Acute myocardial infarction

Extended Review

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Despite improvements in primary prevention and treatment, acute myocardial infarction (AMI) remains a major cause of death in most developed countries. The widespread adoption of thrombolytic therapy and treatment with agents such as aspirin, β-blockers and angiotensin-converting enzyme (ACE) inhibitors has resulted in dramatic improvements in outcome for those patients suffering AMI who reach hospital care. Despite these advances, 10–15% of the estimated 180,000 patients hospitalised annually in the UK with AMI die during hospitalisation and another 15–20% die during the following year. These figures support a need for improved therapeutic strategies in AMI. This article reviews the current treatment options available and newer concepts of management that may be applied to AMI.

Therapies aimed at reperfusion of occluded coronary arteries

Thrombolytic therapy

Following clarification of the central role for thrombotic coronary occlusion in AMI in the early 1980s, it has become recognised that the most important therapeutic goal in the management of AMI is the early, complete and sustained restoration of blood flow to the ischaemic myocardium. The first use of thrombolytic agents was four decades ago, but it was not until 1986 that their benefit was proven in a large randomised trial. The Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI) trial showed an 18% reduction in mortality in patients treated with intravenous (IV) streptokinase within 12 hours of AMI. This beneficial outcome was later confirmed by the Second International Study of Infarct Survival (ISIS-2). Subsequently, a number of large trials have compared different thrombolytic agents and different regimens combining thrombolytic drugs, aspirin, and various anticoagulants, anti-thrombin and other antiplatelet agents. Over 200,000 patients have been randomised to clinical trials of thrombolytic therapy, making this the most extensively investigated therapy in medicine. These studies have conclusively established the role of thrombolysis as an effective mode of treatment for patients with evolving MI.

The most widely used thrombolytic agents in UK are streptokinase and tissue plasminogen activator (t-PA). The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial demonstrated that an accelerated regimen of t-PA with IV heparin given within six hours of the onset of symptoms was associated with mortality as low as 6.3% at 30 days. Overall, administration of t-PA saved 10 lives per 1,000 patients treated, at a cost of two extra strokes compared with streptokinase. In addition, t-PA gave better results for the combined end-point of death plus non-fatal disabling stroke (6.9% vs 7.8%, p < 0.01).

Angiographic studies from the GUSTO trial have demonstrated a
strong correlation between the patency of the infarct-related vessel at 90 minutes following thrombolysis and the reduction in mortality achieved with accelerated t-PA\(^*\). Irrespective of the thrombolytic agent used, an occluded infarct-related artery (Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow) at 90 minutes was associated with an 8.9\% 30-day mortality rate, while patients with complete reperfusion had a 4.0\% mortality rate (Table 1). Furthermore, normal coronary flow (TIMI grade 3) at 90 minutes has been correlated with improved left ventricular (LV) ejection fraction, better regional wall motion in the infarct zone and smaller end-systolic volumes 5–7 days post-AMI, compared to lesser degrees of reperfusion\(^*\). These results confirm the importance of rapid and complete restoration of blood flow to the ischaemic myocardium in the preservation of LV function and reduction in mortality.

The impressively low mortality rates reported in large randomised trials of thrombolytic therapy have not been achieved in routine clinical practice. Underuse and delay in administration of thrombolytic therapy probably represent the two most important reasons why mortality rates in clinical practice remain higher than those reported in large trials.

**Timing of thrombolysis**

The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group\(^*\) reviewed nine trials of thrombolytic therapy that had each randomised more than 1,000 patients. The authors concluded that there is a gradual reduction in benefit with delay in administration of thrombolytic therapy: each hour of delay translates into 1.6 additional lives lost for every 1,000 patients treated, with no marked deviation from this linear trend for very early (0–1 h) thrombolysis. More recently, an alternative analysis of these data has been presented\(^*\). From an analysis of 22 trials comparing thrombolytic therapy with placebo, each of them in at least 100 patients, it was concluded that in the first 1–2 hours after the onset of chest pain the relationship between time of treatment and survival is better described by a non-linear curve (Fig 1). The authors suggested that the benefit of thrombolytic therapy was 65, 37, 26 and 29 lives saved per 1,000 treated patients in the 0–1, 1–2, 2–3 and 3–6 hour intervals, respectively\(^*\). The proportional mortality reduction was 48\% in patients treated within one hour, and significantly higher in patients treated within two hours from the onset of symptoms than in those treated later (44\% vs 20\%).

These findings reiterate the importance of early reperfusion of the occluded coronary artery as the most crucial factor in preventing death and impairment of ventricular function following AMI. One of the important sources of delay from symptom onset to initiation of thrombolytic therapy is the time from summoning help to arrival at the hospital, estimated to range from 80–160 minutes in most regions\(^*\). Other reasons include delay in calling for help, and delays within the hospital.

**Fig 1. Time to thrombolysis and absolute 35-day mortality reduction.** The importance of time to thrombolysis in acute myocardial infarction and the absolute reduction in 35-day mortality are shown in a meta-analysis of over 50,000 patients. The benefit from thrombolytic therapy is greatest when administered within two hours of symptom onset, with a progressively reduced survival benefit as the delay in therapy increases. After two hours, the benefit from thrombolytic therapy fits a linear function in which the benefit falls by approximately 1.6 lives per 1,000 patients per hour of treatment delay. (Adapted from Ref 13 by permission of the *Lancet*.)
from arrival to treatment (door-to-needle time). Mass public education campaigns aimed at reducing patient delay have been disappointing and do not seem to have produced major long-term benefits\textsuperscript{16}. Initiatives aimed at reducing hospital delays are underway, based on identification of sources of delay within different institutions.

Another important means of reducing the time to treatment is the initiation of thrombolytic therapy by general practitioners or paramedics prior to arrival of the patient in hospital. A number of trials have established the safety and feasibility of prehospital thrombolysis in a variety of settings\textsuperscript{16,17}. Several randomised trials comparing prehospital with in-hospital therapy have shown a substantial beneficial effect of very early thrombolytic therapy. Although these studies were too small to show statistical significance, a meta-analysis of the data showed a significantly lower mortality rate in the prehospital treated group (16.7\%) relative reduction\textsuperscript{18}. This translated into 18 extra lives saved per 1,000 patients treated in the community. These encouraging results provide further impetus for organisation and implementation of prehospital thrombolytic programmes, particularly in geographical settings where initiation of treatment outside hospital is likely to reduce treatment delay by more than 90 minutes\textsuperscript{17}. With the development of new fibrinolytic agents, with increased stability and prolonged half-life allowing bolus administration, some of the logistic difficulties associated with prehospital thrombolysis may be overcome (see below).

### Eligibility for thrombolysis

The goal in management of patients with an evolving AMI should be to treat all eligible patients with reperfusion therapy as soon as possible. However, in practice, a much smaller proportion of patients receives thrombolysis. Contraindications to thrombolytic therapy exist in 7–10\% of patients\textsuperscript{19} (Table 2). Ineligibility for thrombolysis does not, however, render the patient ineligible for reperfusion, and percutaneous revascularisation by angioplasty should be considered where available.

### Elderly patients

Thrombolytic therapy has been underused in the elderly\textsuperscript{20}, mainly due to concerns about the increasing haemorrhagic risk in the elderly population. A number of the early thrombolytic trials excluded patients over 75 years of age. These patients, however, represent a significant proportion of patients presenting with AMI, and potentially they have the most to gain from reperfusion because of their high absolute mortality\textsuperscript{21}. Although elderly patients have an increased risk of intracerebral haemorrhage following thrombolysis, the GUSTO-I trial, which had no upper age limit for randomisation, clearly indicated significantly lower mortality rates in all but the oldest patients (\textgtr 85 years) treated with thrombolytic therapy. The net clinical benefit, in terms of deaths plus non-fatal disabling strokes saved, was greater in patients who received accelerated t-PA\textsuperscript{22}. For those over 85 years, the best regimen in GUSTO-I appeared to be streptokinase plus subcutaneous heparin.

### Patients with diabetes

Similarly, diabetic patients have been less frequently treated with thrombolytic agents because of concerns about the increased risk of bleeding, particularly ocular. These patients, however, derive as much benefit from thrombolytic therapy as non-diabetic patients. In fact, in the FTT analysis, the absolute benefit from thrombolytic therapy was even greater among diabetics than non-diabetics (37 vs 15 lives saved per 1,000 treated), although the difference did not reach statistical significance\textsuperscript{22}. The initial

### Table 2. Contraindications to thrombolytic therapy

(adapted from Ref 7).

| Major contraindications                  |
|-----------------------------------------|
| • Any previous history of haemorrhagic stroke |
| • History of stroke, dementia or CNS damage within one year |
| • Head trauma or brain surgery within six months |
| • Known intracranial neoplasm            |
| • Suspected aortic dissection            |
| • Internal bleeding within six weeks     |
| • Active bleeding or known bleeding disorder |
| • Major surgery, trauma or bleeding within six weeks |
| • Traumatic cardiopulmonary resuscitation |

| Relative contraindications               |
|-----------------------------------------|
| • Oral anticoagulant therapy            |
| • Acute pancreatitis                    |
| • Pregnancy or within one week postpartum |
| • Active peptic ulceration              |
| • Transient ischaemic attack within six months |
| • Dementia                              |
| • Infective endocarditis                |
| • Active caviod pulmonary tuberculosis  |
| • Advanced liver disease                |
| • Intracardiac thrombi                  |
| • Uncontrolled hypertension (SBP >180 mmHg, DBP >110 mmHg) |
| • Puncture of non-compressible blood vessel within two weeks |
| • Previous SK therapy (for repeat treatment with SK) |

CNS = central nervous system   SBP = systolic blood pressure
DBP = diastolic blood pressure  SK = streptokinase
concerns about increased haemorrhagic complications in this group which, for example, made proliferative retinopathy an absolute contraindication to thrombolysis, have not been supported by evidence. In the GUSTO-I cohort, none of the 300 patients with proliferative retinopathy treated with thrombolytic therapy suffered a retinal haemorrhage 23.

Subgroup analysis. The FTT overview provided a subgroup analysis based on the ECG abnormality present at the time of randomisation 12. The greatest benefit from thrombolytic therapy was observed in patients with anterior infarction and ST elevation, and in those with bundle branch block on the presenting ECG (37 and 49 lives saved per 1,000 patients treated). Patients with inferior ST elevation derived less benefit from thrombolysis (8 lives saved per 1,000 treated), while patients without ST elevation treated with thrombolysis had a higher 35-day mortality rate than on control treatment, although this did not reach statistical significance. ST segment depression may be the presenting abnormality in true posterior infarction, partial thickness (non-Q wave) infarction or unstable angina. Patients with evolving MI presenting with ST depression on their ECG comprise a substantial proportion of patients (ca 50%); they generally have a poorer outcome than other patients, including those with initial ST segment elevation 24. Several explanations have been put forward for the apparent lack of benefit from thrombolysis in these patients. They include:

- the procoagulant effect of thrombolytic agents, resulting in progression of a non-occlusive mural thrombus
- more extensive underlying coronary disease in patients with non-Q wave infarction
- dilution of the benefit seen in patients with an evolving MI through lack of benefit in those with unstable angina 7.

Alternatively, as recently suggested, the low statistical power and heterogeneity in the designs of the trials included in the FTT analysis may have resulted in a type II statistical error and the false conclusion that patients with ST depression do not benefit from thrombolytic therapy 25. Indeed, in the Late Assessment of Thrombolytic Efficacy (LATE) study 26, one-year mortality was significantly reduced in patients with proven non-Q wave MI with ≥2 mm ST depression who were treated with t-PA 6–24 hours after the onset of chest pain, compared to control treatment. Further clinical trials are needed to establish the true effects of thrombolytic therapy in patients with an evolving infarct who present with ST depression. In the absence of such data, it may be reasonable to consider thrombolytic therapy for patients with a convincing clinical history, and persistent deep (≥2 mm) ST segment depression on the presenting ECG.

Antiplatelet agents

Increasing awareness of the critical role of platelets in the pathogenesis of acute ischaemic syndromes has prompted investigation into therapeutic strategies aimed specifically at inhibition of platelet aggregation 27. Numerous investigators have shown that glycoprotein (GP) IIb/IIIa integrin mediates the final common pathway in platelet aggregation; this has generated intense interest in the development of GP IIb/IIIa antagonists 28. These agents inhibit platelet function by occupying the fibrinogen binding site. In patients with unstable angina/non-Q-wave MI, GP IIb/IIIa blockade may promote stabilisation of the ruptured plaque and change the endothelium into an inert surface incapable of supporting further platelet activity, thereby preventing subsequent cardiovascular events 27.

Four large randomised trials have evaluated the use of IV GP IIb/IIIa antagonists in the setting of unstable angina/non-Q-wave MI 29–32. The largest, the Platelet glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial 32, randomised 10,948 patients to eptifibatide (Integrilin), a cyclic heptapeptide GP IIb/IIIa antagonist, or to placebo, in addition to standard therapy for 72–96 hours. Treatment with eptifibatide significantly reduced the combined incidence of death or MI at 30 days compared with placebo (14.2% vs 15.7%; p = 0.04). There was no significant increase in the rates of major bleeding, stroke or thrombocytopenia. An overview of all four trials demonstrated a similar modest 13% relative reduction in the combined incidence of death or MI at 30 days (13.3% vs 11.7%)28. These encouraging findings confirm the role of GP IIb/IIIa blockade as the first effective new strategy since

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### Key Points

- **Thrombolysis given early is potentially life saving treatment for acute myocardial infarction (AMI), especially in the elderly and in diabetics.**
- **Angioplasty is able to re-open coronary arteries during AMI and should be considered if thrombolysis is impossible or cardiogenic shock is present.**
- **Heparin should be given following successful thrombolysis with t-PA but not routinely after streptokinase.**
- **Beta-blockers are currently underused, both acutely during myocardial infarction and for secondary prevention.**
- **Angiotensin converting enzyme inhibitors have a clear benefit post AMI, especially if left ventricular function is impaired, but nitrates and anti-arrhythmic agents benefit only small subgroups of patients.**
aspirin and heparin to improve clinical outcome in patients with unstable angina/non-Q-wave MI. Moreover, the benefit of GP IIb/IIIa antagonism is sustained whether or not percutaneous revascularisation is performed after initiation of treatment. Further confirmatory results from large trials are required, although the widespread adoption of this therapy may be hindered by its cost.

**New thrombolytic agents**

A number of new thrombolytic agents are in different stages of clinical development, with the aim of improving the efficacy of lysing thrombus and ease of administration. These include mutants of native t-PA such as reteplase, lanoteplase and TNK-TPA. These agents have a prolonged half-life (allowing bolus administration), enhanced fibrin specificity, and resistance to natural inhibitors such as plasminogen activator inhibitor-1. Others include saruplase, a recombinant single-chain urokinase plasminogen activator, and staphylokinase, produced by *Staphylococcus aureus*.

**Reteplase**. Reteplase is a deletion mutant of t-PA, and is the most widely investigated of the third-generation thrombolytic agents. Its half-life is almost twice that of t-PA, making it suitable for bolus administration. In an angiographic study, reteplase administered as two 10-iu boluses 30 minutes apart gave significantly higher rates of TIMI grade 3 flow at 90 minutes compared to accelerated infusion of t-PA (59.9% vs 45.2%)33. However, this improved patency rate at 90 minutes has not resulted in reduced mortality in randomised trials. In the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial in over 6,000 patients with AMI, the same dose of reteplase gave only a small, non-significant benefit over streptokinase34. Similarly, double-bolus reteplase failed to show any benefit over t-PA in patients in terms of mortality in the GUSTO-III trial35. There were no differences in the incidence of stroke or bleeding events between reteplase and the other two thrombolytic agents in either trial. These studies provide evidence that reteplase is safe and as effective as the established thrombolytic agents in the management of AMI.

Further phase III trials with other third-generation thrombolytic agents are currently underway. Specifically, such agents may significantly contribute to the practicality of out-of-hospital thrombolytic treatment strategies, administered either by primary care physicians or by ambulance paramedic teams.

**Primary angioplasty**

The principal goal of treatment of an evolving MI, prompt and complete reperfusion of the infarct-related vessel (TIMI grade 3 flow), can be achieved with the most potent established thrombolytic regimen (accelerated t-PA) in only about 55% of patients31. This major limitation of thrombolytic therapy, together with its rare but life-threatening or catastrophic haemorrhagic complications, has prompted research into mechanical reperfusion of the infarct-related vessel by balloon angioplasty without prior thrombolysis (primary percutaneous transluminal coronary angioplasty [PTCA]). The results of studies of primary PTCA for the treatment of AMI have been impressive, and reperfusion rates in excess of 90% have generally been reported. Ten prospective randomised trials comparing primary PTCA and thrombolytic therapy in 2,606 patients have now been performed, and recently reviewed36. Compared with thrombolytic therapy, primary PTCA resulted in a significantly lower mortality rate (6.5% vs 4.4%) and reduced combined end-point of death plus non-fatal re-infarction (11.9% vs 7.2%). Moreover, the rates of total stroke (2.0% vs 0.7%) and haemorrhagic stroke (1.1% vs 0.1%) were significantly lower in patients treated with primary angioplasty36. These findings convincingly demonstrate the superiority of primary PTCA over thrombolytic therapy in terms of short-term prognosis. The results may be further improved by the use of new antiplatelet agents such as the GP IIb/IIIa antagonists37, and by deployment of intracoronary stents, as suggested by the recently published first randomised trial of primary PTCA versus primary stenting38.

Widespread application of these findings is an unrealistic short-term goal. Studies from the USA39 have shown that primary PTCA may be more cost-effective than thrombolysis by reducing early and late recurrent ischaemic events and facilitating earlier discharge, but the wider applicability of these findings to the NHS is doubtful. In areas where access to cardiologists and catheterisation facilities are established, efforts should be concentrated on making primary PTCA available to those patients at high risk who are most likely to benefit from the procedure, such as patients considered ineligible for thrombolytic therapy (eg postoperative AMI) and those with cardiogenic shock in whom thrombolysis has proved ineffective.

**Adjunctive therapy**

**Heparin**

Successful thrombolysis may paradoxically lead to a period of enhanced platelet and thrombin activity. The prothrombotic effect of thrombolytic agents has been attributed to exposure of thrombin and enhanced thrombin activity with marked pro-aggregatory effects on platelets following lysis of fibrin32. This has prompted the use of anticoagulation and antiplatelet agents following thrombolytic therapy. However, trials in which heparin was used after thrombolysis with agents that were not fibrin-specific (streptokinase, anisoylated plasminogen-streptokinase activator complex [APSAC], urokinase) have only shown marginal benefit, with an increased rate of haemorrhagic stroke40,41. On the other hand, following thrombolysis with the more fibrin-specific agents such as t-PA, there is a role for IV treatment with heparin, as suggested by the GUSTO trial42. The shorter half-life and relatively greater
fibrin specificity of t-PA lead to reduced depletion of systemic fibrinogen compared with the less fibrin-specific agents, and also a higher incidence of reocclusion and reinfarction in the absence of IV heparin.

Following thrombolytic therapy with t-PA, IV heparin can be given as recommended in the GUSTO study protocol: a 5,000 IU bolus at the commencement of treatment, followed by IV infusion for at least 48 hours, maintaining the activated partial thrombin time (APTT) at 65–80 seconds. There is no role for the routine use of subcutaneous or IV heparin following thrombolysis with streptokinase, although it may be considered in certain patients at high risk of thromboembolic complications.

Aspirin

Aspirin is established as a simple, safe and effective immediate treatment for MI and for secondary prevention. In the ISIS-2 study, the aspirin group had a 23% relative reduction in 35-day vascular mortality compared with the control group. Furthermore, there seems to be a synergistic effect between aspirin and thrombolytic therapy: in ISIS-2, the combined administration of streptokinase and aspirin yielded considerably greater benefit than either drug alone. Their combined use gave a 39% reduction in 35-day mortality (7.8%, 10.6%, 10.0% and 12.8% in the streptokinase plus aspirin, aspirin alone, streptokinase alone and placebo groups, respectively), without any excess in major bleeding complications.

Although it is believed that the timing of aspirin ingestion is not critical, recent preliminary evidence suggests that early administration of aspirin prior to thrombolytic therapy may be associated with significantly greater reduction in mortality following AMI compared to later treatment.

All patients with suspected AMI should receive oral aspirin as soon as possible, unless there is a clear history of hypersensitivity or a major bleeding contraindication. The first dose can be administered by the patient's general practitioner or ambulance paramedics. After the acute event, treatment with aspirin should continue for life. A dose greater than 325 mg of aspirin does not substantially increase platelet inhibition, but increases the risk of bleeding. Most experts therefore advocate an initial loading dose of 325 mg, followed by a daily maintenance dose of 75–325 mg.

Beta-blockers

Despite the persuasive evidence for the early use of IV β-adrenergic antagonists after MI, these drugs remain underused in the UK. In the ISIS-4 trial, for example, only 5% of patients enrolled in the UK received IV β-blockade compared to about 30% of those enrolled in America. These agents provide cardio-protection after AMI through their antiarrhythmic, antiischaemic and anti-hypertensive properties. In the prethrombolytic era, more than 28 randomised trials involving over 27,000 patients evaluated the efficacy of IV β-blockers in AMI. The largest, ISIS-1, assessed one-week mortality in more than 16,000 patients randomised to treatment with IV atenolol 5–10 mg at the time of infarction, followed by 100 mg per day orally or placebo. Overall, there was a 15% reduction in mortality from vascular causes in the atenolol group after seven days, which persisted at one year. Moreover, retrospective analysis of the ISIS-1 data indicated that IV β-blockade resulted in a 2.5 times greater reduction in the risk of cardiac rupture, most of this benefit being achieved within the first 24 hours. Pooled analysis of data from all randomised trials of early β-blocker therapy after AMI showed a similar 13% reduction in overall mortality.

Longer-term use of β-blockers following AMI has also been evaluated in a number of trials. The two largest, the Norwegian Multicenter Study (NMS) and the Beta-Blocker Heart Attack Trial (BHAT), randomised patients to oral β-blockade or placebo starting 5–28 days after MI. Both trials demonstrated a significant reduction in mortality in the β-blocker group. In the NMS, timolol reduced overall mortality by 39% at 33 months follow-up; in the BHAT trial, there was a 28% reduction in mortality in the propranolol group after 24 months.

A retrospective analysis, in terms of the use of β-blockers after AMI, of more than 200,000 patients in the Cooperative Cardiovascular Project (CCP) has recently been published. After adjusting for coexisting diseases and other risk factors, patients receiving β-blockers at discharge from hospital had an approximately 40% lower mortality rate at 24 months than patients who did not receive the therapy – an even larger beneficial effect than reported in previous clinical trials. Importantly, this survival advantage was consistent in all the subgroups examined, including those with coexisting conditions perceived as relative contraindications to β-blockade, such as impaired LV function, chronic obstructive pulmonary disease and diabetes mellitus. Moreover, this study showed that subgroups understudied in clinical trials, such as the elderly and patients with non-Q wave infarction, similarly benefit from treatment with β-blockers.

Treatment with β-blockers after MI remains underused in the UK. In the absence of clear contraindications, such as pulmonary oedema, asthma, hypotension, bradycardia or advanced A-V block, all patients presenting with AMI should receive treatment with IV β-blockers followed by oral therapy. If tolerated by the patient, this treatment should continue for at least 2–3 years, although the exact beneficial duration of therapy remains unknown and treatment should be tailored to the individual patient.

Angiotensin-converting enzyme inhibitors

ACE inhibitors have been clearly shown to reduce mortality when used both in the acute phase and long term following MI. These agents have anti-ischaemic effects, reduce LV dysfunction and dilatation, and slow the progression to congestive cardiac failure during and after AMI.
A number of large randomised trials, including ISIS-4\(^1\) and GISSI-3\(^2\), have demonstrated improved survival with oral ACE inhibitor therapy initiated in the early phase of AMI. In ISIS-4, captopril started within 24 hours of the onset of chest pain resulted in a 7% reduction in 35-day mortality compared to the placebo group\(^5\). Similarly, the GISSI-3 trial demonstrated a 12% reduction in mortality at 42 days in patients treated with lisinopril early after the onset of AMI\(^2\). However, in the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II), early treatment with IV enalapril was not shown to be beneficial\(^3\). This negative finding may have resulted from the increased incidence of hypotension following IV enalapril in a subgroup of high-risk elderly patients. A recent meta-analysis of all randomised trials of ACE inhibition in the acute phase of MI revealed a significant 7% reduction in 30-day mortality in the ACE inhibitor-treated group, translating into five lives saved per 1,000 patients treated\(^4\). The absolute benefits were greatest in patients with anterior infarction, tachycardia, previous MI, diabetes and Killip classes II and III.

Compared with the ISIS-4 and GISSI-3 trials, in which ACE inhibitor therapy was initiated within 24 hours in largely unselected patients and continued short term, several trials have evaluated the long-term use of ACE inhibitors following AMI in selected patients with clinical LV failure or objective evidence of impaired LV function. Overall, these trials have demonstrated more impressive results in terms of the beneficial effects of ACE inhibitors. In the Acute Infarction Ramipril Efficacy (AIRE) study\(^5\), in which over 2,000 patients with clinical evidence of heart failure within 3–10 days of AMI were treated with ramipril or placebo, ramipril was associated with a 26% reduction in mortality over a 15-month follow-up period.

The Survival and Ventricular Enlargement (SAVE)\(^6\) and Trandolapril Cardiac Evaluation (TRACE) trials\(^7\) recruited patients following AMI on the basis of objective evidence of LV dys-

function assessed by radionuclide ventriculography (LV ejection fraction (LVEF) ≤40%) and echocardiography (LVEF ≤35%), respectively. In the SAVE trial, captopril reduced mortality by 19% compared to placebo at 42 months\(^8\). Trandolapril produced a similar (22%) relative reduction in mortality in the TRACE study\(^9\). In addition to the beneficial effects in terms of mortality reduction, there were similar significant reductions in progression to severe heart failure in the SAVE and TRACE studies, and a significant reduction in the incidence of sudden death in the TRACE and AIRE trials.

These trials convincingly demonstrate the cardioprotective effects of ACE inhibition following AMI. Furthermore, as suggested by the recently published follow-up data from the AIRE extension (AIREX) study\(^10\), long-term active treatment with an ACE inhibitor may confer additional benefits which are sustained over five years. In the absence of clear contraindications (hypotension, renal failure, bilateral renal artery stenosis, history of angiooedema with previous ACE inhibitor therapy), all patients with AMI with evidence of LV impairment, or other risk factors such as anterior infarction, left bundle branch block or history of previous MI should receive early (within 24 hours) treatment with oral ACE inhibitors. The beneficial duration of therapy remains unknown but, in the presence of LV dysfunction, this treatment should probably continue indefinitely. Another school of thought advocates non-selective initiation of ACE inhibitor therapy early in the acute phase of MI in all patients without contraindications, with later withdrawal of treatment at about six weeks in low-risk patients with no objective evidence of LV dysfunction.

**Nitrates**

Nitrates, both oral and IV, has been established as effective treatment for ischaemic chest pain in patients with angina. In addition to improving blood supply to the ischaemic myocardium by relaxing coronary tone, nitrate therapy reduces myocardial oxygen consumption by reducing venous, and hence intracardiac, diastolic pressure.

A number of small trials of IV nitroglycerin during AMI produced inconclusive results. Treatment with nitrates following AMI was then evaluated in two large randomised trials:

- The ISIS-4 trial\(^11\), in which oral therapy with controlled-release isosorbide mononitrate was initiated within 24 hours of AMI and continued for four weeks. There was a non-significant 3% reduction in 35-day mortality compared to placebo.
- The GISSI-3 trial\(^2\), in which patients were randomised within 24 hours of AMI either to treatment with IV nitroglycerin for 24 hours followed by transdermal nitrate patch for six weeks, or to conventional treatment. Therapy with nitrates was associated with a significantly reduced rate of post-infarction angina and cardiogenic shock. There was also a non-significant 6% reduction in mortality in the nitrate-treated group.

It must be noted that in both these trials, the high rate of cross-over to nitrates, as indicated by occurrence of postinfarction angina, may have diluted the true beneficial effects of nitrate therapy on mortality. A meta-analysis including the ISIS-4 and GISSI-3 trials, and 20 smaller trials of oral or IV therapy with nitrates following AMI, demonstrated a marginal but significant 5.5% relative reduction in mortality in the nitrate-treated patients\(^12\).

Taken together, these trials indicate that therapy with oral or IV nitrates is a safe and effective means of relieving postinfarction ischaemic chest pain. However, the mortality data do not indicate a role for the routine use of nitrates after AMI in the absence of postinfarction angina.

**Antiarrhythmic therapy**

Patients suffering an AMI are at increased risk of potentially fatal ventricular arrhythmias within the first
24–48 hours. This complication also accounts for up to 75% of sudden deaths during the first year following MI. These findings led to a number of randomised trials in the 1970s and 1980s evaluating the prophylactic administration of class I antiarrhythmic drugs, with the aim of reducing the incidence of early post-MI ventricular fibrillation (VF) and early mortality or, on the other hand, to decrease long-term mortality by suppressing the incidence of asymptomatic ventricular premature beats.

The results were generally disappointing. A meta-analysis of the randomised trials of prophylactic lignocaine showed a significant 35% reduction in VF following MI, but this benefit was offset by a non-significant 38% increase in early mortality in the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT).

Both trials randomised patients with an AMI to long-term treatment with oral amiodarone or placebo. In EMIAT, patients had depressed LV function with LVEF less than 40%, while CAMIAT included patients with recurrent ventricular ectopic activity or at least one episode of ventricular tachycardia on 24-hour ambulatory ECG monitoring. Neither trial demonstrated a reduction in all-cause or cardiac mortality in the amiodarone group. EMIAT showed a significant 35% reduction in the risk of arrhythmic death, at the expense of a non-significant 33% increase in non-arhythmic cardiac death in the amiodarone group. In CAMIAT, amiodarone was associated with a 38% reduction in the incidence of the combined primary end-point of resuscitated VF and arrhythmic death, with the greatest absolute risk reduction in patients with congestive heart failure.

Although the results of these trials are more encouraging than those of previous trials of antiarrhythmic therapy following AMI, they do not support the routine prophylactic use of amiodarone following MI. However, the results suggest that amiodarone may have some protective effects against arrhythmic death in high-risk patients with heart failure and recurrent ventricular ectopic activity. The routine administration of lignocaine during AMI or the prophylactic use of class I antiarrhythmic agents to suppress ventricular ectopic activity after MI is not recommended.

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