.[23]

In the USA, for example, first door-to-balloon times of less than 90 min are estimated to be possible for only about a third of patients who do not need transfer, and for even fewer patients who present at hospitals without easy access to primary PCI.[24] For example, historical data from the US National Registry of Myocardial Infarction databases 3 and 4 (n=4278) suggest that total door-to-balloon times of less than 90 min were achieved in only 4·2%, and less than 120 min in 16·2%, of patients with STEMI needing transfer for PCI.[25] These data emphasise the need to establish networks for timely reperfusion delivery, but also show the challenges posed by geography—one approach might not suit all.[26] The inadequacy of timely delivery in the USA, and the realisation that an estimated 80% of the US population live within 60 min of a PCI-capable hospital, led to the development and assessment of nationwide programmes to direct emergency medical services to the nearest primary-PCI centre and invoke rapid-transfer systems.[17,27–30] Fosbol and others[31] have reported that such network systems significantly shorten reperfusion time, with direct transfer to a PCI-capable hospital the gold standard if possible. Findings from a study[32] of US registry data showed that attainment of door-to-balloon times of less than 90 min rose from 64·5% to 88% (p=0·0001) in patients arriving directly at primary-PCI centres between two time periods: Q1–Q2 in 2007 (n=9390) and Q1–Q2 in 2009 (n=11 125). For those who had to be transferred, however, door-to-balloon times remained well below target (from 7·6% in the first period to only 18·7% in the second). Although systems have evolved, and shorter times can now be achieved in many parts of the USA, long times between symptom onset and first medical contact, geography, and non-system delays (eg, when helicopter ambulances cannot be used because of bad weather) remain important barriers to expeditious delivery of primary PCI in some settings. These factors mean that primary PCI might not be the best option in some parts of the USA, since distances needed for transfer are difficult to overcome.[33] Nonetheless, both in the USA and in other parts of the world (eg, Canada, Russia, and Australia), a trend of consistent improvements in some of these factors has contributed to a reduction in overall times to therapy.[34]

The most important barrier to timely, and therefore effective, primary PCI remains the long transport times from rural areas. Even in some urban settings timely primary PCI cannot be achieved. If a patient is initially taken to the nearest hospital and that hospital is not PCI capable (not recommended, but sometimes unavoidable), the wait for transfer vehicles can compromise myocardial viability.[25] Door-in to door-out times in such situations might become the new metric (figure 1). Wang and colleagues[35] noted that that door-in to door-out times of 30 min or less were achieved in only a small proportion of patients transferred for primary PCI, but were associated with shorter reperfusion delays and lower in-hospital mortality.

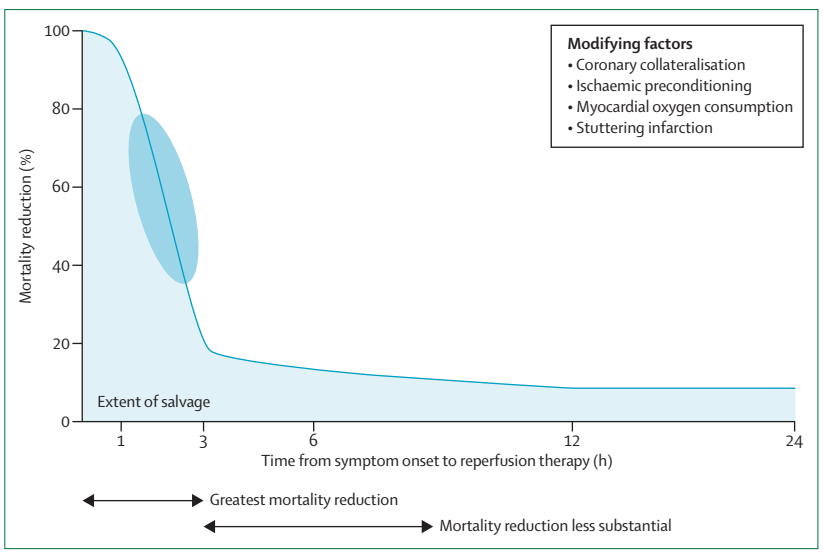

Figure 2: **The association between time to treatment, reduction in mortality, and extent of myocardial salvage**
The greatest benefit gained from reperfusion therapy occurs in the first 2–3 h after symptom onset (shaded dark blue). The duration of this time-critical period can be modified by factors such as extent of coronary-vessel collateralisation, myocardial oxygen consumption, total ischaemic time, and ischaemic preconditioning. The gain in mortality begins to plateau after this period, with time to reperfusion becoming less important. Figure adapted from Gersh et al[5] by permission of the American Medical Association.

Delays to primary-PCI delivery could be especially important in out-of-hours care. For example, analysis of data from the US National Registry of Myocardial Infarction databases 3 and 4 showed that presentation during out-of-hours prolonged door-to-balloon times by 21 min (p=0·001), and reduced the proportion of patients undergoing primary PCI.[36] Although this hurdle has been overcome in some centres, the timely delivery of primary PCI to all eligible patients 24 h a day, 7 days a week, continues to pose substantial logistical challenges.[37]

What if guideline-mandated times for primary PCI are not achieved?

De Luca and colleagues[38] suggested that each minute's delay in reperfusion affects mortality. They reported that, after adjustment for age, sex, diabetes, and previous revascularisation, every delay of 30 min was associated with a relative risk for 1 year mortality of 1·075 (95% CI 1·008–1·15, p=0·041)—ie, roughly 8% excess annual mortality for every 30 min delay.[38] Supporting data suggest that system delays directly affect infarct size. In a study of 219 patients, system delays of up to 120 min were associated with infarct sizes of 8%, increasing to 13% for delays of more than 180 min.[39] The more sensitive the measure of myocardial damage used, the more evident the detrimental effect of time delay becomes: in a cardiac MRI study[40] done at 2 days after primary PCI, mean infarct size progressively increased over time (8% at ≤90 min, 11·7% at >90–150 min, 12·7% at >150–360 min, and 17·9% at >360 min). The amount of salvaged myocardium

substantially decreased if reperfusion occurred after more than 90 min of coronary occlusion.

These and other data suggest that total ischaemic time is essential, and that shorter door-to-balloon times could have more effect in patients presenting early (within <3 h of infarction) than in those presenting later.[41] Thus, shortened door-to-balloon times are pivotal in the context of reduction of total ischaemic time, which includes time from symptom onset to first medical contact, and transfer or door-in to door-out times (figure 1).[35]

Clinical studies also show loss of benefit with primary PCI as time to reperfusion is prolonged. In a systematic review by Lambert and colleagues[42] of 80 hospitals in Canada (n=1832), patients with untimely primary PCI had a risk of death or readmission with heart failure of 13·5%. Any untimely reperfusion was associated with a significantly higher adjusted risk of 30 day mortality (6·6% *vs* 3·3%; odds ratio [OR] 2·14, 95% CI 1·21–3·93) and a non-significant increase in 1 year mortality (9·3% *vs* 5·2%; OR 1·61, 95% CI 1·00–2·66) compared with those who received the treatment within recommended times. The investigators proposed that, at network level after adjustment, each 10% increase in treatment within the recommended times was associated with a decrease in the odds of overall 30 day mortality (OR 0·80, 95% CI 0·65–0·98).[42]

Delivery of reperfusion within the guideline-recommended times should be the absolute aim of all STEMI networks. Such delivery success should be audited nationally, targets set and reviewed, and results distributed to all stakeholders. Performance against targets should be a key objective. Clearly, even with the best efforts, in some scenarios delivery of primary PCI within targeted overall ischaemic times is not possible. Although primary PCI is more effective than fibrinolysis, the incremental benefit of primary PCI is especially susceptible to treatment delays. At the national level, discussions need to take account of the attenuation of primary-PCI benefit over fibrinolysis when the pharmacological option could be delivered more quickly. We need to know the degree of PCI-related delay at which point the better option is to give fibrinolysis at the scene of the STEMI.

Should fibrinolysis ever be used to overcome delays in primary PCI?

Some have suggested that there are no disadvantages to untimely primary PCI when outcomes are compared with those for fibrinolysis and that, for any timepoint from onset of symptoms to delivery of reperfusion therapy, primary PCI is always the superior strategy.[43] In 2006, Boersma and colleagues[43] reported a pooled analysis of randomised clinical trials comparing inhospital fibrinolysis alone with primary PCI (n=7743) at various system delays. Primary PCI was deliverable about 55 min later than was fibrinolysis, but was associated with a significant 37% reduction in 30 day mortality (adjusted OR 0·63, 95% CI 0·42–0·84). The absolute reduction in mortality with use of primary PCI widened over time, from 1·3% at 0–1 h after symptom onset to 4·2% at more than 6 h after symptom onset. However, when the delay related to primary PCI was short (<35 min), the relative (67% *vs* 28%) and absolute (5·4% *vs* 2·0%) reductions in mortality were significantly higher than were those for patients with longer delays. The researchers concluded that primary PCI was associated with significantly reduced 30 day mortality compared with fibrinolysis, irrespective of treatment delay, and thus recommended that despite logistical difficulties the standard approach should be primary PCI for all. They conceded that the benefit of timely treatment emphasised the importance of a comprehensive, unified approach to care in all patients with STEMI.[43] One caveat to full acceptance of the proposal by Boersma and colleagues is the important omission of the CAPTIM study[44] from the analysis, which at the time was the only trial that favoured a pharmacoinvasive strategy. Additionally, no comparison was done in the analysis of reperfusion options given at different times.[19,43]

Others have reported that the difference in ability to deliver either reperfusion strategy is important. Chakrabarti and colleagues[45] noted that any mortality benefit of primary PCI compared with onsite fibrinolysis was nullified when the time delay to primary PCI was 120 min or more, and that the number needed to treat to show superiority went from 23 to 250 when PCI-related delay increased from more than 60 min to more than 90 min. The same group also assessed importance of patients' characteristics, with use of hierarchical models that adjusted simultaneously for both patient-level risk factors and hospital-level covariates to assess the association between PCI-related delay, patient-related risk factors, and inhospital mortality.[46] In 192 509 patients at 645 hospitals in the National Registry of Myocardial Infarction, not only were longer door-to-balloon and door-to-needle times associated with increased mortality (p<0·0001), but the times at which benefit of primary PCI was attenuated also varied in accordance with patients' characteristics—eg, PCI-related delays that nullified benefits of the treatment were as short as 40 min in young men with large anterior infarctions but substantially longer in other subsets of patients.

Terkelsen and colleagues[47] also reported that system delays degraded the benefits of primary PCI. In a review of Danish registry data for mortality after primary PCI (median 3·4 years), a system delay of 0–60 min corresponded to a mortality rate of 15·4%, which increased to 30·8% with a delay of 181–360 min. A multivariate analysis, which adjusted for other predictors of mortality, suggested that system delay was independently associated with mortality (adjusted hazard ratio [HR] 1·10 per 1 h delay, 95% CI 1·04–1·16), as were its components, prehospital system delay and door-to-balloon delay (figure 3). Findings from a follow-up analysis[48] of the DANAMI-2 study clearly showed the effect of PCI delay in reduction of mortality benefit for

primary PCI compared with fibrinolysis. In 1572 patients with 30 day and 8 year mortality follow-up, shorter system delays were associated with reduced absolute mortality in both groups.

The benefits of primary PCI, by comparison with prompt fibrinolysis, reduce in relation to the extent of delay incurred by transport and delivery. Importantly, outcomes for the two treatments seem to equalise as these delays move beyond the 90 min timepoint when prehospital fibrinolysis could be given.

Is fibrinolysis enough?

Use of fibrinolytic drugs alone could result in sub-optimum outcomes for patients. Optimisation of fibrinolytic therapy with adjunctive measures might, however, lessen differences in outcomes compared with primary PCI. Findings from the REACT trial[49] showed the usefulness of a strategy in which fibrinolytic success was established by recording of an ECG 90 min after reperfusion therapy, with rescue angioplasty done then if needed. The GRACIA 1 study[50] also suggested that angiography within 24 h of successful fibrinolysis was beneficial. Incorporating these findings, albeit in a non-systematic way, the CAPTIM study[44] tested early (prehospital) fibrinolysis plus rescue angioplasty against primary PCI. At 5 year follow-up, patients included within 2 h of STEMI and given prehospital fibrinolysis had lower mortality rates (5·8%) than did patients who received primary PCI included within 2 h (11·1%; HR 0·50, 95% CI 0·25–0·97, p=0·04); patients included after 2 h had 5 year mortality rates of 14·5% for prehospital fibrinolysis versus 14·4% for primary PCI.[51] This finding suggested that fibrinolysis with adjunctive angiography and PCI (if needed) was the appropriate comparator for primary PCI. In a combined analysis of the CAPTIM and WEST pharmacoinvasive trials, an interaction between presentation times and outcome was apparent. Patients who presented early (within 2 h of symptom onset) and received early fibrinolysis had non-significant reductions in 1 year mortality rates compared with patients who presented early and received PCI. There was no difference between the two treatment strategies for patients presenting later.[45,52,53]

Management of patients after early fibrinolysis has also been the subject of several studies. Findings from the TRANSFER-AMI[54] and CARESS-in-AMI[55] trials suggested that transfer of patients to a PCI-capable hospital within 6 h is associated with fewer ischaemic complications than is transfer after 24 h. However, findings from the ASSENT-4 study[56] (in which PCI was done irrespective of whether fibrinolysis was successful and very soon afterwards) not only showed no benefit for immediate PCI in all post-fibrinolysis patients, but also showed that this strategy was disadvantageous. As a result of these findings, the optimum treatment strategy might be early fibrinolysis followed by rapid transfer to a PCI-capable hospital, rescue angioplasty if fibrinolysis is unsuccessful, and coronary angiography only in patients with successful fibrinolysis after 4 h but before 24 h.[56]

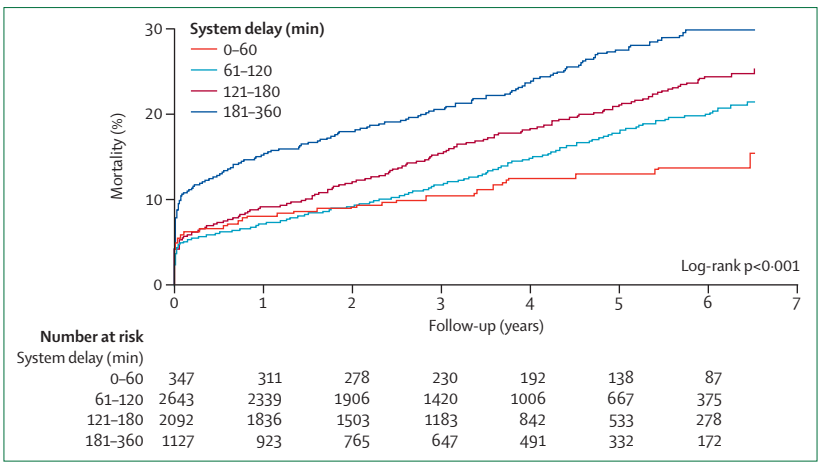

Figure 3: **Association between health-care-system delays and long-term mortality**
Health-care-system delays (ie, time from first medical contact to primary percutaneous coronary intervention) have the strongest association with long-term mortality among modifiable acute-phase covariates, with a hazard ratio of 1·22 (p<0·001) per 1 h increase in system delay. Figure reproduced from Terkelsen et al,[47] by permission of the American Medical Association.

The STREAM trial[57] investigated this optimum pharmacoinvasive strategy. It needs to be emphasised that this strategy is different from so-called facilitated PCI, in which all patients (irrespective of lytic success) go directly to the catheter laboratory as soon as they arrive to the hospital. This strategy was not shown to be of value in the prematurely discontinued ASSENT-4 trial.[56] By contrast, STREAM (n=1892) was designed for rapid intervention only in those with failed fibrinolysis (as defined by the ECG)—all other trial participants were intervened on after 6 h. This study thus compared a pharmacoinvasive strategy (fibrinolysis with bolus tenecteplase, followed by rescue angioplasty if fibrinolysis failed or angiography 6–24 h after randomisation if fibrinolysis was successful) with primary PCI in patients presenting within 3 h who could not receive primary PCI within an hour of first medical contact. The 30 day primary endpoint (a composite of death, shock, congestive heart failure, or reinfarction) occurred in 12·4% of the fibrinolysis group and 14·3% of the primary-PCI group (relative risk 0·86, 95% CI 0·68–1·09, p=0·21). Emergency angiography was needed in 36% of patients assigned to fibrinolysis, with the remainder undergoing angiography at a median of 17 h after randomisation. As such, 64% of patients did not need emergency intervention because the fibrinolytic (on exclusion criteria) seemed to be successful. Intracranial haemorrhage occurred more often in the fibrinolysis group (1·0% *vs* 0·2%, p=0·04). The need for rescue PCI was consistent with other such trials (eg, CAPTIM[44]), with failure of fibrinolysis being the trigger to act. The trial protocol was amended after the first 400 patients, with the fibrinolytic dose halved in patients older than 75 years after the suggestion of excess intracranial haemorrhage. After the protocol amendment, no

overall difference in rates of intracranial haemorrhage was noted between the two groups (0·5% for fibrinolysis *vs* 0·3% for primary PCI, p=0·45).

Findings from this trial showed that there could be a place for fibrinolysis if specific criteria are met. Fibrinolysis should be given early (preferably prehospital) to patients with no contraindications (eg, recent bleeding or stroke, or to elderly patients) and followed by timely coronary angiography (within 24 h) or rescue PCI for those with fibrinolytic failure. As such, fibrinolysis could be an important strategy in patients unable to receive PCI after STEMI within 1 h of first medical contact; this approach overcomes the disadvantages associated with delayed primary PCI. Intriguingly, coronary flow data from the STREAM trial[57] showed that more than 70% of patients receiving early fibrinolysis had TIMI flow grades of 2 or 3, compared with 20% of those arriving for primary PCI. Although TIMI flow grades in both groups were equal after treatment, significantly more patients in the fibrinolytic group travelled to hospital with more open arteries than did patients in the primary-PCI group, which could (on the assumption that more myocardium was salvaged earlier) lead to clinical benefits at longer-term follow-up.

Conclusions

The preferred reperfusion option for patients with STEMI is timely primary PCI, although the recommendation for this approach was based on comparisons with inhospital fibrinolysis alone.[1,2,14] Delay to delivery of reperfusion, which predominantly affects primary PCI, leads to an attenuation of benefit compared with fibrinolysis. When the difference in delivery between the two strategies is more than 60 min they seem equal. Furthermore, a pharmacoinvasive strategy of prehospital fibrinolysis plus planned angiography (at 6–24 h in haemodynamically stable patients) and rescue angioplasty for failed fibrinolysis has now been shown to be equivalent (by results of the STREAM trial[57]) or better (by results of the CAPTIM trial[44,51]) to primary PCI in patients who present early. As such, this strategy could be useful if primary PCI cannot be done within 2 h of first medical contact, or if fibrinolysis can be given more than 60 min earlier than can primary PCI, irrespective of whether the network catchment is rural, urban, or mixed. The guidelines indicate this possibility, and evidence to lend support to this strategy in selected patients is now available.

Fibrinolysis still seems to have an important part to play in the management of patients with STEMI, especially in those who cannot reach a PCI centre quickly. However, a treatment strategy based on pharmacoinvasive therapy is contingent on adequate paramedic training to administer prehospital fibrinolytics, and network efficiency. The threshold below which the pharmacoinvasive strategy becomes inefficient will depend somewhat on local, regional, or national frameworks, but in a particular region with long transfer times, delivery in less than 10% of all patients with STEMI might be thought unworkable.

The key to STEMI reperfusion is to deliver the therapy as quickly as possible to all patients who will benefit. The choice of strategy depends on many factors, including geography, weather, local resources, and the organisation of regional and national health systems. National planning groups might look again at their strategic options for reperfusion. The effectiveness of therapy, rather than its nature, is paramount, and in this context one size does not fit all.

Contributors

AHG wrote the paper in its entirety. All authors were involved in conception, design, and critical revision of the paper for important intellectual content. All authors have seen and given final approval of the final version for submission.

Conflicts of interest

AHG reports receiving support for travel and time spent for STREAM trial investigators from Boeringher Ingelheim. APB declares receiving research funding from Boston Scientific. FWAV reports receiving speaker's fees and consultancy honoraria from Boeringher Ingelheim. The remaining authors declare that they have no conflicts of interest.

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References

1 Steg PG, James SK, Atar D, et al, for the Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33:** 2569–619.

2 O'Gara PT, Kushner FG, Ascheim DD, et al, for the CF/AHA Task Force. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; **127:** 529–55.

3 Huber K, Goldstein P, Danchin N, Fox KA. Network models for large cities: the European experience. *Heart* 2010; **96:** 164–69.

4 Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 1979; **40:** 633–44.

5 Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? *JAMA* 2005; **293:** 979–86.

6 Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardio (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; **327:** 397–402.

7 Franzosi MG, Santoro E, De Vita C, et al, for the GISSI Investigators. Ten-year follow-up of the first megatrial testing thrombolytic therapy in patients with acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 study. *Circulation* 1998; **98:** 2659–65.

8 Langer A, Goodman SG, Topol EJ, et al, for the LATE Study Investigators. Late assessment of thrombolytic efficacy (LATE) study: prognosis in patients with non-Q wave myocardial infarction. *J Am Coll Cardiol* 1996; **27:** 1327–32.

9 Gibson CM, Cannon CP, Piana RN, et al. Angiographic predictors of reocclusion after thrombolysis: results from the Thrombolysis in Myocardial Infarction (TIMI) 4 trial. *J Am Coll Cardiol* 1995; **25:** 582–89.

10 Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. *JAMA* 2000; **283:** 2686–92.

11 Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; **348:** 771–75.

12 Stone GW, Grines CL, Browne KF, et al. Predictors of in-hospital and 6-month outcome after acute myocardial infarction in the reperfusion era: the Primary Angioplasty in Myocardial Infarction (PAMI) trial. *JAMA* 1980; **25:** 370–77.

13 Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA* 1997; **278:** 2093–98.

14 Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **361:** 13–20.

15 McNamara RL, Wang Y, Herrin J, et al, for the NRMI Investigators. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2006; **47:** 2180–86.

16 Rathore SS, Curtis JP, Chen J, et al. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. *BMJ* 2009; **338:** b1807.

17 Krumholz HM, Bradley EH, Nallamothu BK, et al. A campaign to improve the timeliness of primary percutaneous coronary intervention. Door-to-balloon: an alliance for quality. *JACC Cardiovasc Interv* 2008; **1:** 97–104.

18 Flynn A, Moscucci M, Share D, et al. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Arch Intern Med* 2010; **170:** 1842–49.

19 Gersh BJ, Antman EM. Selection of the optimal reperfusion strategy for STEMI: does time matter? *Eur Heart J* 2006; **27:** 761–63.

20 Denktas AE, Anderson HV, McCarthy J, Smalling RW. Total ischemic time: the correct focus of attention for optimal ST-segment elevation myocardial infarction care. *JACC Cardiovasc Interv* 2011; **4:** 599–604.

21 Department of Health Vascular Programme Team. Treatment of heart attack national guidance. Final report of the National Infarct Angioplasty Project (NIAP). 2008. http://www.bcis.org.uk/resources/documents/NIAP%20Final%20Report.pdf (accessed July 25, 2013).

22 Ranasinghe I, Turnbull F, Tonkin A, Clark RA, Coffee N, Brieger D. Comparative effectiveness of population interventions to improve access to reperfusion for ST-segment-elevation myocardial infarction in Australia. *Circ Cardiovasc Qual Outcomes* 2012; **5:** 429–36.

23 Peterson MC, Syndergaard T, Bowler J, Doxey R. A systematic review of factors predicting door to balloon time in ST-segment elevation myocardial infarction treated with percutaneous intervention. *Int J Cardiol* 2012; **157:** 8–23.

24 McNamara RL, Herrin J, Bradley EH, et al, for the NRMI Investigators. Hospital improvement in time to reperfusion in patients with acute myocardial infarction, 1999 to 2002. *J Am Coll Cardiol* 2006; **47:** 45–51.

25 Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM, for the NRMI Investigators. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. *Circulation* 2005; **111:** 761–67.

26 Tarantini G, Razzolini R, Napodano M, Bilato C, Ramondo A, Iliceto S. Acceptable reperfusion delay to prefer primary angioplasty over fibrin-specific thrombolytic therapy is affected (mainly) by the patient's mortality risk: 1 h does not fit all. *Eur Heart J* 2010; **31:** 676–83.

27 Nallamothu BK, Bates ER, Wang Y, Bradley EH, Krumholz HM. Driving times and distances to hospitals with percutaneous coronary intervention in the United States: implications for prehospital triage of patients with ST-elevation myocardial infarction. *Circulation* 2006; **113:** 1189–95.

28 Jollis JG, Mehta RH, Roettig ML, Berger PB, Babb JD, Granger CB. Reperfusion of acute myocardial infarction in North Carolina emergency departments (RACE): study design. *Am Heart J* 2006; **152:** 851.e1–11.

29 Jollis JG, Al-Khalidi HR, Monk L, et al, for the Regional Approach to Cardiovascular Emergencies (RACE) Investigators. Expansion of a regional ST-segment-elevation myocardial infarction system to an entire state. *Circulation* 2012; **126:** 189–95.

30 Jollis JG, Granger CB, Henry TD, et al. Systems of care for ST-segment-elevation myocardial infarction: a report from the American Heart Association's Mission: Lifeline. *Circ Cardiovasc Qual Outcomes* 2012; **5:** 423–28.

31 Fosbol EL, Granger CB, Jollis JG, et al. The impact of a statewide pre-hospital STEMI strategy to bypass hospitals without percutaneous coronary intervention capability on treatment times. *Circulation* 2013; **127:** 604–12.

32 Roe MT, Messenger JC, Weintraub WS, et al. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. *J Am Coll Cardiol* 2010; **56:** 254–63.

33 Swaminathan RV, Wang TY, Kaltenbach LA, et al. Non-system reasons for delay in door-to-balloon time and associated in-hospital mortality: a report from the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2013; **61:** 1688–95.

34 Miedema MD, Newell MC, Duval S, et al. Causes of delay and associated mortality in patients transferred with ST-segment-elevation myocardial infarction. *Circulation* 2011; **124:** 1636–44.

35 Wang TY, Nallamothu BK, Krumholz HM, et al. Association of door-in to door-out time with reperfusion delays and outcomes among patients transferred for primary percutaneous coronary intervention. *JAMA* 2011; **305:** 2540–47.

36 Magid DJ, Wang Y, Mcnamara RL, et al. Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute ST-segment elevation myocardial infarction. *JAMA* 2005; **294:** 803–12.

37 Nestler DM, Noheria A, Haro LH, et al. Sustaining improvement in door-to-balloon time over 4 years: the Mayo clinic ST-elevation myocardial infarction protocol. *Circ Cardiovasc Qual Outcomes* 2009; **2:** 508–13.

38 De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 2004; **109:** 1223–25.

39 Lønborg J, Schoos MM, Kelbæk H, et al. Impact of system delay on infarct size, myocardial salvage index, and left ventricular function in patients with ST-segment elevation myocardial infarction. *Am Heart J* 2012; **164:** 538–46.

40 Francone M, Bucciarelli-Ducci C, Carbone I, et al. Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *J Am Coll Cardiol* 2009; **54:** 2145–53.

41 Brodie BR, Gersh BJ, Stuckey T, et al. When is door-to-balloon time critical? Analysis from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials. *J Am Coll Cardiol* 2010; **56:** 407–13.

42 Lambert L, Brown K, Segal E, Brophy J, Rodes-Cabau J, Bogaty P. Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. *JAMA* 2010; **303:** 2148–55.

43 Boersma E, and the Primary Coronary Angioplasty *vs* Thrombolysis Group. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 2006; **27:** 779–88.

44 Bonnefoy E, Lapostolle F, Leizorovicz A, et al, for the Comparison of Angioplasty and Prehospital Thromboysis in Acute Myocardial Infarction study group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet* 2002; **360:** 825–29.

45 Chakrabarti AK, Gibson CM, Pinto DS. Optimal selection of STEMI treatment strategies in the current era: benefit of transferring STEMI patients for PCI compared with administration of onsite fibrinolytic therapy. *Curr Opin Cardiol* 2012; **27:** 651–54.

46 Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation* 2006; **114:** 2019–25.

47 Terkelsen CJ, Sørensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA* 2010; **304:** 763–71.

48 Nielsen PH, Terkelsen CJ, Nielsen TT, et al, for the Danami-2 Investigators. System delay and timing of intervention in acute myocardial infarction (from the Danish Acute Myocardial Infarction-2 [DANAMI-2] trial). *Am J Cardiol* 2011; **108:** 776–81.

49 Gershlick AH, Stephens-Lloyd A, Hughes S, et al, for the REACT Trial Investigators. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 2005; **353:** 2758–68.

50 Fernandez-Avilés F, Alonso JJ, Castro-Beiras A, et al, for the GRACIA (Grupo de Análisis de la Cardiopatía Isquémica Aguda) Group. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004; **364:** 1045–53.

51 Bonnefoy E, Steg PG, Boutitie F, et al, for the CAPTIM Investigators. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. *Eur Heart J* 2009; **30:** 1598–606.

52 Westerhout CM, Bonnefoy E, Welsh RC, Steg PG, Boutitie F, Armstrong PW. The influence of time from symptom onset and reperfusion strategy on 1-year survival in ST-elevation myocardial infarction: a pooled analysis of an early fibrinolytic strategy versus primary percutaneous coronary intervention from CAPTIM and WEST. *Am Heart J* 2011; **161:** 283–90.

53 Armstrong PW, and the WEST Steering Committee. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. *Eur Heart J* 2006; **27:** 1530–38.

54 Cantor WJ, Fitchett D, Borgundvaag B, et al, for the TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med* 2009; **360:** 2705–18.

55 Di Mario C, Dudek D, Piscione F, et al, for the CARESS-in-AMI (Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction) Investigators. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet* 2008; **371:** 559–68.

56 Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006; **367:** 569–78.

57 Armstrong PW, Gershlick AH, Goldstein P, et al, for the STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013; **368:** 1379–87.

ST-segment Elevation Myocardial Infarction 2

What is the optimum adjunctive reperfusion strategy for primary percutaneous coronary intervention?

Nicholas Curzen, Paul A Gurbel, Aung Myat, Deepak L Bhatt, Simon R Redwood

Acute ST-segment elevation myocardial infarction (STEMI) is a dynamic, thrombus-driven event. As understanding of its pathophysiology has improved, the central role of platelets in initiation and orchestration of this process has become clear. Key components of STEMI include formation of occlusive thrombus, mediation and ultimately amplification of the local vascular inflammatory response resulting in increased vasoreactivity, oedema formation, and microvascular obstruction. Activation, degranulation, and aggregation of platelets are the platforms from which these components develop. Therefore, prompt, potent, and predictable antithrombotic therapy is needed to optimise clinical outcomes after primary percutaneous coronary intervention. We review present pharmacological and mechanical adjunctive therapies for reperfusion and ask what is the optimum combination when primary percutaneous coronary intervention is used as the mode of revascularisation in patients with STEMI.

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This the second in a **Series** of three papers about ST-segment elevation myocardial infarction

Wessex Cardiothoracic Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK (Prof N Curzen PhD); **Sinai Center for Thrombosis Research, Cardiac Catheterisation Laboratory, Sinai Hospital of Baltimore, Baltimore, MD, USA** (Prof P A Gurbel MD); **King's College London BHF Centre of Research Excellence, Cardiovascular Division, The Rayne Institute, St Thomas' Hospital, London, UK** (A Myat MRCP, Prof S R Redwood FRCP); **VA Boston Healthcare System, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA** (Prof D L Bhatt MD)

Correspondence to:
Prof Nicholas Curzen, University Hospital Southampton NHS Foundation Trust, Southampton SO16 6YD, UK
nick.curzen@uhs.nhs.uk

Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is a dynamic, thrombus-driven event in which platelets have a central role (figure 1). Antithrombotic therapy optimises clinical outcomes for patients after primary percutaneous coronary intervention (PCI). Contemporary European and US guidelines for treatment of STEMI have assigned a class IA recommendation for primary PCI as the reperfusion strategy of choice when done by an experienced team within 90 min of first medical contact.[1,2] However, various preprocedural and periprocedural pharmacotherapeutic options are available to combat the prothrombotic milieu that exists both as a direct sequel of the vaso-occlusive process allied to the vessel trauma, and distal embolisation caused by mechanical revascularisation. In this Series paper we focus solely on adjuvant therapies for reperfusion and seek to establish an optimum treatment strategy based on present evidence.

Oral antiplatelet therapy

Aspirin irreversibly inhibits cyclooxygenase and thereby blocks eventual production of thromboxane A2, a vasoconstrictor and highly potent stimulant of platelet aggregation (figure 1). Results from the landmark ISIS-2 trial[3] irrefutably showed the efficacy of aspirin to reduce cardiovascular morbidity and mortality when given to patients with suspected acute myocardial infarction, either as a stand-alone therapy or in combination with streptokinase. Clopidogrel, a thienopyridine, selectively and irreversibly binds the platelet surface receptor P2Y12 (also known as P2RY12), which is responsible for initiation of the platelet activation response to the agonist ADP (figure 1). Aspirin and clopidogrel work via complementary mechanisms and provide synergistic inhibition of the platelet aggregation pathway, hence the development of dual antiplatelet therapy for patients with STEMI treated in the thrombolysis era.[4,5] However, a wealth of evidence, reviewed in detail elsewhere,[1,2,6] has left little room for doubt that timely, guideline-mandated primary PCI is the best treatment strategy for patients with STEMI when compared with fibrinolysis. In this context the indication for antiplatelet agents broadens; not only might they offer benefit as medical therapies in their own right, but they are also needed to prevent the thrombotic–ischaemic complications of coronary stent deployment.

In recent years, concerns have grown over the heterogeneous nature of individuals' response to clopidogrel. Specifically, several reports have shown a link between high-on-treatment platelet reactivity and subsequent ischaemic complications, including stent thrombosis, in patients given clopidogrel.[7] Because this link is consistent across different populations of patients treated with primary PCI, the practice of administration of a standard dose of clopidogrel to all patients, without monitoring of individual responses, might not be robust or optimum. The situation is complicated by the absence of a reliable, quick, easy-to-use, reproducible, and clinically validated point-of-care test for clopidogrel response.[8] Concerns about potential functional resistance to clopidogrel are heightened by the inflammatory milieu in STEMI, a clinical setting in which there is a perceived need for

Search strategy and selection criteria

We searched the Cochrane Library, Medline, PubMed, Embase, and references from relevant articles with use of a combination of the search terms "STEMI", "primary percutaneous coronary intervention", "aspirin", "clopidogrel", "prasugrel", "ticagrelor", "cangrelor", "bivalirudin", "glycoprotein IIb IIIa inhibitor", and "manual aspiration thrombectomy". We largely selected publications from the past 10 years, but did not exclude widely referenced and highly regarded older publications. All studies published in English between Jan 1, 1980, and May 31, 2013, were included in the search.

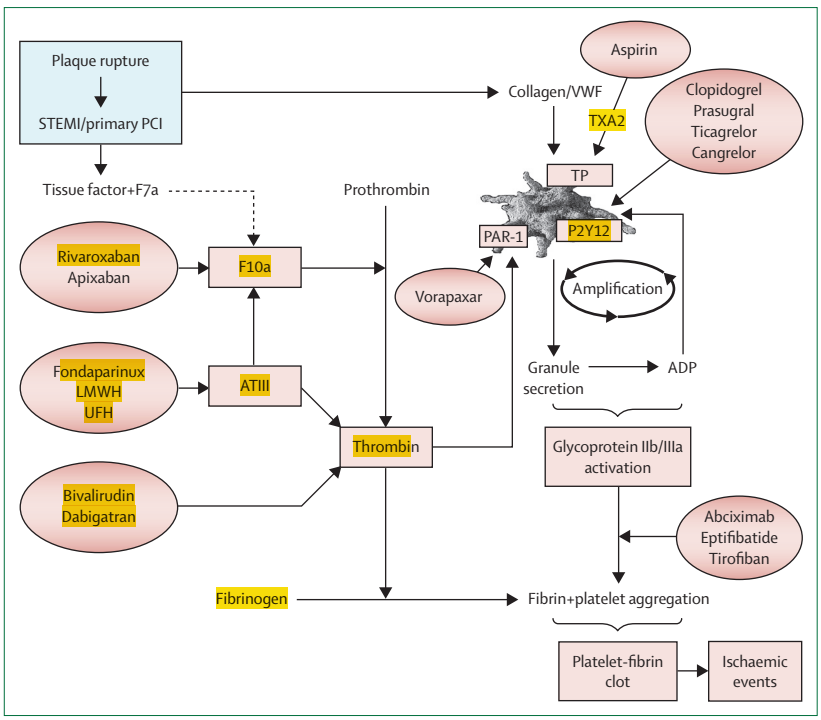

Figure 1: **Platelet activation, adhesion, and aggregation cascade, and targets for antithrombotic drug therapy to support primary PCI**

De-novo plaque rupture can lead to STEMI. Exposure of the subendothelial matrix and subsequent release of vasoactive factors enable platelet activation and release of important secondary agonists, thromboxane A2 and ADP. Through autocrine and paracrine mechanisms, these locally generated secondary agonists have an essential role in the sustained activation of glycoprotein IIb/IIIa receptors and stable platelet aggregation. Plaque rupture also results in tissue factor exposure that binds to activated factor VII (F7a) to form a complex which activates factor X (F10) to F10a. Initial formation of small amounts of thrombin results in perpetuation of the coagulation process on the surface of activated platelets, where large amounts of thrombin are generated. Thrombin finally catalyses the conversion of soluble fibrinogen to insoluble strands of fibrin, thereby initiating clot formation. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. VWF=von Willebrand factor. TXA2=thromboxane A2. TP=thromboxane A2 receptor. PAR-1=coagulation factor II (thrombin) receptor. P2Y12=purinergic receptor P2Y, G-protein coupled, 12. LMWH=low-molecular-weight heparin. ATIII=antithrombin III. UFH=unfractionated heparin.

antiplatelet agents that provide a more rapid onset, and more potent and consistent inhibition of P2Y12, than is provided by clopidogrel. These factors supplied the motivation for clinical trials that compared prasugrel and ticagrelor with clopidogrel in patients presenting with a spectrum of acute coronary syndromes, which included subgroups of patients with STEMI. These trials provide evidence that both prasugrel and ticagrelor are superior to clopidogrel in the populations studied, and that this benefit might be extended to patients with STEMI.

Prasugrel is a third-generation thienopyridine prodrug that, like clopidogrel, causes irreversible inhibition of P2Y12 (figure 1). Unlike clopidogrel, however, it needs only one oxidative step to form its active moiety, which is generated much faster, more efficiently, and in much higher concentrations. Results from the TRITON-TIMI 38 trial[9] showed a 2·3% absolute reduction in the rate of a combined endpoint of death, myocardial infarction, and stroke in patients given prasugrel. Notably, the rate of stent thrombosis was significantly lower in the prasugrel group than in the clopidogrel group. By contrast, rates of thrombolysis in myocardial infarction (TIMI) major bleeding and fatal bleeding were significantly higher in the prasugrel group. Overall life-threatening bleeding occurred in 1·4% of the prasugrel group versus 0·9% of the clopidogrel group (p=0·01).[9]

Ticagrelor is a reversibly binding oral antagonist of P2Y12 (figure 1), and was the first such drug to be approved. Unlike thienopyridines, it does not need hepatic biotransformation for activity. Ticagrelor has been associated with a significant reduction in the combined rate of death from vascular causes, myocardial infarction, and stroke compared with clopidogrel.[10] The rate of death, a prespecified secondary endpoint, was also significantly lower in patients receiving ticagrelor in the PLATO trial.[10] However, the rate of major bleeding not related to coronary artery bypass grafting (roughly 10% of the study group underwent this procedure) was significantly higher in the ticagrelor group.

The overall use of either prasugrel or ticagrelor with primary PCI is growing rapidly, replacing clopidogrel as the default P2Y12 inhibitor. For example, prasugrel was used as the P2Y12 inhibitor of choice in 22·2% of primary PCI cases in the UK in 2011.[11] However, the enthusiastic uptake of these newer drugs in STEMI might be premature. Subgroup analyses of the STEMI populations in the TRITON-TIMI 38[12] and PLATO[13] trials showed no significant benefit in primary endpoints for prasugrel or ticagrelor versus clopidogrel for patients receiving primary PCI, but showed highly significant reductions in primary endpoint events in patients with STEMI as a whole, driven by patients who received PCI later in their admission (secondary PCI).[12]

One explanation for the absence of significant benefit for these newer drugs in primary PCI could be insufficient numbers of patients in the subgroups to yield adequate statistical power. Indeed, the subgroup results in these trials for primary PCI were consistent with the overall findings. If this is the case, it is arguable whether the lack of robust evidence justifies the large-scale switch towards newer agents observed for patients undergoing primary PCI, particularly when the increased bleeding risk is taken into account. Another explanation for this potential lack of clinical effectiveness might be that prasugrel and clopidogrel are not as rapidly acting in this clinical setting as earlier data would suggest. This possibility is particularly important, because the immediacy of primary PCI means that substantial benefit would be expected from drugs that are pharmacokinetically faster acting, pharmacodynamically stronger, and have a more homogeneous effect. In one randomised study[14] of ticagrelor and prasugrel in patients undergoing primary PCI, the onset of effective inhibition of platelet reactivity was unexpectedly slow compared with non-STEMI populations, leading the investigators to conclude that both drugs seemed to exhibit an initial delay in the onset of their antiplatelet action. Additionally, any benefit

of ticagrelor or prasugrel compared with clopidogrel in terms of reduced periprocedural enzyme rise might not be detected as a result of the design of the TRITON-TIMI 38 and PLATO trials.

Although there are reservations with respect to efficacy and increased bleeding risks, prasugrel and ticagrelor have received class IB recommendations as adjunctive treatments for primary PCI in the most recent iteration of the European STEMI guidelines, whereas clopidogrel has been assigned a class IC indication.[1] Despite the theoretical attractiveness of tailored P2Y12 therapy, in which only patients shown to be hyporesponsive to clopidogrel receive a stronger drug, no large-scale randomised trials have shown clinical benefit for such a strategy. Such trials are needed to resolve this uncertainty.[15,16]

Parenteral antiplatelet therapy

Cangrelor

The ultimate goal of parenteral antithrombotic (antiplatelet and anticoagulant) therapy is to provide a rapid onset of pharmacodynamic effect and durable myocardial reperfusion by prevention of stent thrombosis and periprocedural myocardial infarction, with avoidance of catheter thrombosis and serious bleeding.

Although not yet licensed for routine clinical use, cangrelor is a fast-acting and rapidly reversible parenteral P2Y12 inhibitor (figure 1). These pharmacodynamic characteristics are very appealing to the interventional cardiologist looking for powerful and rapid-onset platelet inhibition. In a recent all-comers PCI trial,[17] patients given cangrelor (compared with a 600 mg load of clopidogrel) immediately after angiography had a 22% reduction in the primary endpoint of death, myocardial infarction, ischaemia-driven revascularisation, or stent thrombosis at 48 h. In the STEMI subgroup (17% of the total trial population), there was a consistent 25% reduction in the primary endpoint and a non-significant 84% higher rate of bleeding. Overall, patients treated with cangrelor had significantly lower rates of stent thrombosis than those receiving clopidogrel. The clinical efficacy of cangrelor compared with glycoprotein IIb/IIIa inhibitors and the more potent oral P2Y12 inhibitors prasugrel and ticagrelor remains untested.

Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibitor therapy is the most pharmacodynamically potent treatment strategy for inhibition of platelet function. By blocking downstream at the fibrinogen receptor, glycoprotein IIb/IIIa receptor inhibitors provide immediate inhibition of platelet aggregation stimulated by all agonists (figure 1). Most randomised clinical trials of glycoprotein IIb/IIIa inhibitors in patients with STEMI have studied abciximab. The usefulness of glycoprotein IIb/IIIa inhibitors was first shown in the balloon angioplasty era, before routine use of dual antiplatelet therapy, the advent of radial artery interventions, and thrombus aspiration. Glycoprotein IIb/IIIa inhibitor therapy is associated with a reduction in major adverse cardiovascular events at the expense of increased bleeding and thrombocytopenia.[18] However, in the era of stenting and dual antiplatelet therapy with high-loading doses of clopidogrel, a net benefit for glycoprotein IIb/IIIa inhibitors has not been uniformly reported.

In a study[18] of relatively low-risk patients with STEMI, given ticlopidine and aspirin and randomly assigned to balloon angioplasty versus stenting with or without abciximab, investigators noted reduced rates of subacute thrombosis and recurrent ischaemia needing target vessel revascularisation during the first few weeks of treatment in both abciximab groups. However, abciximab was associated with less benefit in stented patients than in patients who received balloon angioplasty, and did not significantly improve TIMI flow grade, angiographic restenosis rates, or late reocclusion and cardiac events irrespective of the method of revascularisation.[18] In the BRAVE-3 trial,[19] abciximab did not reduce infarct size or 30 day major adverse cardiovascular events in patients with STEMI given 600 mg clopidogrel before primary PCI. By contrast, Antoniucci and colleagues[20] reported a significant reduction in a composite endpoint of death, reinfarction, or target vessel revascularisation at 30 days in a higher risk STEMI population randomised to bare-metal stenting of the infarct-related artery alone or with abciximab. Although aspirin was given preprocedurally, ticlopidine or clopidogrel were only given after stenting, a potential confounder to the trial's results.

At present, the routine use of glycoprotein IIb/IIIa inhibitors in combination with unfractionated heparin or bivalirudin might be considered in patients without contraindications, and has been assigned a class IIb recommendation with level of evidence A for abciximab, and level of evidence B for tirofiban and eptifibatide, by European STEMI guidelines.[1] US guidelines give a class IIa recommendation in selected patients, particularly those treated with heparin and not pretreated with a P2Y12 inhibitor (which is the same level of evidence as given by European guidelines).[2]

Upfront glycoprotein IIb/IIIa inhibitors

Precatheterisation compared with periprocedural use of abciximab in facilitated PCI has been associated with similar rates of both the restoration of coronary flow rate (as judged by TIMI flow grade 2–3) and 90 day mortality, but is associated with a trend to increased major bleeding.[21] However, patients given early abciximab had reduced 1 year mortality rates compared with patients given abciximab later.[22] Furthermore, ambulance administration of high-dose tirofiban, in addition to 600 mg clopidogrel therapy, improved ST-segment resolution both before and after PCI, compared with downstream use.[23] In a meta-analysis[24] of seven randomised trials, early abciximab compared with late periprocedural abciximab was

associated with a significant reduction in mortality and improvements in preprocedural and postprocedural coronary blood flow and ST-segment resolution, but no differences in complications due to major bleeding.

The use of glycoprotein IIb/IIIa inhibitors before arrival at the catheterisation laboratory in patients with STEMI remains controversial, receiving a class IIb recommendation in recent guidelines.[1,2] In the era of potent and fast-acting P2Y12 blockers (prasugrel and ticagrelor), the usefulness of early therapy with glycoprotein IIb/IIIa inhibitors might be further reduced. However, there are no randomised data available to compare early glycoprotein IIb/IIIa inhibitors with potent oral P2Y12 blockers in STEMI. Glycoprotein IIb/IIIa inhibitor therapy could be associated with greatest benefit in patients with STEMI not pretreated with P2Y12 blockers, in whom risk of thrombotic events outweighs risk of bleeding, but more data are needed to fully establish their usefulness in primary PCI.

Intracoronary glycoprotein IIb/IIIa inhibitors

The rapid achievement of local platelet inhibition (potentially resulting in improved myocardial perfusion) forms the rationale for intracoronary administration of glycoprotein IIb/IIIa inhibitors.[25] In a small (n=154) randomised study,[26] intracoronary abciximab was associated with smaller median infarct sizes, less microvascular obstruction (measured by delayed-enhancement MRI), and better ST-segment resolution than was intravenous abciximab. In a trial[27] largely based on surrogate markers of efficacy, patients with STEMI undergoing primary PCI and receiving bivalirudin, who were randomly assigned to local delivery of abciximab, had reduced 30 day infarct size compared with patients who received no abciximab. However, no improvement in abnormal wall motion score, ST-segment resolution, post-primary-PCI coronary flow, or myocardial perfusion was shown for intracoronary administration. A major shift to local delivery of glycoprotein IIb/IIIa inhibitors has not occurred after findings from a study[28] showed that intracoronary abciximab was associated with a similar rate of the primary endpoint (a composite of death, reinfarction, or congestive heart failure) to intravenous abciximab, whereas only the incidence of new congestive heart failure fell in the intracoronary group. In a substudy,[29] cardiac MRI showed no benefit of intracoronary abciximab compared with intravenous abciximab for myocardial damage or reperfusion injury. In line with these findings and a recent meta-analysis,[30] European STEMI guidelines suggest intracoronary administration of glycoprotein IIb/IIIa inhibitors could be considered, but intravenous administration remains the standard of care, if indicated.[1]

Parenteral anticoagulant therapy

Fibrin is abundant in the STEMI thrombus, and as such anticoagulant therapy is mandatory in primary PCI.[1,2] Options include unfractionated heparin adjusted with use of the activated clotting time (the agent associated with the greatest experience, albeit a generally weak evidence base), low-molecular-weight heparin (enoxaparin), and bivalirudin. There is a class I recommendation for unfractionated heparin in both European and US guidelines if patients are not given bivalirudin or enoxaparin.[1,2] Lower doses of unfractionated heparin are recommended if glycoprotein IIb/IIIa inhibitors are also given.

The usefulness of enoxaparin in primary PCI has not been widely investigated. Consequently, no recommendation is given by US guidelines for this particular treatment strategy.[2] Findings from the only randomised trial comparing enoxaparin with unfractionated heparin were neutral with respect to the primary endpoint.[31] However, in European guidelines there is a class IIb recommendation for enoxaparin compared with unfractionated heparin, because of the benefits noted in composite secondary endpoints.[31] Because of the high rate of catheter thrombosis recorded in the OASIS-6 trial,[32] fondaparinux should not be used as the sole background anticoagulant for primary PCI.[1,2]

Bivalirudin, a direct thrombin inhibitor, was compared with periprocedural abciximab or eptifibatide plus unfractionated heparin in the landmark HORIZONS-AMI trial[33] (n=3602). Bivalirudin therapy was associated with a significant reduction in the overall net clinical outcome, a result dominated by a significant reduction in major bleeding. Furthermore, bivalirudin therapy was associated with lower cardiac mortality, despite a higher rate of acute stent thrombosis within the first 24 h. Stent thrombosis in the bivalirudin group might have been related to lower loading doses of clopidogrel and the absence of heparin before randomisation. Indeed, major adverse cardiovascular events tended to be higher in patients not pretreated with heparin in the bivalirudin group.[33] Remarkably, the mortality benefits of bivalirudin therapy persisted at 3 year follow-up.[34] The difference in bleeding could have been enhanced as a result of extended infusion of glycoprotein IIb/IIIa inhibitors, whereas bivalirudin therapy was stopped at the end of the PCI procedure. Use of a radial approach (in about 5% of the HORIZONS-AMI primary-PCI cohort) might reduce major bleeding with both drugs, and potentially lessen the difference between therapies. Although use of the new P2Y12 inhibitors (prasugrel or ticagrelor) with bivalirudin has been proposed as a replacement for glycoprotein IIb/IIIa inhibitors, there are no randomised data to support this proposal. In the TRITON-TIMI 38[9] and PLATO[10] invasive studies, the benefits of prasugrel and ticagrelor versus clopidogrel were noted irrespective of glycoprotein IIb/IIIa inhibitor therapy. Because of concerns about acute stent thrombosis in the bivalirudin group of the HORIZONS-AMI study, the combination of prasugrel

plus bivalirudin will be compared with high-loading-dose clopidogrel plus unfractionated heparin in the BRAVE-4 trial (NCT00976092).

On the basis of this evidence, bivalirudin has been assigned a class IB recommendation with or without previous heparin therapy by European and US STEMI guidelines.[1,2] In patients at high risk of bleeding, preferential use of bivalirudin monotherapy compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors is given a class IIa recommendation in US guidelines.[2] Of note, 2357 of 3602 patients enrolled in the HORIZONS-AMI trial received a prerandomisation bolus of unfractionated heparin. In the HORIZONS -SWITCH analysis,[35] 30 day and 2 year outcomes for the switch group (who received prerandomisation unfractionated heparin followed by bivalirudin) were compared with a control group (who received pre-randomisation unfractionated heparin followed by unfractionated heparin plus glycoprotein IIb/IIIa inhibitor). The switch group had significantly lower rates of 30 day major bleeding and cardiac mortality, which persisted for 2 years. The apparent benefit of a bolus of unfractionated heparin plus bivalirudin is lent support by similar results from a large Swedish registry analysis of primary PCI.[36]

Thrombus aspiration

Despite appropriate and timely epicardial recanalisation of the infarct-related artery, a significant proportion (up to 65% undergoing primary PCI in the absence of cardiogenic shock) of patients with STEMI do not achieve optimum myocardial reperfusion downstream of the occlusion.[37,38] Distal embolisation of plaque debris during mechanical instrumentation, combined with varying degrees of ischaemia or reperfusion injury, a prothrombotic milieu, and microcirculatory obstruction, can result in so-called no-reflow—defined as reduced or absent antegrade flow despite angiographic evidence of

	Year of publication	Selection criteria	Method of embolisation protection	Number of trials	Number of patients	Notable outcomes
Bavry and colleagues[47]	2008	All trials from January, 1996, to June, 2008, were open to selection; inclusion criteria were patients randomly assigned within 12 h of acute MI with embolisation protection before primary PCI versus primary PCI alone; exclusion criteria were device versus device studies; patient-level data were not available	Thrombus aspiration; mechanical thrombectomy; embolic protection devices	30	6415	All-cause mortality • Thrombus aspiration at mean of 6·2 months: 2·7% versus 4·4% (p=0·018) • Mechanical thrombectomy at mean of 4·6 months: 5·3% versus 2·8% (p=0·050) • Embolic protection devices at mean of 3·7 months: 3·1% versus 3·4% (p=0·69) Stroke risk • Significant increase in the risk of stroke (RR 3·01, p=0·024) when outcome data from thrombus aspiration and mechanical thrombectomy studies were combined
De Luca and colleagues[48]	2008	All trials from January, 1990, to May, 2008, were open to selection; inclusion criteria were randomised treatment allocation and availability of complete clinical data; exclusion criteria were outcome data available in <90% of patients, ongoing studies, or trials with <50 patients; patient-level data were not available	Manual thrombus aspiration only	9	2417	30 day mortality • 1·7% versus 3·1% (p=0·04) TIMI flow grade 3 • 87·2% versus 81·2% (p<0·0001) MBG • 52·1% versus 31·7% (p<0·0001) Angiographic distal embolisation • 7·9% versus 19·5% (p<0·0001)
Burzotta and colleagues[49]	2009	All trials of PCI for STEMI with or without thrombectomy from October, 2003, to February, 2008, were open to selection; inclusion criteria were randomised treatment allocation; exclusion criteria were equivocal treatment allocation processes; a pooled analysis of patient-level data was done	Manual or non-manual thrombectomy	11	2686	Thrombectomy overall • Reduced all-cause mortality (log-rank p=0·049) • Significantly fewer MACE (log-rank p=0·011) • Significantly fewer deaths or MIs (log-rank p=0·015) • NNT=62 (at 1 year) to prevent 1 death Manual thrombectomy • Significantly fewer deaths (log-rank p=0·011) • NNT=34 (at 1 year) to prevent 1 death Non-manual thrombectomy • Similar mortality with standard PCI (log-rank p=0·481)
Mongeon and colleagues[50]	2010	All trials up to October, 2009, were open to selection; inclusion criteria were patients referred for primary or rescue PCI for acute STEMI within 12 h of symptom onset, patients given adjunctive thrombectomy only, or patients randomly allocated to primary PCI with or without thrombectomy; patient-level data were not available	Thrombus aspiration and mechanical thrombectomy devices	21	4299	30 day mortality • No significant change with any device (OR 0·94, 95% CI 0·47–1·80) or with an aspiration device (OR 0·58, 95% CI 0·28–1·22) Surrogate markers of myocardial reperfusion • Most patients achieved >50% ST-segment resolution (OR 2·22, 95% CI 1·60–3·23) • Less frequent no-reflow (OR 0·39, 95% CI 0·18–0·69) • Less frequent distal embolisation (OR 0·46, 95% CI 0·28–0·70)

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	Year of publication	Selection criteria	Method of embolisation protection	Number of trials	Number of patients	Notable outcomes
(Continued from previous page)						
Tamhane and colleagues[51]	2010	All trials randomly assigning patients with STEMI to thrombectomy before primary PCI versus conventional primary PCI alone from 1996 to December, 2009, were open to selection	Thrombus aspiration and mechanical thrombectomy	17	3909	30 day mortality • No difference in mortality between thrombectomy and conventional primary PCI overall (OR 0·84, 95% CI 0·54–1·29, p=0·42) • Trend towards higher mortality with mechanical devices (OR 2·07, 95% CI 0·95–4·48, p=0·07) • Significant reduction in mortality with manual aspiration thrombectomy (OR 0·59, 95% CI 0·35–1·01, p=0·05) Stroke • Significant increase in the risk of stroke with thrombectomy overall (OR 2·88, 95% CI 1·06–7·85, p=0·04)
Jang and colleagues[52]	2012	All randomised, case-control, and cohort studies of adjunctive devices to prevent distal embolisation in patients with STEMI from January, 2002, to May, 2012, were open to selection	Adjunctive thrombectomy devices	22	7229	Thrombectomy devices • Significant reduction in MACE (OR 0·81, 95% CI 0·68–0·98, p=0·03) • No difference in mortality (OR 0·97, 95% CI 0·73–1·29, p=0·81) • Significantly higher ST-segment resolution (OR 2·04, 95% CI 1·50–2·78, p<0·001) • Significantly higher rate of MBG 3 (OR 2·26, 95% CI 1·34–3·81, p=0·002)
Kumbhani and colleagues[53]	2013	All studies that randomly assigned patients within 12 h of acute MI to aspiration thrombectomy plus primary PCI versus primary PCI alone, or mechanical thrombectomy plus primary PCI versus primary PCI alone, reported from January, 1996, to December, 2012, were included	Thrombus aspiration and mechanical thrombectomy	25	5534	Aspiration thrombectomy plus primary PCI • Significant reduction in MACE (RR 0·76, 95% CI 0·63–0·92, p=0·006) and all-cause mortality (RR 0·71, 95% CI 0·51–0·99, p=0·049) • Improvement in ST-segment resolution at 60 min (RR 1·31, 95% CI 1·16–1·48, p<0·0001) and TIMI blush grade 3 post procedure (RR 1·37, 95% CI 1·19–1·59, p<0·0001) Mechanical thrombectomy plus primary PCI • No significant differences in the incidence of MACE (RR 1·10, 95% CI 0·59–2·05, p=0·77), mortality (p=0·57), MI (p=0·32), target vessel revascularisation (p=0·19), or final infarct size (p=0·47)

PCI=percutaneous coronary intervention. MI=myocardial infarction. RR=risk ratio. TIMI=thrombolysis in myocardial infarction. MBG=myocardial blush grade. STEMI=ST-segment elevation myocardial infarction. MACE=major adverse cardiovascular events. NNT=number needed to treat. OR=odds ratio.

Table: **Contemporary meta-analyses of adjunctive thrombectomy before primary PCI for acute MI**

a patent epicardial artery.[39] Knowledge of these incipient pathophysiological processes has resulted in the evolution of several devices for adjunctive thrombectomy, designed to minimise the risk of distal embolisation before or during primary angioplasty. These devices have now largely superseded those for embolic protection.[40,41]

Several randomised trials of upfront aspiration or mechanical thrombectomy before primary PCI have been plagued by small sample sizes, truncated follow-up, and a reliance on surrogate markers of myocardial reperfusion as a metric of efficacy—eg, ST-segment resolution, myocardial blush grade, macroscopic distal embolisation (which is prone to operator biases), or TIMI flow grade. Most were significantly underpowered to test for hard clinical endpoints, and have thus produced conflicting findings on the rate of major adverse cardiovascular events in the subacute post-infarct phase. Results from the TAPAS trial,[42] the largest thrombus aspiration trial to date, showed no difference in clinical outcomes at 30 day follow-up. At 1 year follow-up, however, rates of cardiac death and cardiac death plus non-fatal reinfarction were both significantly reduced in the aspiration thrombectomy cohort.[43] These findings have been reproduced in other trials.[44–46]

Direct comparisons of aspiration with mechanical thrombectomy are not available, but several meta-analyses (dominated by the TAPAS trial) have shown a slight mortality benefit for thrombectomy in the long term (table). Despite the inherent limitations of these meta-analyses (variation in inclusion and exclusion criteria, devices under investigation, availability of patient-level data, endpoints, and follow-ups, and operator-dependent procedural inconsistencies) they show a trend towards better outcomes with manual thrombus aspiration than with mechanical devices. Most of these meta-analyses pre-date findings from the JETSTENT trial (n=501),[54] which showed significantly improved rates of major adverse cardiovascular events at 6 month and 1 year event-free survival with mechanical rheolytic thrombectomy. The meta-analyses also show a significantly greater risk of stroke after thrombectomy,

possibly secondary to entrainment of air during aspiration or antegrade or retrograde embolisation of plaque debris as the clot is disrupted.[47,51]

Negative results[27,55,56] have cast a shadow on adjunctive thrombectomy in primary PCI, which has resulted in class IIa (level of evidence B) recommendations for use of routine thrombus aspiration in European and US guidelines for management of STEMI.[1,2] Indeed, data from the US CathPCI Registry showed that thrombectomy was done in only 18·9% of patients with primary PCI. This finding is a poignant reminder of how interpretation of conflicting trial results can transfer into real-world clinical practice.[57]

The search for an optimum adjunctive reperfusion strategy

Adjunctive reperfusion therapies for primary PCI are rapidly evolving. Non-enteric-coated aspirin (300–325 mg), chewed and swallowed before PCI, is mandatory in the absence of a clear allergy. A loading dose of 300 mg clopidogrel can also be given before primary PCI, although it would be expected to take several hours to have its full effect. Therefore, 600 mg clopidogrel is often given; this dose would be expected to have a more rapid onset of activity, although will still probably take 2 h before optimum platelet inhibition occurs. A loading dose of 60 mg prasugrel has been studied in patients with STEMI,[9,12,58,59] and a loading dose of 180 mg ticagrelor has also been studied in acute coronary syndromes, including STEMI.[10,13,60,61] However, even these more potent oral drugs might not adequately inhibit platelets in patients with STEMI.[14,62] The ATLANTIC trial (NCT01347580)[63] is enrolling up to 1770 patients with STEMI to establish whether prehospital ticagrelor loading can optimise primary-PCI outcomes even further.

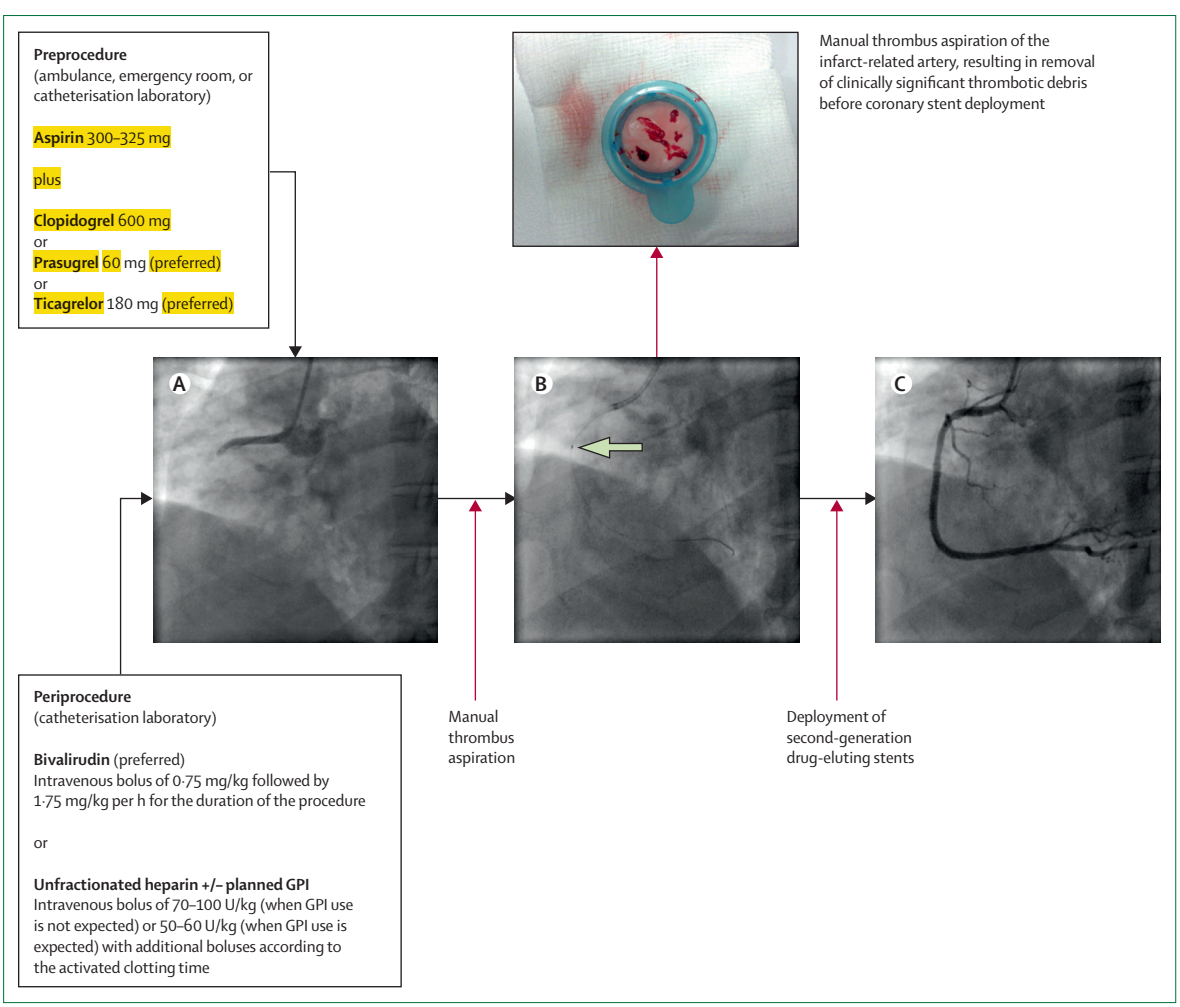

Figure 2: **An optimum strategy for adjunctive reperfusion in primary PCI**
(A) Coronary angiography showing a total occlusion of the proximal right coronary artery leading to an inferior ST-segment elevation myocardial infarction. (B) Before coronary stent deployment, manual thrombus aspiration is done to remove as much thrombus material as possible to prevent distal embolisation. Note the tip of the thrombectomy catheter (green arrow). (C) Restoration of TIMI flow grade 3 after stent deployment. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction. GPI=glycoprotein IIb/IIIa inhibitor.

In the catheterisation laboratory, anticoagulation needs to be given. Intravenous unfractionated heparin is often the default strategy, and in many parts of the world intravenous glycoprotein IIb/IIIa inhibitors are given as well. However, in view of its improved safety and potentially lower mortality, bivalirudin seems to be the preferred anticoagulant in primary PCI, with bailout glycoprotein IIb/IIIa inhibitors reserved only for thrombotic complications.[33,34,64] Patients randomly assigned to bivalirudin in the HORIZONS-AMI trial had increased rates of stent thrombosis within the first 24 h. If more potent oral or intravenous antiplatelet inhibitors had been given with bivalirudin, this excess risk might have been reduced or negated, increasing the risk–benefit ratio of a bivalirudin-based treatment strategy (assuming bleeding was not increased with the more potent antiplatelet therapy). Potentially, the intravenous reversible antiplatelet drug cangrelor could neatly fill a gap in the treatment strategies available at present, providing almost instantaneous P2Y12 inhibition that is also rapidly reversible. The EUROMAX trial (NCT01087723) is underway to investigate whether prehospital administration of bivalirudin will improve 30 day outcomes compared with the present standard of care in patients with STEMI undergoing primary PCI.

Although pharmacotherapy is an essential component of the adjunctive options available for primary PCI, procedural aspects are also important. Before stenting, routine, manual catheter aspiration of thrombus seems to reduce ischaemic complications. Meta-analyses have generally supported this benefit (table), although individual studies have produced conflicting results. Findings from two large multicentre randomised trials of manual thrombus aspiration versus standard primary PCI—the TASTE trial (NCT01093404)[65] and the TOTAL trial (NCT01149044)—should provide an answer to the present conundrum because they are powered for hard clinical endpoints including mortality.

Routine thromboaspiration during STEMI has afforded the opportunity to study thrombus architecture, its relation to total ischaemic time (ie, symptom onset to PCI), and its effect on myocardial reperfusion. In a well designed study, Silvain and colleagues[66] noted that retrieved thrombi can be dichotomised as old fibrin-rich thrombi, corresponding to an ischaemic time of more than 3 h, and fresh platelet-rich thrombi from patients presenting within 1 h of symptom onset. Despite no reported differences in reperfusion, studies such as this and that of Kramer and colleagues[67] might provide improved understanding of the effectiveness of specific therapies for adjunctive reperfusion therapies in accordance with time of administration.

The choice of stent also seems to be important, because it relates to thrombotic risk.[68,69] For example, second-generation drug-eluting stents have been shown by findings of meta-analyses to have lower rates of stent thrombosis than have either first-generation drug-eluting stents or bare-metal stents.[70,71] The choice of stent remains contentious, and there are discrepant data with respect to advantages of bare-metal versus drug-eluting stents, specifically whether some second-generation drug-eluting stents offer improved clinical outcomes compared with first-generation or bare-metal stents. More data are needed to answer this question.[72,73]

Conclusions

Platelets play a fundamental role in the genesis of STEMI; therefore, prompt and potent platelet inhibition, along with parenteral anticoagulant therapy, is essential. Aspirin is the bedrock antiplatelet agent. Evidence from the latest trials support the usefulness of P2Y12 inhibitors that are associated with more potent pharmacodynamic effects than is clopidogrel (ie, prasugrel or ticagrelor). Despite the greater antiplatelet potency of glycoprotein IIb/IIIa inhibitors, their use in STEMI remains largely controversial, as reflected in the guidelines.

We have endeavoured to formulate an optimum, guideline-driven strategy for adjunctive reperfusion in primary PCI on the basis of the present evidence base and ideal circumstances (figure 2). Adoption of such a strategy, however, will depend largely on operator preference, experience, and skills, lesion characteristics, local and national protocols, reimbursement policies, and the logistics of the particular health-care system in which the procedure is done.

Contributors

All authors wrote specific sections of the paper. All authors were involved in conception, design, and critical revision. All authors have seen and approved the final submitted version.

Conflicts of interest

NC has received unrestricted research grants from Haemonetics, St Jude Medical, and Medtronic, and speaker and consultancy fees from Haemonetics, St Jude Medical, Abbott Vascular, Daichii-Sankyo, Boston Scientific, and Medtronic. PAG has consulted for Daiichi Sankyo, Lilly, Pozen, Novartis, Bayer, AstraZeneca, Accumetrics, Nanosphere, Sanofi-Aventis, Boehringher Ingelheim, Merck, Medtronic, Iverson Genetics, CSL, and Haemonetics, and has lectured or served on speakers' bureaus for Lilly, Daiichi Sankyo, Nanosphere, Sanofi-Aventis, Merck, and Iversen Genetics. DLB has served on the advisory boards of Elsevier PracticeUpdate (Cardiology), Medscape Cardiology, and Regado Biosciences; is on the board of directors of Boston VA Research Institute and the Society of Chest Pain Centers; has chaired the American Heart Association Get With The Guidelines steering committee; has received honoraria from the American College of Cardiology (served as Editor, Clinical Trials, CardioSource), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (served on the clinical trial steering committees), Population Health Research Institute (served on a clinical trial steering committee), Slack Publications (served as Chief Medical Editor, *Cardiology Today's Intervention*), WebMD (served on the CME steering committees); has served as Senior Associate Editor, *Journal of Invasive Cardiology*, and on the data monitoring committees of the COMPLETE (Complete versus culprit revascularisation in STEMI) and TOTAL (A randomised trial of routine aspiration thrombectomy with PCI versus PCI alone in patients with STEMI undergoing primary PCI) trials; has received research grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi-Aventis, and The Medicines Company (co-Principal Investigator of the CHAMPION trials); and has done unfunded research for FlowCo, PLx Pharma, and Takeda. AM and SRR declare that they have no conflicts of interest.

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References

1 Steg PG, James SK, Atar D, et al, for the Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33:** 2569–619.

2 O'Gara PT, Kushner FG, Ascheim DD, et al, for the ACCF/AHA Task Force. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; **127:** 529–55.

3 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **332:** 349–60.

4 Sabatine MS, Cannon CP, Gibson CM, et al, for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; **352:** 1179–89.

5 Chen ZM, Jiang LX, Chen YP, et al, for the COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366:** 1607–21.

6 Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **361:** 13–20.

7 Sambu N, Curzen N. Monitoring the effectiveness of antiplatelet therapy: opportunities and limitations. *Br J Clin Pharmacol* 2011; **72:** 683–96.

8 Gurbel PA, Tantry US. Do platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents? Platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents. *Circulation* 2012; **125:** 1276–87.

9 Wiviott SD, Braunwald E, McCabe CH, et al, for the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357:** 2001–15.

10 Wallentin L, Becker RC, Budaj A, et al, for the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361:** 1045–57.

11 Ludman P. BCIS audit returns adult interventional procedures. http://www.bcis.org.uk/resources/D56_BCIS_Audit_2011_data_for_web_11102012.pdf (accessed April 2, 2013).

12 Montalescot G, Wiviott SD, Braunwald E, et al, for the TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009; **373:** 723–31.

13 Steg PG, James S, Harrington RA, et al, for the PLATO Study Group. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation* 2010; **122:** 2131–41.

14 Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2012; **5:** 797–804.

15 Curzen N. Antiplatelet therapy in acute coronary syndromes: beyond aspirin and clopidogrel. *Heart* 2012; **98:** 1617–19.

16 Myat A, Gershlick AH. The contemporary use of antiplatelet therapy in interventional cardiology. In: Redwood S, Curzen N, Thomas M, eds. Oxford textbook of interventional cardiology. Oxford: Oxford University Press, 2010: 419–40.

17 Bhatt DL, Stone GW, Mahaffey KW, et al, for the CHAMPION PHOENIX Investigators. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013; **368:** 1303–13.

18 Stone GW, Grines CL, Cox DA, et al, for the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002; **346:** 957–66.

19 Mehilli J, Kastrati A, Schulz S, et al, for the Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) Study Investigators. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 2009; **119:** 1933–40.

20 Antoniucci D, Rodriguez A, Hempel A, et al. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. *J Am Coll Cardiol* 2003; **42:** 1879–85.

21 Ellis SG, Tendera M, de Belder MA, et al, and the FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008; **358:** 2205–17.

22 Dziewierz A, Siudak Z, Rakowski T, Kleczyński P, Dubiel JS, Dudek D. Early administration of abciximab reduces mortality in female patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the EUROTRANSFER Registry). *J Thromb Thrombolysis* 2012; published online Oct 14. DOI:10.1007/s11239-012-0826-3.

23 van't Hof AWJ, Ten Berg J, Heestermans T, et al, for the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008; **372:** 537–46.

24 De Luca G, Bellandi F, Huber K, et al. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty-abciximab long-term results (EGYPT-ALT) cooperation: individual patient's data meta-analysis. *J Thromb Haemost* 2011; **9:** 2361–70.

25 Gurbel PA, Tantry US. Delivery of glycoprotein IIb/IIIa inhibitor therapy for percutaneous coronary intervention: why not take the intracoronary highway? *Circulation* 2010; **121:** 739–41.

26 Thiele H, Schindler K, Friedenberger J, et al. Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: the randomized Leipzig immediate percutaneous coronary intervention abciximab IV versus IC in ST-elevation myocardial infarction trial. *Circulation* 2008; **118:** 49–57.

27 Stone GW, Maehara A, Witzenbichler B, et al, for the INFUSE-AMI Investigators. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA* 2012; **307:** 1817–26.

28 Thiele H, Wöhrle J, Hambrecht R, et al. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. *Lancet* 2012; **379:** 923–31.

29 Eitel I, Wöhrle J, Suenkel H, et al. Intracoronary compared with intravenous bolus abciximab application during primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: cardiac magnetic resonance substudy of the AIDA STEMI trial. *J Am Coll Cardiol* 2013; **61:** 1447–54.

30 Kubica J, Koziński M, Navarese EP, et al. Updated evidence on intracoronary abciximab in ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized clinical trials. *Cardiol J* 2012; **19:** 230–42.

31 Montalescot G, Zeymer U, Silvain J, et al, for the ATOLL Investigators. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. *Lancet* 2011; **378:** 693–703.

32 Yusuf S, Mehta SR, Chrolavicius S, et al, for the OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006; **295:** 1519–30.

33 Stone GW, Witzenbichler B, Guagliumi G, et al, for the HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; **358:** 2218–30.

34 Stone GW, Witzenbichler B, Guagliumi G, et al, for the HORIZONS-AMI Trial Investigators. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet* 2011; **377:** 2193–204.

35 Dangas GD, Mehran R, Nikolsky E, et al, for the HORIZONS-AMI Trial Investigators. Effect of switching antithrombin agents for primary angioplasty in acute myocardial infarction: the HORIZONS-SWITCH analysis. *J Am Coll Cardiol* 2011; **57:** 2309–16.

36 Koutouzis M, Lagerqvist B, James S, et al. Unfractionated heparin administration in patients treated with bivalirudin during primary percutaneous coronary intervention is associated lower mortality and target lesion thrombosis: a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Heart* 2011; **97:** 1484–88.

37 van't Hof AWJ, Liem A, Suryapranata H, Hoorntje JCA, de Boer M-J, Zijlstra F, for the Zwolle Myocardial Infarction Study Group. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. *Circulation* 1998; **97:** 2302–06.

38 De Luca G, van't Hof AWJ, Ottervanger JP, et al. Unsuccessful reperfusion in patients with ST-segment elevation myocardial infarction treated by primary angioplasty. *Am Heart J* 2005; **150:** 557–62.

39 Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. *J Am Coll Cardiol* 2009; **54:** 281–92.

40 Stone GW, Webb J, Cox DA, et al, for the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) Investigators. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. *JAMA* 2005; **293:** 1063–72.

41 Burzotta F, Testa L, Giannico F, et al. Adjunctive devices in primary or rescue PCI: a meta-analysis of randomized trials. *Int J Cardiol* 2008; **123:** 313–21.

42 Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 2008; **358:** 557–67.

43 Vlaar PJ, Svilaas T, van der Horst IC, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet* 2008; **371:** 1915–20.

44 Ikari Y, Sakurada M, Kozuma K, et al, for the VAMPIRE Investigators. Upfront thrombus aspiration in primary coronary intervention for patients with ST-segment elevation acute myocardial infarction: report of the VAMPIRE (VAcuuM asPIration thrombus REmoval) trial. *JACC Cardiovasc Interv* 2008; **1:** 424–31.

45 Sardella G, Mancone M, Bucciarelli-Ducci C, et al. Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial. *J Am Coll Cardiol* 2009; **53:** 309–15.

46 Sardella G, Mancone M, Canali E, et al. Impact of thrombectomy with EXPort Catheter in Infarct-Related Artery during Primary Percutaneous Coronary Intervention (EXPIRA Trial) on cardiac death. *Am J Cardiol* 2010; **106:** 624–29.

47 Bavry AA, Kumbhani DJ, Bhatt DL. Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction: a comprehensive meta-analysis of randomized trials. *Eur Heart J* 2008; **29:** 2989–3001.

48 De Luca G, Dudek D, Sardella G, Marino P, Chevalier B, Zijlstra F. Adjunctive manual thrombectomy improves myocardial perfusion and mortality in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis of randomized trials. *Eur Heart J* 2008; **29:** 3002–10.

49 Burzotta F, De Vita M, Gu YL, et al. Clinical impact of thrombectomy in acute ST-elevation myocardial infarction: an individual patient-data pooled analysis of 11 trials. *Eur Heart J* 2009; **30:** 2193–203.

50 Mongeon F-P, Bélisle P, Joseph L, Eisenberg MJ, Rinfret S. Adjunctive thrombectomy for acute myocardial infarction: A bayesian meta-analysis. *Circ Cardiovasc Interv* 2010; **3:** 6–16.

51 Tamhane UU, Chetcuti S, Hameed I, Grossman PM, Moscucci M, Gurm HS. Safety and efficacy of thrombectomy in patients undergoing primary percutaneous coronary intervention for acute ST elevation MI: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 2010; **10:** 10.

52 Jang J-S, Kim T-J, Kim J-K, et al. Impact of adjunctive thrombectomy on myocardial perfusion in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction: an updated meta-analysis. *J Am Coll Cardiol* 2012; **60** (suppl)**:** B145 (abstr).

53 Kumbhani DJ, Bavry AA, Desai MY, Bangalore S, Bhatt DL. Role of aspiration and mechanical thrombectomy in patients with acute myocardial infarction undergoing primary angioplasty: an updated meta-analysis of randomized trials. *J Am Coll Cardiol* 2013; published online May 9. DOI:10.1016/j.jacc.2013.04.025.

54 Migliorini A, Stabile A, Rodriguez AE, et al, for the JETSTENT Trial Investigators. Comparison of AngioJet rheolytic thrombectomy before direct infarct artery stenting with direct stenting alone in patients with acute myocardial infarction: the JETSTENT trial. *J Am Coll Cardiol* 2010; **56:** 1298–306.

55 De Carlo M, Aquaro GD, Palmieri C, et al. A prospective randomized trial of thrombectomy versus no thrombectomy in patients with ST-segment elevation myocardial infarction and thrombus-rich lesions: MUSTELA (MUltidevice Thrombectomy in Acute ST-Segment ELevation Acute Myocardial Infarction) trial. *JACC Cardiovasc Interv* 2012; **5:** 1223–30.

56 Onuma Y, Thuesen L, van Geuns R-J, et al, for the TROFI Investigators. Randomized study to assess the effect of thrombus aspiration on flow area in patients with ST-elevation myocardial infarction: an optical frequency domain imaging study—TROFI trial. *Eur Heart J* 2013; **34:** 1050–60.

57 Owan TE, Roe MT, Messenger JC, Dai D, Michaels AD. Contemporary use of adjunctive thrombectomy during primary percutaneous coronary intervention for ST-elevation myocardial infarction in the United States. *Catheter Cardiovasc Interv* 2012; **80:** 1173–80.

58 Bhatt DL. Intensifying platelet inhibition—navigating between Scylla and Charybdis. *N Engl J Med* 2007; **357:** 2078–81.

59 Bhatt DL. Prasugrel in clinical practice. *N Engl J Med* 2009; **361:** 940–42.

60 Cannon CP, Harrington RA, James S, et al, for the PLATelet inhibition and patient Outcomes Investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 2010; **375:** 283–93.

61 Bhatt DL. Antiplatelet therapy: ticagrelor in ACS—what does PLATO teach us? *Nat Rev Cardiol* 2009; **6:** 737–38.

62 Agrawal K, Bhatt DL. Antiplatelet therapy: does prasugrel or ticagrelor suffice in patients with STEMI? *Nat Rev Cardiol* 2013; **10:** 121–22.

63 Montalescot G, Lassen JF, Hamm CW, et al. Ambulance or in-catheterization laboratory administration of ticagrelor for primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: rationale and design of the randomized, double-blind Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) study. *Am Heart J* 2013; **165:** 515–22.

64 Mehran R, Lansky AJ, Witzenbichler B, et al, for the HORIZONS-AMI Trial Investigators. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet* 2009; **374:** 1149–59.

65 Fröbert O, Lagerqvist B, Gudnason T, et al. Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform. Study design and rationale. *Am Heart J* 2010; **160:** 1042–48.

66 Silvain J, Collet J-P, Nagaswami C, et al. Composition of coronary thrombus in acute myocardial infarction. *J Am Coll Cardiol* 2011; **57:** 1359–67.

67 Kramer MCA, van der Wal AC, Koch KT, et al. Presence of older thrombus is an independent predictor of long-term mortality in patients with ST-elevation myocardial infarction treated with thrombus aspiration during primary percutaneous coronary intervention. *Circulation* 2008; **118:** 1810–16.

68 Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med* 2013; **368:** 254–65.

69 Bavry AA, Bhatt DL. Appropriate use of drug-eluting stents: balancing the reduction in restenosis with the concern of late thrombosis. *Lancet* 2008; **371:** 2134–43.

70 Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117762 patient-years of follow-up from randomized trials. *Circulation* 2012; **125:** 2873–91.

71 Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012; **379:** 1393–402.

72 Sabate M, Cequier A, Iñiguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 2012; **380:** 1482–90.

73 Bhatt DL. EXAMINATION of new drug-eluting stents—top of the class! *Lancet* 2012; **380:** 1453–55.

ST-segment Elevation Myocardial Infarction 3

Future treatment strategies in ST-segment elevation myocardial infarction

Stephan Windecker, Jeroen J Bax, Aung Myat, Gregg W Stone, Michael S Marber

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This is the third in a Series of three papers about ST-segment elevation myocardial infarction

Department of Cardiology, Bern University Hospital, Bern, Switzerland (Prof S Windecker MD); **Department of Cardiology, Leiden University Medical Centre, Leiden, Netherlands** (Prof J J Bax MD); **Cardiovascular Division, Rayne Institute, King's College London British Heart Foundation Centre of Research Excellence, St Thomas' Hospital, London, UK** (A Myat MRCP, Prof M S Marber FRCP); **and Center for Interventional Vascular Therapy and the Cardiovascular Research Foundation, New York-Presbyterian Hospital and Columbia University Medical Centre, New York, NY, USA** (Prof G W Stone MD)

Correspondence to: Prof Stephan Windecker, Department of Cardiology, Bern University Hospital, 3010 Bern, Switzerland
stephan.windecker@insel.ch

Over the past five decades, management of acute ST-segment elevation myocardial infarction (STEMI) has evolved substantially. Current treatment encompasses a systematic chain of network activation, antithrombotic drugs, and rapid instigation of mechanical reperfusion, although pharmacoinvasive strategies remain relevant. Secondary prevention with drugs and lifestyle modifications completes the contemporary management package. Despite a tangible improvement in outcomes, STEMI remains a frequent cause of morbidity and mortality, justifying the quest to find new therapeutic avenues. Ways to reduce delays in doing coronary angioplasty after STEMI onset include early recognition of symptoms by patients and prehospital diagnosis by paramedics so that the emergency room can be bypassed in favour of direct admission to the catheterisation laboratory. Mechanical reperfusion can be optimised by improvements to stent design, whereas visualisation of infarct size has been improved by developments in cardiac MRI. Novel treatments to modulate the inflammatory component of atherosclerosis and the vulnerable plaque include use of bioresorbable vascular scaffolds and anti-proliferative drugs. Translational efforts to improve patients' outcomes after STEMI in relation to cardioprotection, cardiac remodelling, and regeneration are also being realised.

Introduction

Management of ST-segment elevation myocardial infarction (STEMI) has evolved substantially over the past five decades. Today, there is a systematic treatment chain in place that encompasses STEMI network activation, administration of potent antithrombotic drugs, and rapid reperfusion, primarily by mechanical means. Secondary prevention thereafter includes use of drugs and lifestyle modifications. Implementation of these measures—proven in past clinical trials—has led to impressive declines in mortality, reinfarction, and heart failure. This systematic approach forms the foundation on which new treatments are tested. As a result, current and future clinical trials now need many thousands of patients to have adequate power to ascertain reductions in these same endpoints. Mortality, reinfarction, and heart failure are fairly rare and binary events. Other manifestations of STEMI are often continuous and can be assessed in every enrolled patient—eg, cardiac MRI measurements of left-ventricular geometry and systolic function, myocardial area at risk, final infarct size, and extent of salvaged myocardium. These outcome measures are now used increasingly in clinical trials as surrogates for heart failure and death. Final infarct size is an especially strong predictor of functional recovery and long-term outcome after infarction and is generally estimated by measurement of markers of myocardial necrosis, such as troponin in serum samples.

Here, we describe innovations for the acute phase of STEMI and summarise their effect on clinical or surrogate outcomes. We highlight novel ideas to reduce patient-related and health-system-related delays after onset of STEMI and ways in which mechanical reperfusion can be augmented. We discuss translational efforts to optimise patients' outcomes after STEMI by reducing myocardial infarction, improving ventricular remodelling, and enhancing myocardial regeneration, and we look at how these processes can be measured by advances in cardiac imaging, to provide surrogate endpoints that promise prognostic benefit. Finally, we present anti-inflammatory and related interventions designed to pacify active atherosclerotic plaques to prevent future cardiovascular events.

Search strategy and selection criteria

We searched the Cochrane Library, Medline, PubMed, and Embase between 1980 and 2013 with combinations of the terms: "STEMI", "myocardial infarction", "drug eluting stent", "bare metal stent", "cardioprotection", "myocardial ischaemia", "cardiac remodeling", "cardiac regeneration", "cardiac miRNA", and "cardiac stem cells". We largely selected publications from the past 10 years, but we did not exclude commonly referenced and highly regarded older publications. We restricted our search to publications in English. We also searched reference lists of articles identified by this search strategy and selected those we judged relevant. Reviews are cited to provide readers with further details and additional references. We included abstracts and reports from meetings when they related directly to previously published work.

Reduction of treatment delays

Reperfusion treatment for STEMI patients is most beneficial if it is given within the first 3 h after symptom onset.[1] During this period, substantial myocardial salvage can be achieved and survival is increased; however, only a minority of patients undergo treatment during this time.[2] Delays can arise between symptom onset and first medical contact (patient-related) and between first

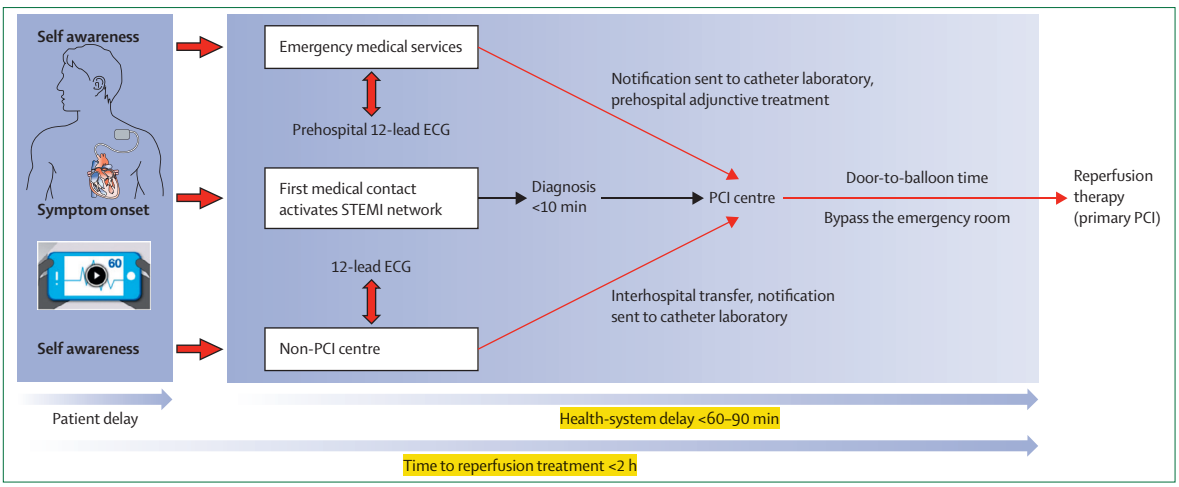

Figure 1: **Patient-related and health-system delays in the STEMI management continuum**
There is a time-critical therapeutic window starting with symptom onset until reperfusion therapy for STEMI. Red arrows show where specific delays could potentially be reduced. Monitoring devices (either implantable or via a smartphone) could help to lessen patient delays. ECG=electrocardiogram. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction.

medical contact and reperfusion treatment (health-system-related; figure 1).[3]

Health-system delays could be reduced if emergency doctors were able to activate centres for percutaneous coronary intervention (PCI), if a single-call system was available to activate PCI facilities, if the catheterisation laboratory was notified while the patient was en route to hospital, if an attending cardiologist was available permanently on site, and if catheterisation laboratory staff were expected within 20 min of notification.[4] Furthermore, the recording of prehospital 12-lead electrocardiograms (ECGs) by trained paramedics accelerates STEMI diagnosis, eliminates the need for in-hospital ECGs, and activates PCI-capable centres early, bypassing the emergency room, which can shorten the door-to-balloon time by 15–60 min.[5] Health-system-related delays correlate with mortality in STEMI patients undergoing primary PCI. Of note, any 15 min reduction in door-to-balloon time from between 150 min to less than 90 min is associated with six fewer deaths per 1000 treated patients.[6] Performance monitoring can identify areas for improvement and lead to increased quality of care.[3]

Delays attributable to the patient account for up to two-thirds of the overall ischaemic time before reperfusion[7] and are most likely to arise in older individuals, women, people with pre-existing diabetes, and patients of low socioeconomic status.[8] Beyond public campaigns, doctors and health-care providers can boost awareness of the typical symptoms of myocardial infarction among people at increased risk—such as those with established coronary artery disease, symptoms of angina, or diabetes. In a sex-specific analysis of the APEX-AMI trial,[9] the presence of baseline Q-waves in STEMI patients undergoing primary PCI was a stronger predictor of 90 day mortality than was time from symptom onset to PCI, particularly in women, showing that Q-waves are an important prognostic marker.

A novel idea to increase patients' self-awareness is to monitor at-risk individuals continuously in the community, enabling them to seek medical attention promptly in case of suspected myocardial infarction. The AngelMed Guardian system (Angel Medical Systems, Shrewsbury, NJ, USA) is an implantable medical device that analyses intracardiac ECGs recorded from a standard right-ventricular lead. In case of acute ECG changes, this early-warning system will alert the patient by vibration and send radiofrequency signals to an external pager, giving additional auditory and visual alerts (figure 1).[10] This device is under investigation in the ALERTS study (ClinicalTrials.gov identifier NCT00781118) in patients at increased risk of acute coronary syndromes—eg, those with diabetes or renal failure or who have a thrombolysis in myocardial infarction (TIMI) risk score of 3 or higher. Of note, findings of the ST DETECT trial (NCT00930969)—in which high-fidelity intracardiac electrogram signals were used to detect ischaemic ST deviation derived from implantable cardioverter defibrillator leads—were disappointing and the trial was interrupted early because of unexpectedly low event rates.

A single-lead ECG can also be recorded with custom-made electrode cases designed for smartphones (figure 1). The signal is detected through contact from the fingers of each hand (or placement on the patient's chest), and then displayed, stored, and transmitted wirelessly to doctors. The AliveCor (AliveCor, San Francisco, CA, USA) mobile heart monitor has received US Food and Drug Administration (FDA) approval and can be prescribed to patients.

Establishing a robust STEMI network is important in improving patients' outcomes after successful resuscitation from out-of-hospital cardiac arrest. The idea of cardiac receiving centres emerged from the proven

success of the trauma centre model, in which an integrated and multidisciplinary-care package exists to manage every facet of patients' needs.[11] As such, centres undertaking primary PCI should aim to coordinate their emergency medicine, cardiology, and critical care services, to safeguard delivery of mild therapeutic hypothermia (cooling to a core temperature of 32–34°C for 12–24 h followed by controlled rewarming) for selected comatose patients, emergent coronary angiography, early haemodynamic stabilisation, rapid response to rearrest, and appropriate electrophysiological assessment before discharge.[12–14] In 2010, the International Liaison Committee on Resuscitation (ILCOR) published treatment recommendations stating that immediate angiography and subsequent PCI should be considered in patients with STEMI (or new left-bundle-branch block) once a return of spontaneous circulation is achieved after out-of-hospital cardiac arrest.[15] European and US guidelines for STEMI treatment reinforce this guidance with recommendations not only for immediate angiography in STEMI patients on post-resuscitation ECG but also for mild therapeutic hypothermia for individuals who are comatose or in deep sedation.[16,17] The validity of emergent angiography in resuscitated patients without ST-segment

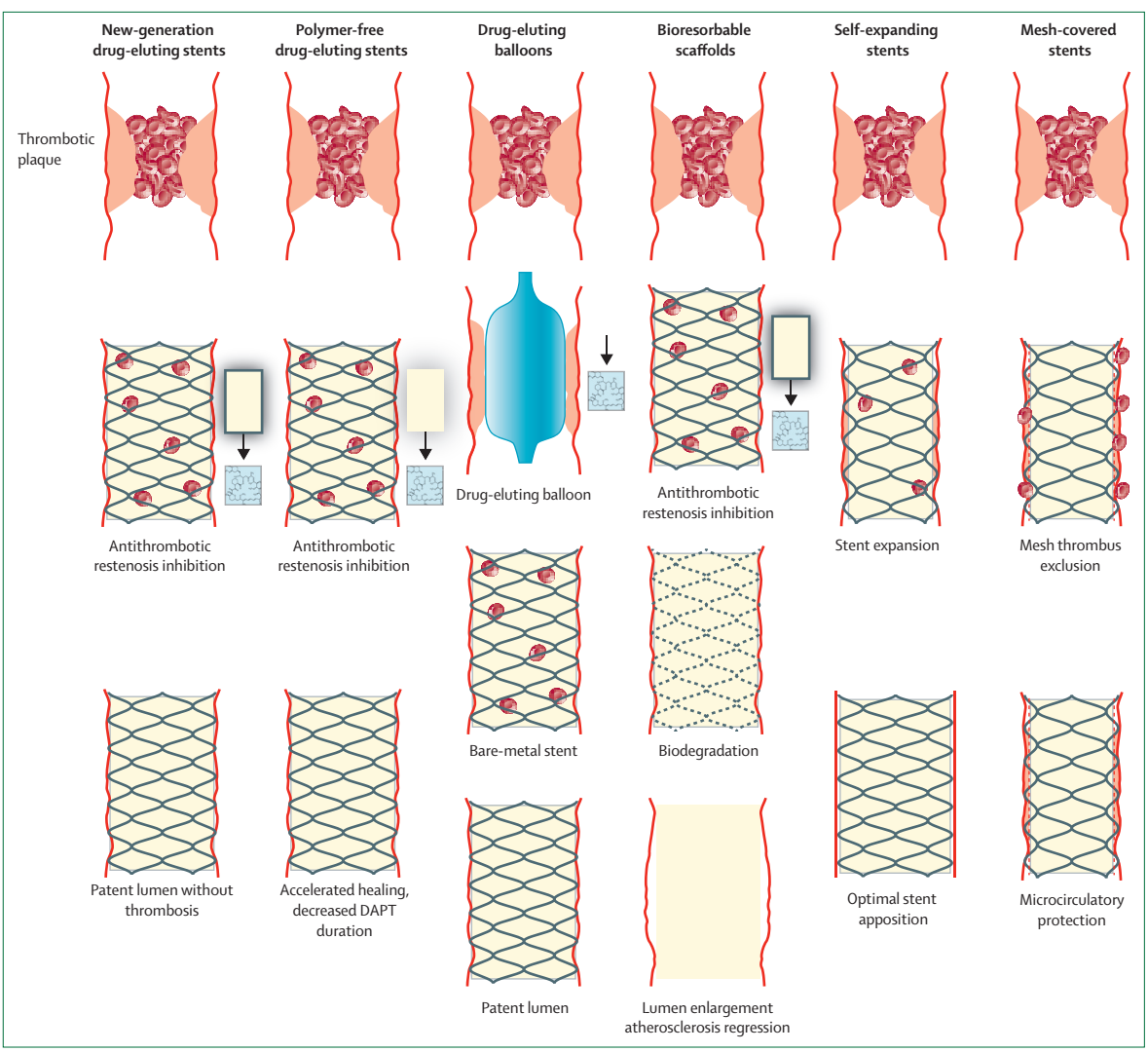

Figure 2: **Novel intracoronary devices and putative mechanisms to improve outcomes of mechanical reperfusion**
New-generation drug-eluting stents release antiproliferative drugs over a period of weeks to months to reduce restenosis. The long-term outcome is lumen patency without thrombotic complications. Polymer-free drug-eluting stents release antiproliferative drugs over a period of days to weeks via various mechanisms of drug binding and release. Their aim is to accelerate arterial healing and maintain lumen patency. Drug-eluting balloons could be applied either before or after implantation of a bare-metal stent, with the aim to suppress neointimal hyperplasia within the stent, to maintain vessel patency. Bioresorbable scaffolds have a biodegradable coating that releases antiproliferative drugs over a period of weeks to months and a metallic or polymer stent backbone that biodegrades over months to years. The scaffolded segment undergoes vessel remodelling to increase long-term vessel patency and adaptive shear stress, resume vasomotion, and induce regression of atherosclerosis. Self-expanding stents aim to overcome stent undersizing caused by vessel constriction and thrombus apposition. Mesh-covered stents target distal embolisation and associated no-reflow by means of thrombus exclusion and microcirculatory protection. DAPT=dual antiplatelet therapy.

elevation on ECG continues to be debated,[18] and results of automated mechanical versus manual chest compressions are conflicting.[19,20] Ongoing clinical trials such as NORCAST (NCT01239420), LUCAT (NCT01521208), and a Finnish assessment of the quality of resuscitation in patients after cardiac arrest (NCT00951704) might shed light in this area.

Mechanical reperfusion

In STEMI patients, mechanical reperfusion of epicardial coronary arteries is the treatment of choice because, compared with fibrinolysis, mechanical reperfusion increases vessel patency, diminishes risk of reinfarction, cuts stroke risk, and boosts survival.[21] Stent implantation has proven effectiveness over balloon angioplasty, as noted in European Society of Cardiology (ESC) guidelines for management of STEMI.[17] However current stent-based reperfusion has shortcomings, such as stent thrombosis, restenosis, stent malapposition, and impaired myocardial perfusion attributable to distal embolisation of plaque and thrombus, all of which could be reduced by future technologies.

Compared with bare-metal stents, early-generation drug-eluting stents have cut the risk of repeat revascularisation without affecting mortality or reinfarction. Efficacy benefits seem to be offset in some patients by an increased risk of very late stent thrombosis secondary to impaired vessel healing[22] and by accelerated neoatherosclerosis.[23] New-generation drug-eluting stents aim to produce a patent lumen within the stented segment, without thrombotic complications (figure 2). They feature cobalt-chromium or platinum-chromium platforms with thinner struts, increased biocompatibility, and reduced thickness of durable or biodegradable polymers, which are used to lessen restenosis. Experimental data suggest that some polymers have antithrombotic properties. New-generation drug-eluting stents release antiproliferative drugs—eg, sirolimus, everolimus, zotarolimus, biolimus A9, novolimus, and myolimus—over a period of weeks to months (table 1).[24]

	Drug (concentration)	Drug release	Platform material	Strut thickness (μm)	Polymer material	Polymer type	Coating location (thickness)
Xience Xpedition (Abbott Vascular)	Everolimus (100 μg/cm²)	80% over 30 days	Cobalt-chromium L605	81	PBMA and PVDF	Durable	Conformal (8 μm)
Promus Element (Boston Scientific)	Everolimus (100 μg/cm²)	80% over 30 days	Platinum-chromium	81	PBMA and PVDF	Durable	Conformal (8 μm)
Endeavour Resolute (Medtronic)	Zotarolimus (160 μg/cm²)	85% over 60 days	Cobalt-chromium	91	PBMA, PHMA, PVP, and PVA	Durable	Conformal (6 μm)
DESyne (Elixir Medical)	Novolimus (5 μg/mm)	80% over 90 days	Cobalt-chromium	80	PBMA	Durable	Conformal (<3 μm)
BioMatrix Flex (Biosensors)	Biolimus A9 (15·6 μg/mm)	45% over 30 days	Stainless steel	112	PDLLA	Degradable (6–9 months)	Abluminal (10 μm)
Nobori (Terumo)	Biolimus A9 (15·6 μg/mm)	45% over 30 days	Stainless steel	112	PDLLA	Degradable (6–9 months)	Abluminal (10 μm)
SYNERGY (Boston Scientific)	Everolimus (6 μg/mm)	50% over 30 days	Platinum-chromium	74	PLGA	Degradable (3–4 months)	Abluminal (4 μm)
DESyne BD (Elixir Medical)	Novolimus (5 μg/mm)	90% over 90 days	Cobalt-chromium	81	PDLLA	Degradable (6–9 months)	<3 μm
Elixir Myolimus (Elixir Medical)	Myolimus (3 μg/mm)	90% over 90 days	Cobalt-chromium	80	PDLLA	Degradable (6–9 months)	<3 μm
Orsiro (Biotronik)	Sirolimus (1·4 μg/mm²)	50% over 30 days	Cobalt-chromium L605	60	PLLA	Degradable (>12 months)	Asymmetrical (7 μm)
MiStent (Micell)	Crystalline sirolimus (2·4 μg/mm²)	100% over 60 days	Cobalt-chromium L605	64	PLGA	Degradable (3–4 months)	NA
Supralimus (Sahajand Medical)	Sirolimus (125 μg/19 mm)	50% over 10 days	Stainless steel	80	PLLA, PLGA, PLC, PVO	Degradable	NA
Excel (JM Medical)	Sirolimus (195–376 μg)	45% over 30 days	Stainless steel	119	PDLLA	Degradable (6–9 months)	15 μm
Firehawk (Microport)	Sirolimus (55 μg/18 mm)	75% over 30 days	Cobalt-chromium with grooves	NA	PDLLA, abluminal groove filled	Degradable (6–9 months)	NA
Combo (Orbus Neich)	Endothelial progenitor cells and sirolimus (5 μg/mm)	95% over 30 days	Stainless steel	100	PDLLA, PLGA	Degradable (3 months)	Abluminal (5 μm)

NA=not applicable. PBMA=polybutyl methacrylate. PHMA=polyhexyl methacrylate. P(D)LLA=poly-(D)L-lactic acid. PLGA=polylactic-*co*-glycolic acid. PVA=polyvinyl alcohol. PVDF=polyvinylidene fluoride. PVO=polyvinyl octal. PVP=polyvinyl pyrrolidone. PLC=polymer liquid crystal.

Table 1: **New-generation drug-eluting stents**

In 1504 STEMI patients in the EXAMINATION trial,[25] new-generation everolimus-eluting stents with a durable fluoropolymer showed a similar risk of death, myocardial infarction, or any revascularisation compared with bare-metal stents (11·9% *vs* 14·2%; p=0·19). Notably, everolimus-eluting stents were associated with a lower risk of target lesion revascularisation (2·1% *vs* 5·0%; p=0·003) and stent thrombosis (0·5% *vs* 1·9%; p=0·019) at 1 year. Similarly, in 1161 STEMI patients, new-generation biolimus A9-eluting stents with a biodegradable polymer lowered the risk of cardiac death, target-vessel reinfarction, and target lesion revascularisation at 1 year, compared with bare-metal stents (4·3% *vs* 8·7%; p=0·004).[26] These observations suggest that, for mechanical reperfusion of STEMI, new-generation drug-eluting stents further extend the benefits of bare-metal stents, a hypothesis to be investigated in future trials.

Drug-eluting bioresorbable vascular scaffolds are intracoronary prostheses that provide temporary scaffolding but, over a period of several months to years, are resorbed fully by biochemical reactions.[27] They have a biodegradable coating from which antiproliferative drugs are released over a period of weeks to months, which might promote vessel remodelling, resulting in late lumen enlargement and reduction of the necrotic core and plaque size, thereby decreasing the risk of late adverse events (figure 2). These devices promise benefit beyond current metallic stent platforms by avoiding permanent caging of the stented segment with the potential to increase long-term vessel patency, vasomotion, adaptive shear stress, sealing of plaques, and access to side branches.[28] In STEMI patients with ruptured plaques, bioresorbable vascular scaffolds could overcome the issue of impaired arterial healing, thereby eliminating concerns over incomplete strut endothelialisation, neoatherosclerosis, stent thrombosis, and the collateral effect of prolonged dual antiplatelet treatment. They might also form a new cap on rupture-prone plaques, thereby stabilising a vulnerable plaque.[29] Several bioresorbable vascular scaffolds have undergone clinical investigation (table 2), with most clinical experience gathered from poly-L-lactic acid-based everolimus-eluting vascular scaffolds in low-risk patients without STEMI.[30,31]

Several other platforms are under investigation for mechanical reperfusion in the setting of STEMI (figure 2). Self-expanding stents aim to overcome undersizing of balloon-expandable stents caused by vessel constriction and thrombus apposition. Mesh-covered stents are intended to mitigate distal embolisation and associated no-reflow by thrombus exclusion and microcirculatory protection. Polymer-free stents are implanted to avoid polymer-related late adverse events and to increase arterial healing while maintaining lumen patency. Finally, drug-eluting balloons could be inserted—either before or after implantation of a bare-metal stent—into ruptured, thrombotic plaques of patients with STEMI to suppress neointimal hyperplasia and to maintain vessel patency. These devices transfer highly lipophilic anti-proliferative agents passively from a carrier on the balloon surface into the coronary artery intima.

Findings from intracoronary imaging and pathological studies show that patients who present with acute coronary syndromes have many plaques vulnerable to

	Scaffold material	Scaffold design	Scaffold resorption time (months)	Strut thickness (μm)	Drug (concentration)	Drug release	Coating material for drug release	Polymer type for drug release	Deployment
Absorb BVS 1·1 (Abbott Vascular)	PLLA	In-phase zig-zag hoops linked by bridges	24	156	Everolimus (100 μg/cm²)	80% over 30 days	PDLLA	Degradable (6–9 months)	Balloon expansion
DESOLVE (Elixir Medical)	PLLA	NA	12	150	Novolimus	80% over 30 days	PDLLA	NA	Balloon expansion
REZOLVE sirolimus-eluting scaffold (REVA Medical)	Tyrosine poly (desamino-tyrosyltyrosine ethyl ester) carbonate	Helical stent with locking mechanism	12–18	114–228	Sirolimus (80 μg)	NA	None	NA	Slide and lock mechanism
IDEAL (Xenogenics)	Poly-anhydride ester-based on salicylic acid and adipic acid anhydride	Tube with laser-cut voids	9–12	175	Sirolimus (8·3 μg/mm)	>90% over 30 days	Salicylate plus different linker	NA	Balloon expansion
ART 18AZ (Arterial Remodelling Technology)	PDLLA	NA	18	170	None	NA	None	NA	Balloon expansion
DREAMS-1 (Biotronik)	Magnesium alloy	Sinusoidal out-of-phase hoop linked by straight bridges	9–12	120 (rectangular)	Paclitaxel (0·07 μg/mm²)		PLGA (thickness, 1 μm)	Degradable (3–4 months)	Balloon expansion

NA=not applicable. P(D)LLA=poly-(D)L-lactic acid. PLGA=polylactic-*co*-glycolic acid.

Table 2: **Bioresorbable scaffolds with ongoing or completed clinical trials**

rupture, beyond the culprit lesion.[32–34] Moreover, affected individuals are at risk of recurrence, with events in more than half of patients related to plaque progression, rupture, or erosion of previously untreated lesions.[35] In addition to autopsy reports, cross-sectional imaging of coronary arteries, using intravascular ultrasound and optical coherence tomography, has characterised lesions at risk for recurrent events as thin-cap fibroatheromas. Features include lipid-rich cores and a cap thickness of less than 65 μm, with a large plaque burden accommodated by unusual outward remodelling of the vessel, a small lumen area, or a combination of these.[35,36]

Mechanisms leading to thrombotic complications of atherosclerosis are related to inflammation mediated by activated T cells and macrophages in the central lipid core and vessel intima and media.[37] Release of interferon γ prevents collagen synthesis, a compound that is important to maintain the integrity of the fibrous cap separating blood flow from the thrombogenic lipid core. Moreover, macrophages produce metalloproteinases—interstitial collagenases that accelerate the breakdown of collagen. The above processes form the conceptual framework linking inflammation to superficial weakening of plaques by progressive thinning and eventually rupture. Findings of genome-wide association studies confirm that the genetic basis of coronary artery disease is related to genes linked to lipid metabolism and inflammation. Using intravascular ultrasound, low shear stress has been recognised as an independent predictor of plaque growth and thinning of the fibrous cap.[38]

Therapeutic strategies to prevent complications of atherosclerosis aim to reduce systemic and local inflammation and to stabilise the fibrous cap surface. Beyond their lipid-lowering effect, it seems that statins decrease inflammation, increase collagen of the fibrous cap, and shrink plaque size, effectively reducing the risk of ischaemic events.[39–42] Additional systemic treatments include inhibitors of lipoprotein-associated phospholipase and anti-inflammatory drugs such as methotrexate, ciclosporin, and inhibitors of mammalian target of rapamycin (mTOR). Stent-based delivery of everolimus promotes macrophage autophagy in rabbit atherosclerotic plaques.[43] As such, interest is growing to promote stabilisation of vulnerable plaques within bioresorbable vascular scaffolds that release mTOR inhibitors and, on complete resorption, induce positive vessel remodelling with plaque regression, restoration of vasomotion, and fibrous cap thickening.[29]

Cardioprotection

Cardioprotection is a common term that includes drugs and devices used in the outpatient setting to reduce the risk of future cardiac events. Here, we define cardioprotection as interventions that are initiated in the first minutes to hours after onset of symptoms to reduce at least one of the manifestations of STEMI—ST-elevation, arrhythmia, contractile dysfunction, microvascular dysfunction, scar volume, and troponin release. Furthermore, since these events are typically codependent, consistency of effect should be seen. Ultimately, manifestations of STEMI lie on pathophysiological pathways that lead to the clinically relevant endpoints of heart failure and death. However, because these events are relatively rare, use of surrogate endpoints in clinical trials is common.

Despite intensive basic and clinical research efforts, only reperfusion is consistently cardioprotective. Unless there is substantial collateral flow, an area of myocardium is rendered ischaemic after coronary artery occlusion (figure 3). Early ischaemia manifests as a wall motion abnormality or oedema, which can be seen on MRI and SPECT. If the occlusion persists, infarction starts in the endocardial myocardium and progresses transmurally. Eventually, without reperfusion, ischaemic myocardium transforms irreversibly to infarction. Basic research almost four decades ago showed the time dependence of STEMI and laid the foundation for successful clinical trials of reperfusion.[44,45] New cardioprotective strategies are needed to add benefit to existing systems and devices designed to achieve rapid and complete reperfusion.

Cardioprotective interventions aim to reduce the amount of necrosis after myocardial ischaemia and reperfusion. However, in many animal models, putative cardioprotective treatment is delivered before coronary artery occlusion and continues throughout ischaemia and reperfusion. Thus, it is often unclear if benefit results from protection during ischaemia, reperfusion, or a combination of the two. Such discrimination is crucial in the clinical setting because reperfusion is achieved rapidly after first contact with the patient and little opportunity

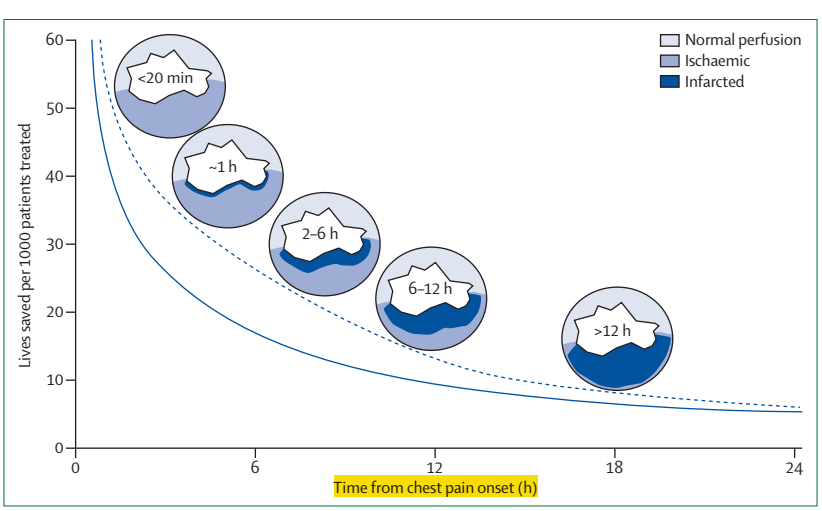

Figure 3: **Relation between time to reperfusion and benefit accrued**
Heart cross-sections show the left ventricle at increasing durations of epicardial coronary artery occlusion. This idea of progressive necrosis is modelled on experimental data.[44] The benefit of reperfusion in terms of lives saved at 35 days (solid line) is time-dependent and modelled on benefit seen in patients randomised to thrombolysis versus placebo.[45] In the first hour after symptom onset, reperfusion significantly reduces mortality. However, benefit slows rapidly, possibly because of progressive infarction shown in the heart cross-sections. The relation between an effective cardioprotective intervention and reperfusion is depicted by the dotted line.

exists for anti-ischaemic treatment. Although effective interventions to limit necrosis are available (eg, cardioplegia during cardiac surgery), achieving similarly consistent protection at reperfusion is proving more difficult, particularly in the setting of phase 3 clinical trials. Up to now, no cardioprotective interventions have been included in guidelines or clinical practice;[46,47] however, several are currently under investigation (table 3).

See Online for appendix

Interruption of reperfusion with short periods of ischaemia is a cardioprotective intervention known as

	Intervention	Target	Patients (n)	Outcome
Ion flux or metabolism				
EMIP-FR	Trimetazidine	Glucose metabolism	19 725	No difference in mortality at 35 days
MAGIC	Magnesium	Membrane stabilisation	6213	No difference in mortality at 30 days
CHILL-MI	Cooling to 35°C	Metabolism	120	Percentage reduction in myocardial infarct size (as % of myocardium at risk), by MRI at 4 days
CREATE-ECLA	Glucose, insulin, potassium	Metabolism	20 201	No difference in mortality at 30 days
ESCAMI	Eniporide	Sodium accumulation	430 (stage 1); 959 (stage 2)	No difference in myocardial infarct size, by enzyme
Lonborg et al	Exenatide by intravenous infusion for 6 h	GLP1 receptor	107	Increase in myocardial salvage index at 90 days, by MRI
J-WIND-KTP	Nicorandil bolus then 72 h infusion	ATP-sensitive potassium channel	545	No difference in myocardial infarct size, by enzyme or 6 month left-ventricular ejection fraction
Inflammation				
APEX-MI	Pexelizumab bolus then 24 h infusion	Complement	5745	No difference in mortality at 30 days
FIRE	FX06 boluses	Inflammation	232	No difference in myocardial infarct size, by MRI at 5 days or 4 months
Kinase signalling pathways				
PROTECTION-AMI	Delcasertib infusion for 24 h	Protein kinase C	1083	No difference in myocardial infarct size
J-WIND-ANP	Carperitide 72 h infusion	Natriuretic peptide receptor	569	15% reduction in myocardial infarct size, by enzyme and 2·0% absolute increase in left-ventricular ejection fraction
HEBE-III	Epoetin alfa	Protective kinases	529	No difference in left-ventricular ejection fraction at 6 weeks or myocardial infarct size, by enzyme or troponin T
REVIVAL-3	Epoetin beta for 48 h	Protective kinases	138	No difference in left-ventricular ejection fraction or myocardial infarct size at 6 months, by MRI
REVEAL	Intravenous epoetin beta for 48 h	Protective kinases	138	No difference in myocardial infarct size at 6 days or 3 months, by MRI
Hahn et al	Oral atorvastatin before and after primary PCI	Lipids and protective kinases	173	No difference in myocardial infarct size at 5–14 days, by SPECT
Preconditioning, post conditioning, remote conditioning				
Lonborg et al	Four 30 s intracoronary balloon occlusions	Post conditioning	118	No difference in troponin T or left-ventricular ejection fraction; 19% reduction in myocardial infarct size and 31% increase in salvage index, by MRI
POST	Four 60 s intracoronary balloon occlusions	Post conditioning	700	No difference in quality of reperfusion, by ST resolution or TIMI flow
Botker et al	Four 5 min upper-limb ischaemia	Remote conditioning	142	No difference in myocardial infarct size, by SPECT and troponin; increase in myocardial salvage index at 30 days, by MRI
Hyperoxia				
AMIHOT I	Intracoronary hyperbaric hyperoxaemic reperfusion for 90 min	..	269	No difference in myocardial infarct size at 14 days, by SPECT
AMIHOT II	Intracoronary hyperbaric hyperoxaemic reperfusion for 90 min	..	281	Reduction in infarct size by SPECT (with prespecified Bayesian pooling from AMIHOT I)
Notable forthcoming or ongoing studies				
CIRCUS	Ciclosporin	..	972	..
CYCLE	Ciclosporin	..	444	..
EMBRACE	Bendavia	..	200	..
MitoCare	TRO40303	..	180	..
DETO$_2$X-AMI	Oxygen	..	6600	..
PRESERVATION 1	IK-5001	..	306	..
MVO	Vasodilators	..	297	..
GIPS-III	Metformin	..	380	..
NOMI	Nitric oxide	..	230	..

References or NCT identifiers of trials are provided in the appendix (pp 1–2). PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. TIMI=thrombolysis in myocardial infarction.

Table 3: **Cardioprotection trials of more than 100 STEMI patients**

post conditioning. Reperfusion can be accompanied by striking changes in oxygen tension, pH, and intracellular distribution of Ca^{2+} and Na^{+}. Thus, by gradation of reperfusion, necrosis might be diminished. Post conditioning periods of intermittent ischaemia can also be applied to tissue remote from the heart; findings of intermittent upper-limb ischaemia, achieved with a simple blood pressure cuff, are encouraging.[48] The intracellular process targeted largely by post conditioning is thought to be reduced opening of a non-specific mitochondrial channel known as the permeability pore. The proteins that form this pore are not known completely, but permeability can be reduced by ciclosporin, which is also cardioprotective when administered at reperfusion.[49] Ciclosporin and other drugs that alter mitochondrial pore permeability are under investigation in clinical trials (table 3).

Pressure-controlled intermittent coronary sinus occlusion is a technique that perturbs coronary flow at reperfusion by intermittent occlusion of coronary venous drainage.[50] An added benefit could be preferential redistribution of microcirculatory flow to vulnerable myocardium surrounding the core area of necrosis. This intervention uses a balloon-tipped catheter that is advanced into the coronary sinus via the venous circulation, to intermittently increase coronary venous pressure.

Achieving patency of the epicardial coronary artery does not guarantee myocardial perfusion. Plaque material and thrombi can block the distal vasculature, and endothelial dysfunction, leucocyte plugs, and external compression resulting from interstitial oedema and cardiac myocyte contraction can compromise the microcirculation. These processes cause inadequate perfusion of the myocardium despite coronary artery patency. Whether such low reflow is a cause or a result of myocardial infarction is debatable, but it can be seen on MRI (figure 4).[51] Similarly, myocardial haemorrhage caused by complete disruption of the endothelial barrier can be visualised with T2 star-weighted cardiac MRI.[51] These images assist measurement of myocardial scar formation by T1-weighted (late enhancement) imaging[52] and help assess the effect of scarring on left-ventricular dimensions and contraction by cine MRI[52] and echocardiography. Advanced imaging techniques are used increasingly as surrogate endpoints in clinical trials of novel treatments because they provide additional mechanistic information (figure 5).[53]

Cardiac remodelling and regeneration

Reparative versus reactive fibrosis

Adverse left-ventricular remodelling of the infarct zone and circumferential residual viable myocardium leads to thinning and dilatation of the affected myocardial wall. Subsequent hypertrophic transformation of viable myocardium—due to increased volume load coupled with a proinflammatory cascade—leads to interstitial fibrosis and further dilatation of infarcted tissue.[54,55] The balance between reparative and reactive fibrosis needs to be addressed. Reparative fibrosis maintains overall structural integrity of the infarcted myocardium and prevents left-ventricular rupture. Reactive fibrosis takes place away from the infarct zone and is characterised by increased myocardial stiffness and arrhythmogenicity, evolving diastolic dysfunction, and heart failure.[55] Reactive fibrosis is especially rife in ischaemic cardiomyopathy and novel treatments are needed.

In the EPHESUS trial,[56] the benefit of mineralocorticoid receptor blockade was noted 3–14 days after onset of acute myocardial infarction complicated by left-ventricular systolic dysfunction. Findings from experimental models of either cardiomyocyte-specific mineralocorticoid receptor deficiency or use of a mineralocorticoid receptor antagonist suggest substantial improvements in wound healing post infarct and virtual attenuation of adverse left-ventricular remodelling.[57,58] Can immediate or early mineralocorticoid receptor blockade after acute myocardial infarction blunt adverse left-ventricular remodelling? The ALBATROSS trial (NCT01059136) aims to test superiority of mineralocorticoid receptor blockade with spironolactone initiated within 72 h of onset of acute myocardial infarction, compared with standard treatment alone. Similarly, the REMINDER trial (NCT01176968), is studying the effect of eplerenone administered within 24 h of acute myocardial infarction in patients without heart failure.

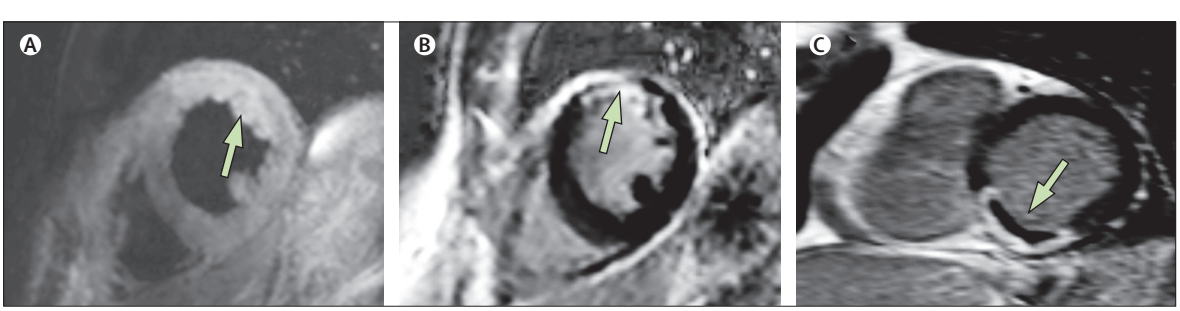

Figure 4: **Cardiac MRI in acute myocardial infarction**
(A) T2-weighted image of oedema (arrow) after acute anterior myocardial infarction in a 47-year-old man. (B) In the same patient, T1-weighted image (late enhancement) showing the final infarct (arrow). (C) T1-weighted image in a 62-year-old man with inferior infarction, showing infarcted tissue (white) with no reflow in the centre (black; arrow).

Targeted chronic pacing around the infarct, to attenuate left-ventricular remodelling, has also attracted attention. In the MENDMI study,[59] patients who had anterior myocardial infarction with an ejection fraction of 35% or less and wall-motion abnormalities in more than five of 16 myocardial segments were randomised 2–14 days after the event to either control (implantable cardioverter defibrillator only) or biventricular pacing with peri-infarct left-ventricular lead placement (cardiac resynchronisation). The primary endpoint was change in left-ventricular end-diastolic volume, which did not differ between groups at 12 months; neither did hospitalisations or mortality. However, a sustained reduction in wall motion abnormalities was noted in the pacing group; overall, pre-excitation pacing was judged safe. Researchers in the PRomPT study (NCT01213251) are randomising patients recruited within 10 days of acute myocardial infarction (all locations) to either single-site pacing (cardiac resynchronisation via left-ventricular lead), dual-site pacing (cardiac resynchronisation via left-ventricular and right-ventricular leads), or no intervention at all. By contrast with MENDMI, PRomPT will include larger infarcts, with no ejection fraction limitation, and longer follow-up of 18 months.

Myocardial regeneration

On average the left ventricle consists of about 4 billion cardiomyocytes.[60] After acute myocardial infarction, late heart failure develops when roughly 25% of the left ventricle dies and cardiogenic shock ensues when 40% of myocardium is affected.[60] For functional recovery to be achieved after acute myocardial infarction, we need to replenish these lost cells on a purely numerical basis, maintain electrical synchronicity between new and old cells, and ensure mechanical integration for contractility. New cardiomyocytes can be sourced endogenously from within the heart or exogenously via delivery of autologous or allogeneic stem cells.[61–65]

Cardiac stem cells in the adult heart can replace myocytes lost naturally.[66] The mechanics of this auto-regeneration have fuelled research into the molecular switch that could start the regeneration process by promoting cell-cycle re-entry.

MicroRNAs (miRNAs) are a class of short (18–25 nucleotides) non-coding regulators of post-transcriptional output that could be the triggers for cardiac regeneration (figure 6). These molecules bind directly to mRNA and could inhibit downstream translation into specific cellular proteins (ie, miRNA-guided RNA silencing).[67] Several miRNAs have been implicated in ischaemia-reperfusion injury, angiogenesis, and myocardial remodelling.[68–71] Two miRNAs have been isolated that could induce cell-cycle re-entry of adult murine cardiomyocytes ex vivo.[72,73]

The rate of myocardial auto-regeneration, and whether it can be sufficient to restore the number of cells lost after a large anterior myocardial infarction is unclear. Formation of scar tissue after acute myocardial infarction, rather than regeneration of healthy myocardium, argues against adequate functional growth reserve. However, similar scar formation is associated with infarction of liver, bone marrow (eg, sickle-cell crises), kidney, and intestine, despite these organs being highly regenerative.[61,62] Reports are conflicting regarding the prevalence of myocyte mitosis and about whether quiescent cells at the border of, and distant from, the infarct can be coerced into bolstering ventricular mass and performance.[66,74–76] Methods to quantify myocyte division need testing, yet this idea provides a glimpse to the future of STEMI management.[63]

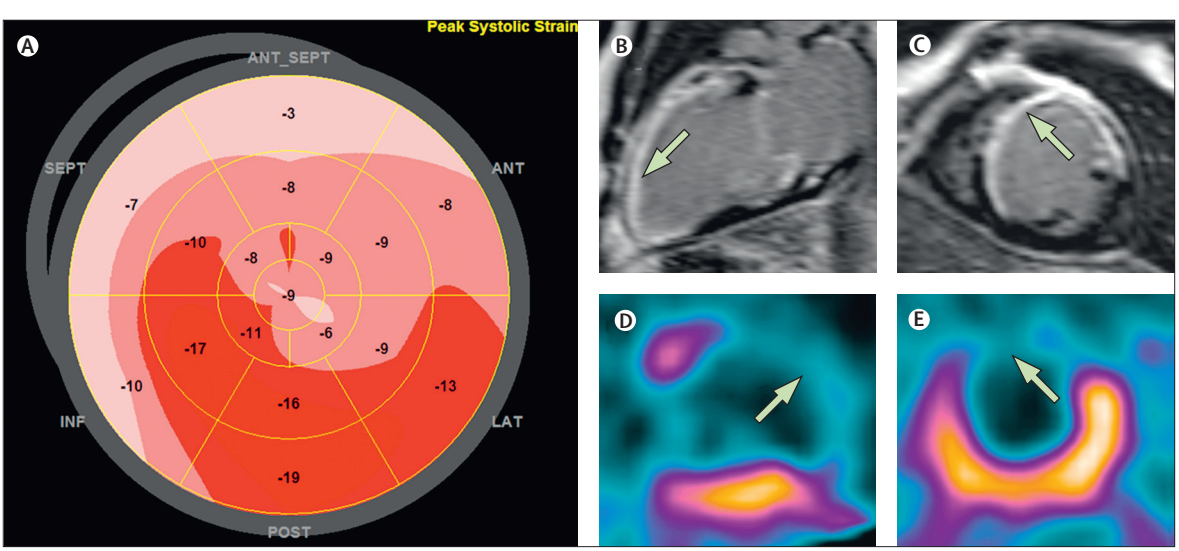

Figure 5: **Assessment of final infarct size in a patient with previous anteroseptal myocardial infarction**
(A) Echocardiography strain map; pink area with strain values around –8 represent infarcted area (normal strain values –16 to –20). (B, C) T1-weighted cardiac MRI and late enhancement showing the infarcted area (white; arrows). (D, E) SPECT perfusion imaging shows absence of tracer uptake (technetium-99m tetrofosmin) in the infarcted area (arrows).

Cardiac stem cells

Autologous mononuclear bone marrow-derived stem cells were used for management of ischaemic heart failure after acute myocardial infarction more than a decade ago.[77,78] Since then, despite only modest gains in left-ventricular ejection fraction and other functional measures of left-ventricular remodelling,[64,79] exogenous delivery of stem and progenitor cells from various sources[80–86] to injured myocardium for cardiac repair has expanded. Research is needed into the best route of cell delivery (intracoronary *vs* endocardial intramyocardial *vs* epicardial intramyocardial), standardisation of cell-preparation techniques, and the amount of cells needed to propagate optimum regeneration (figure 7).

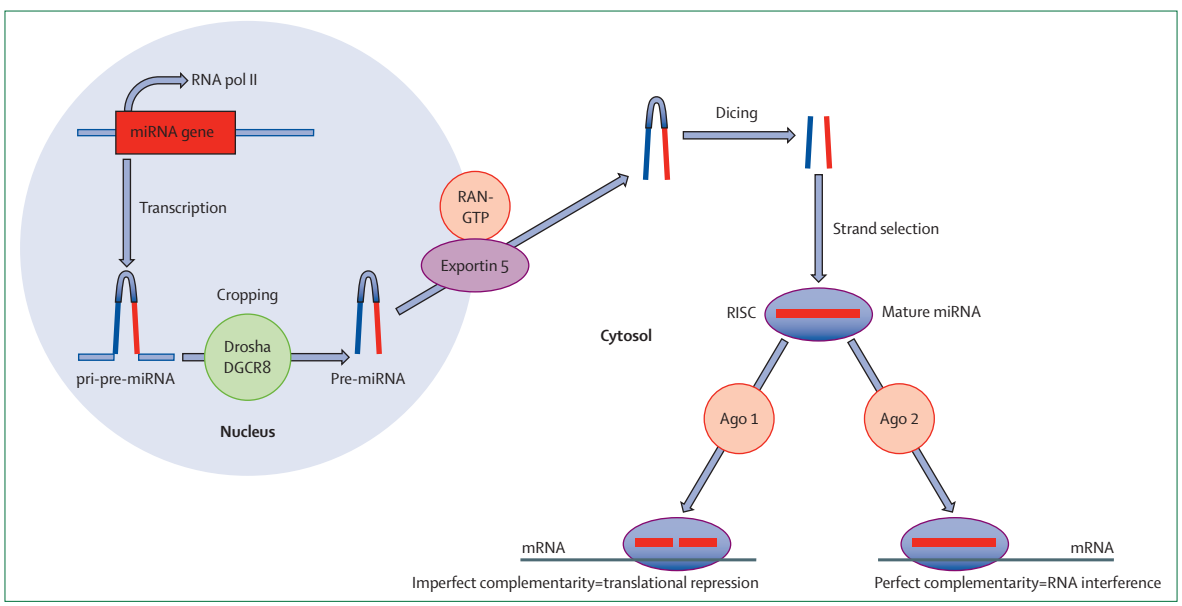

Figure 6: **microRNA biogenesis pathway**
Transcription of the microRNA (miRNA) gene is mediated by RNA polymerase II (RNA pol II), which generates the primary transcript (pri-pre-miRNA). The microprocessor complex (Drosha DGCR8) crops the primary transcript to a pre-miRNA of about 70 nucleotides. A signature motif on the pre-miRNA is recognised by exportin 5 (and its cofactor Ran-GTP), subsequently forming a transport complex that extrudes the pre-miRNA from the nucleus. The miRNA is further processed to a duplex. Cleavage occurs, with one strand becoming the mature miRNA that is incorporated into the RNA-induced silencing complex (RISC; Ago 1 and Ago 2 are catalytic components of RISC). miRNA and its complementary mRNA target interact, resulting in either translational repression, RNA interference or degradation, or adenylation, depending on the degree of matching achieved between base pairs. The remaining miRNA strand can degrade, although it has innate potential to function.

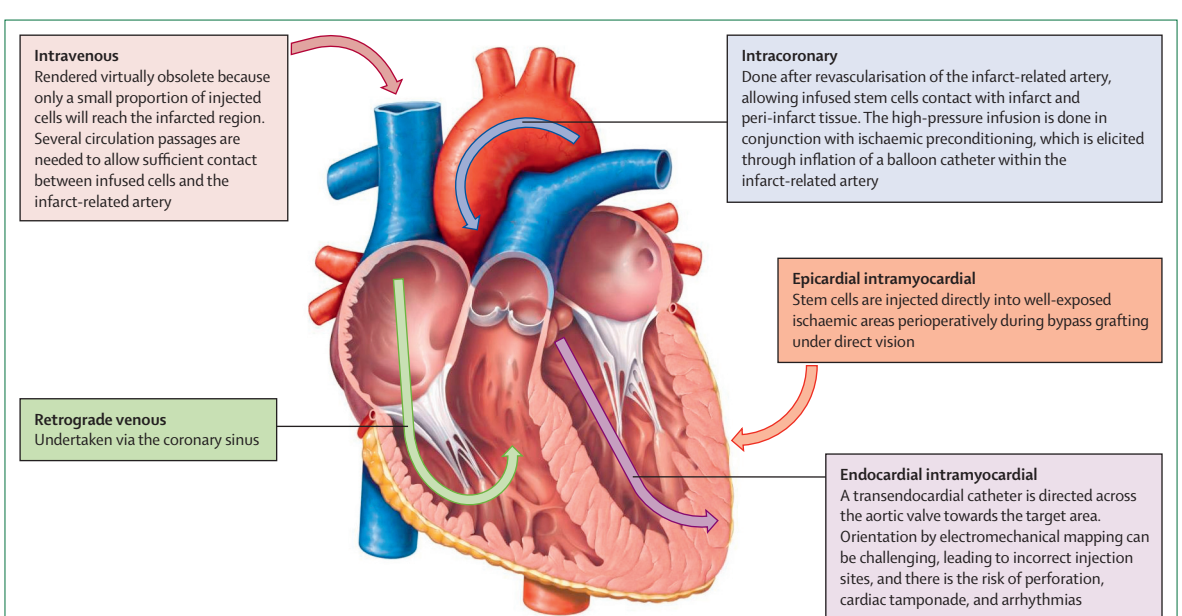

Figure 7: **Stem cell delivery to the heart**

	Stem-cell type	Route of application	Time of application	Study type	Primary outcome measure(s)	Estimated enrolment	Estimated study completion date
COAT (NCT01625949)	Autologous mononuclear bone marrow cells	Intracoronary via infarct-related artery	During percutaneous coronary intervention of totally occluded infarct-related artery 24 h after and 6 months before acute myocardial infarction	Randomised, open label	Changes in left-ventricular function and myocardial viability at 3 months	40	June, 2014
ESTIMATION (NCT01394432)	Autologous mesenchymal stem cells	NA	7–10 days after percutaneous coronary intervention for thrombolysed acute myocardial infarction	Randomised, double-blind	Reduction in left-ventricular systolic volume at 12 months	50	November, 2013
AMICI (NCT01781390)	Mesenchymal precursor cells	Intracoronary via infarct-related artery	During percutaneous coronary intervention of infarct-related artery 2–12 h from symptom onset	Randomised, double-blind	Frequency of MACCE at 24 months	225	June, 2016
R^2ACE (NCT01414452)	Endothelial progenitor cells	NA	Within 90 min of primary percutaneous coronary intervention	Observational, cohort	Extent of ST-segment resolution at 90 min	250	December, 2013
PreSERVE-AMI (NCT01495364)	Autologous bone marrow-derived CD34+ selected cells	Intracoronary	Within 3 days of admission with STEMI	Randomised, double-blind	Safety and effect of stem-cell therapy on myocardial perfusion at 6 months	160	June, 2016
SELECT-AMI (NCT00529932)	Autologous bone marrow-derived progenitor cells	Intracoronary	During primary percutaneous coronary intervention for acute STEMI 2–24 h after onset of chest pain	Randomised, double-blind	Atherosclerotic burden around stent at 6 months; thickening of non-viable left-ventricular wall segments at 6 and 24 months	60	December, 2013
ADVANCE (NCT01216995)	Adipose-derived regenerative cells	Intracoronary	NA	Randomised, double-blind	Reduction in infarct size at 6 months	216	September, 2017

MACCE=major adverse cardiac and cerebrovascular event. STEMI=ST-segment elevation myocardial infarction. NA=not available.

Table 4: **Trials of stem cells in acute myocardial infarction that are actively recruiting patients**

Embryonic stem cells have the greatest potential for differentiation into cardiomyocytes, vascular endothelial cells, and smooth muscle cells. However, the risks of teratoma formation and immunogenicity, and lingering ethical concerns, have hampered use of these cells in clinical trials.[55] Induced pluripotent stem cells—differentiated from autologous adult somatic cells such as dermal fibroblasts—can be reprogrammed into a pluripotent state by forced transduction of up to four defined transcription factors.[87] Induced pluripotent stem cells can then undergo directed differentiation into the three cellular components of the heart, without the ethical issues linked with embryonic stem cells.[62] Viral delivery of reprogramming factors, which heightened the risk of neoplastic transformation, has been replaced by non-viral alternatives; thus, induced pluripotent stem cells could represent the future of cardiac regeneration. Synergistic novel techniques such as cell priming, tissue engineering, and bionanotechnology are in development.[55,62]

Preliminary results have shown efficacy (augmentation of left-ventricular ejection fraction and reduction of infarct area) and safety of autologous intracoronary infusion of cardiac stem cells applied a mean 113 days after coronary-artery bypass grafting for ischaemic cardiomyopathy.[88] Similarly, an infusion of autologous cardiosphere-derived cells via the infarct-related artery after acute myocardial infarction was judged safe and effective, with recorded reductions in scar mass and increased measures of left-ventricular contractility.[89] Several clinical trials of stem cell-instigated cardiac regeneration after acute myocardial infarction are in progress (table 4).

Conclusions

Treatments for STEMI continue to evolve in several areas, not least in the development of cardioprotective drugs. However, the most rapid changes have been seen in hardware used to achieve and maintain mechanical reperfusion and in organisational structures to promote patients' awareness of symptoms and to facilitate their transfer to hospital. Although cell-based treatments remain an active area of preclinical and early clinical research, they will not affect routine care in the near future.

Contributors

All authors contributed ideas to the Review and helped with design, writing, and revision of the report. All authors have seen and approved the final version of the submitted manuscript.

Conflicts of interest

SW has received research contracts to his institution from Abbott, Boston Scientific, Biosensors, Biotronik, Cordis, Medtronic, and St Jude. GWS has received consulting fees from Boston Scientific, AstraZeneca, Eli Lilly, Daiichi-Sankyo, Atrium, Janssen, Miracor, TherOx, VeloMedix, and InspireMD. JJB declares receiving research grants to the department from GE Healthcare, Lantheus, Edwards Lifescience, Servier, Biotronik, Medtronic, and Boston Scientific. AM and MSM declare that they have no conflicts of interest.

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References

1 Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? *JAMA* 2005; **293:** 979–86.

2 Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM, and the NRMI Investigators. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. *Circulation* 2005; **111:** 761–67.

3 Huber K, Goldstein P, Danchin N, et al. Enhancing the efficacy of delivering reperfusion therapy: a European and North American experience with ST-segment elevation myocardial infarction networks. *Am Heart J* 2013; **165:** 123–32.

4 Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med* 2006; **355:** 2308–20.

5 Ting HH, Krumholz HM, Bradley EH, et al, and the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, and the American Heart Association Council on Cardiovascular Nursing, and the American Heart Association Council on Clinical Cardiology. Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. *Circulation* 2008; **118:** 1066–79.

6 Nallamothu BK, Bradley EH, Krumholz HM. Time to treatment in primary percutaneous coronary intervention. *N Engl J Med* 2007; **357:** 1631–38.

7 Eagle KA, Nallamothu BK, Mehta RH, et al, and the Global Registry of Acute Coronary Events (GRACE) Investigators. Trends in acute reperfusion therapy for ST-segment elevation myocardial infarction from 1999 to 2006: we are getting better but we have got a long way to go. *Eur Heart J* 2008; **29:** 609–17.

8 Ting HH, Bradley EH, Wang Y, et al. Factors associated with longer time from symptom onset to hospital presentation for patients with ST-elevation myocardial infarction. *Arch Intern Med* 2008; **168:** 959–68.

9 Kaul P, Fu Y, Westerhout CM, Granger CB, Armstrong PW. Relative prognostic value of baseline Q wave and time from symptom onset among men and women with ST-elevation myocardial infarction undergoing percutaneous coronary intervention. *Am J Cardiol* 2012; **110:** 1555–60.

10 Hopenfeld B, John MS, Fischell DR, Medeiros P, Guimarães HP, Piegas LS. The Guardian: an implantable system for chronic ambulatory monitoring of acute myocardial infarction. *J Electrocardiol* 2009; **42:** 481–86.

11 Lurie KG, Idris A, Holcomb JB. Level 1 cardiac arrest centers: learning from the trauma surgeons. *Acad Emerg Med* 2005; **12:** 79–80.

12 Nichol G, Aufderheide TP, Eigel B, et al, and the American Heart Association Emergency Cardiovascular Care Committee, and the Council on Arteriosclerosis, Thrombosis, and Vascular Biology, and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, and the Council on Cardiovascular Nursing, and the Council on Clinical Cardiology, and the Advocacy Committee, and the Council on Quality of Care and Outcomes Research. Regional systems of care for out-of-hospital cardiac arrest: a policy statement from the American Heart Association. *Circulation* 2010; **121:** 709–29.

13 Kern KB. Cardiac receiving centers: beyond hypothermia. *Curr Opin Crit Care* 2012; **18:** 246–50.

14 Kern KB. Optimal treatment of patients surviving out-of-hospital cardiac arrest. *JACC Cardiovasc Interv* 2012; **5:** 597–605.

15 Hazinski MF, Nolan JP, Billi JE, et al. Part 1: executive summary—2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2010; **122** (suppl 2)**:** S250–75.

16 O'Gara PT, Kushner FG, Ascheim DD, et al, and the CF/AHA Task Force. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary—a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; **127:** 529–55.

17 Steg PG, James SK, Atar D, et al, and the task force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33:** 2569–619.

18 Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. *Circ Cardiovasc Interv* 2010; **3:** 200–07.

19 Hallstrom A, Rea TD, Sayre MR, et al. Manual chest compression *vs* use of an automated chest compression device during resuscitation following out-of-hospital cardiac arrest: a randomized trial. *JAMA* 2006; **295:** 2620–28.

20 Ong MEH, Ornato JP, Edwards DP, et al. Use of an automated, load-distributing band chest compression device for out-of-hospital cardiac arrest resuscitation. *JAMA* 2006; **295:** 2629–37.

21 Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **361:** 13–20.

22 Nakazawa G, Finn AV, Vorpahl M, Ladich ER, Kolodgie FD, Virmani R. Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents. *J Am Coll Cardiol* 2011; **57:** 390–98.

23 Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol* 2011; **57:** 1314–22.

24 Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. *N Engl J Med* 2013; **368:** 254–65.

25 Sabate M, Cequier A, Iñiguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 2012; **380:** 1482–90.

26 Räber L, Kelbæk H, Ostojic M, et al, and the COMFORTABLE AMI Trial Investigators. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA* 2012; **308:** 777–87.

27 Onuma Y, Serruys PW. Bioresorbable scaffold: the advent of a new era in percutaneous coronary and peripheral revascularization? *Circulation* 2011; **123:** 779–97.

28 Serruys PW, Garcia-Garcia HM, Onuma Y. From metallic cages to transient bioresorbable scaffolds: change in paradigm of coronary revascularization in the upcoming decade? *Eur Heart J* 2012; **33:** 16–25b.

29 Brugaletta S, Radu MD, Garcia-Garcia HM, et al. Circumferential evaluation of the neointima by optical coherence tomography after ABSORB bioresorbable vascular scaffold implantation: can the scaffold cap the plaque? *Atherosclerosis* 2012; **221:** 106–12.

30 Ormiston JA, Serruys PW, Regar E, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. *Lancet* 2008; **371:** 899–907.

31 Serruys PW, Ormiston JA, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. *Lancet* 2009; **373:** 897–910.

32 Burke AP, Farb A, Malcom GT, Liang Y-H, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med* 1997; **336:** 1276–82.

33 Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol* 2006; **47** (suppl)**:** C13–18.

34 Braunwald E. Epilogue: what do clinicians expect from imagers? *J Am Coll Cardiol* 2006; **47** (suppl)**:** C101–03.

35 Stone GW, Maehara A, Lansky AJ, et al, and the PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; **364:** 226–35.

36 Narula J, Nakano M, Virmani R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. *J Am Coll Cardiol* 2013; **61:** 1041–51.

37 Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med* 2013; **368:** 2004–13.

38 Stone PH, Saito S, Takahashi S, et al, and the PREDICTION investigators. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION study. *Circulation* 2012; **126:** 172–81.

39 Takarada S, Imanishi T, Kubo T, et al. Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. *Atherosclerosis* 2009; **202:** 491–97.

40 Hattori K, Ozaki Y, Ismail TF, et al. Impact of statin therapy on plaque characteristics as assessed by serial OCT, grayscale and integrated backscatter-IVUS. *JACC Cardiovasc Imaging* 2012; **5:** 169–77.

41 Tang TY, Howarth SPS, Miller SR, et al. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) study: evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. *J Am Coll Cardiol* 2009; **53:** 2039–50.

42 Tawakol A, Fayad ZA, Mogg R, et al. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multi-center FDG-PET/CT feasibility study. *J Am Coll Cardiol* 2013; published online May 30. DOI:10.1016/j.jacc.2013.04.066.

43 Verheye S, Martinet W, Kockx MM, et al. Selective clearance of macrophages in atherosclerotic plaques by autophagy. *J Am Coll Cardiol* 2007; **49:** 706–15.

44 Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death: II—transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 1979; **40:** 633–44.

45 Boersma E, Maas ACP, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; **348:** 771–75.

46 Heusch G. Cardioprotection: chances and challenges of its translation to the clinic. *Lancet* 2013; **381:** 166–75.

47 Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. *J Clin Invest* 2013; **123:** 92–100.

48 Bøtker HE, Kharbanda R, Schmidt MR, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet* 2010; **375:** 727–34.

49 Piot C, Croisille P, Staat P, et al. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med* 2008; **359:** 473–81.

50 Van de Hoef TP, Nolte F, Delewi R, et al. Intracoronary hemodynamic effects of pressure-controlled intermittent coronary sinus occlusion (PICSO): results from the First-In-Man Prepare PICSO study. *J Interv Cardiol* 2012; **25:** 549–56.

51 Friedrich MG, Abdel-Aty H, Taylor A, Schulz-Menger J, Messroghli D, Dietz R. The salvaged area at risk in reperfused acute myocardial infarction as visualized by cardiovascular magnetic resonance. *J Am Coll Cardiol* 2008; **51:** 1581–87.

52 Kim HW, Farzaneh-Far A, Kim RJ. Cardiovascular magnetic resonance in patients with myocardial infarction: current and emerging applications. *J Am Coll Cardiol* 2009; **55:** 1–16.

53 Atar D, Petzelbauer P, Schwitter J, et al, and the FIRE investigators. Effect of intravenous FX06 as an adjunct to primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction results of the FIRE (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) trial. *J Am Coll Cardiol* 2009; **53:** 720–29.

54 Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. *Lancet* 2006; **367:** 356–67.

55 Fraccarollo D, Galuppo P, Bauersachs J. Novel therapeutic approaches to post-infarction remodelling. *Cardiovasc Res* 2012; **94:** 293–303.

56 Pitt B, Remme W, Zannad F, et al, and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348:** 1309–21.

57 Fraccarollo D, Berger S, Galuppo P, et al. Deletion of cardiomyocyte mineralocorticoid receptor ameliorates adverse remodeling after myocardial infarction. *Circulation* 2011; **123:** 400–08.

58 Fraccarollo D, Galuppo P, Schraut S, et al. Immediate mineralocorticoid receptor blockade improves myocardial infarct healing by modulation of the inflammatory response. *Hypertension* 2008; **51:** 905–14.

59 Chung ES, Dan D, Solomon SD, et al. Effect of peri-infarct pacing early after myocardial infarction: results of the prevention of myocardial enlargement and dilatation post myocardial infarction study. *Circ Heart Fail* 2010; **3:** 650–58.

60 Murry CE, Reinecke H, Pabon LM. Regeneration gaps: observations on stem cells and cardiac repair. *J Am Coll Cardiol* 2006; **47:** 1777–85.

61 Anversa P, Kajstura J, Rota M, Leri A. Regenerating new heart with stem cells. *J Clin Invest* 2013; **123:** 62–70.

62 Laflamme MA, Murry CE. Heart regeneration. *Nature* 2011; **473:** 326–35.

63 Leri A, Kajstura J, Anversa P. Role of cardiac stem cells in cardiac pathophysiology: a paradigm shift in human myocardial biology. *Circ Res* 2011; **109:** 941–61.

64 Strauer B-E, Steinhoff G. 10 years of intracoronary and intramyocardial bone marrow stem cell therapy of the heart: from the methodological origin to clinical practice. *J Am Coll Cardiol* 2011; **58:** 1095–104.

65 Segers VFM, Lee RT. Stem-cell therapy for cardiac disease. *Nature* 2008; **451:** 937–42.

66 Beltrami AP, Urbanek K, Kajstura J, et al. Evidence that human cardiac myocytes divide after myocardial infarction. *N Engl J Med* 2001; **344:** 1750–57.

67 Small EM, Frost RJA, Olson EN. MicroRNAs add a new dimension to cardiovascular disease. *Circulation* 2010; **121:** 1022–32.

68 Roy S, Khanna S, Hussain S-RA, et al. MicroRNA expression in response to murine myocardial infarction: miR-21 regulates fibroblast metalloprotease-2 via phosphatase and tensin homologue. *Cardiovasc Res* 2009; **82:** 21–29.

69 Bonauer A, Carmona G, Iwasaki M, et al. MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice. *Science* 2009; **324:** 1710–13.

70 Thum T, Gross C, Fiedler J, et al. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. *Nature* 2008; **456:** 980–84.

71 van Rooij E, Sutherland LB, Thatcher JE, et al. Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. *Proc Natl Acad Sci USA* 2008; **105:** 13027–32.

72 Eulalio A, Mano M, Dal Ferro M, et al. Functional screening identifies miRNAs inducing cardiac regeneration. *Nature* 2012; **492:** 376–81.

73 Mercola M. Cardiovascular biology: a boost for heart regeneration. *Nature* 2012; **492:** 360–62.

74 Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. *Science* 2009; **324:** 98–102.

75 Urbanek K, Torella D, Sheikh F, et al. Myocardial regeneration by activation of multipotent cardiac stem cells in ischemic heart failure. *Proc Natl Acad Sci USA* 2005; **102:** 8692–97.

76 Kajstura J, Urbanek K, Perl S, et al. Cardiomyogenesis in the adult human heart. *Circ Res* 2010; **107:** 305–15.

77 Strauer B-E, Brehm M, Zeus T, et al. Intracoronary, human autologous stem cell transplantation for myocardial regeneration following myocardial infarction. *Dtsch Med Wochenschr* 2001; **126:** 932–38 (in German).

78 Stamm C, Westphal B, Kleine HD, et al. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. *Lancet* 2003; **361:** 45–46.

79 Abdel-Latif A, Bolli R, Tleyjeh IM, et al. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch Intern Med* 2007; **167:** 989–97.

80 Schächinger V, Erbs S, Elsässer A, et al, and the REPAIR-AMI investigators. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 2006; **355:** 1210–21.

81 Traverse JH, Henry TD, Pepine CJ, et al, and the Cardiovascular Cell Therapy Research Network (CCTRN). Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. *JAMA* 2012; **308:** 2380–89.

82 Assmus B, Schächinger V, Teupe C, et al. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation* 2002; **106:** 3009–17.

83 Roncalli J, Mouquet F, Piot C, et al. Intracoronary autologous mononucleated bone marrow cell infusion for acute myocardial infarction: results of the randomized multicenter BONAMI trial. *Eur Heart J* 2011; **32:** 1748–57.

84 Hirsch A, Nijveldt R, van der Vleuten PA, et al, and the HEBE investigators. Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE trial. *Eur Heart J* 2011; **32:** 1736–47.

85 Huikuri HV, Kervinen K, Niemelä M, et al, and the FINCELL investigators. Effects of intracoronary injection of mononuclear bone marrow cells on left ventricular function, arrhythmia risk profile, and restenosis after thrombolytic therapy of acute myocardial infarction. *Eur Heart J* 2008; **29:** 2723–32.

86 Lunde K, Solheim S, Aakhus S, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. *N Engl J Med* 2006; **355:** 1199–209.

87 Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; **131:** 861–72.

88 Bolli R, Chugh AR, D'Amario D, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet 2011; **378:** 1847–57.

89 Makkar RR, Smith RR, Cheng K, et al. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. *Lancet* 2012; **379:** 895–904.