

# Myocardial infarction and angina

## *Current drug therapy*

By A. TOPOL, MSc, MRPharmS, A. BIJARBONEH, BSc, MRPharmS,  
A. BAKHAI, MBBS, MRCP, and R. GOODMAN, MSc, MRPharmS

*The second part of our special feature discusses established and newer treatments for myocardial infarction and angina*

**T**his article is divided into two sections. The first section discusses unstable angina and non-ST elevation myocardial infarction

*Mrs Topol is medicines information manager, Miss Bijarboneh is cardiology pharmacist, Dr Bakhai is senior clinical research fellow in the clinical trials and evaluation unit, and Mr Goodman is chief pharmacist at Royal Brompton and Harefield NHS Trust, London*

(MI), which are known together as acute coronary syndromes (ACS). The second section discusses acute MI. The management of these two conditions is complex and frequently changing.

### ACUTE CORONARY SYNDROMES

The National Service Framework on Coronary Heart Disease (standard eight) states that “people with symptoms of

angina or suspected angina should receive appropriate investigation and treatment to relieve their pain and reduce their risk of coronary events”.<sup>1</sup>

Each year, about 120,000 people are admitted to hospital with the ACS of unstable angina and non-ST elevation MI.<sup>2</sup> The British Cardiac Society (BCS)<sup>3</sup> and the NSF on coronary heart disease recommend the following medical treatment for patients admitted with ACS:

- aspirin — initially 300mg, then 150mg daily unless contraindicated
- heparin — intravenous (IV) heparin or subcutaneous (SC) low molecular weight heparin for two to five days
- $\beta$ -blockers — unless contraindicated
- calcium channel blockers: if there is a contraindication to  $\beta$ -blockers, a calcium channel blocker that slows the heart can be used in patients without evidence of heart failure or left ventricular dysfunction
- nitrates — taken by either the intravenous or oral route
- potassium channel openers — if there are recurrent symptoms despite  $\beta$ -blocker and calcium antagonists
- intravenous small molecule glycoprotein IIb/IIIa platelet inhibitors — for high risk patients given for up to 96 hours

**Aspirin and clopidogrel** Aspirin irreversibly inhibits cyclo-oxygenase, the main enzyme involved in the synthesis of prostaglandins and ultimately thromboxane, thereby blocking this pathway of platelet aggregation. Doses as low as 10mg have an effect which is detectable for up to 10 days, the lifespan of a platelet.<sup>4</sup>

Several trials have clearly demonstrated a beneficial role for aspirin in the treatment of unstable angina.<sup>5</sup> The doses of aspirin used in the trials varied from 75mg to 1,300mg daily, but they all consistently demonstrated a significant decrease in the incidence of death or non-fatal MI without any further incremental benefit at higher doses.

There is no role for aspirin in primary prevention for all patients. However, the Primary Prevention Project<sup>6</sup> carried out in high risk individuals (those with hypertension, hypercholesterolaemia, diabetes, obesity or family history of premature MI) was stopped prematurely because aspirin significantly reduced cardiovascular deaths.

Clopidogrel should be considered for patients allergic to aspirin. The preliminary results from the CURE trial (Table 1), not yet published, suggest that clopidogrel, in addition to aspirin, provides a further 20 per cent risk reduction of death or MI in patients with acute coronary syndromes. Results have shown a significant and clinically important benefit of clopidogrel when given in addition to aspirin for the chronic treatment of ACS.

**Heparin** Current practice guidelines support the use of the combination of unfractionated heparin (UFH) and aspirin for the treatment of unstable angina.<sup>7</sup> The recommended duration of continuous infusion in patients with no further symptoms after admission is 48 hours.<sup>8</sup> However, if symptoms persist, the infusion is continued until an invasive intervention can be performed, or for between two and five days.

*Table 1: Preliminary results of the CURE trial*

Endpoint	Aspirin	Aspirin plus clopidogrel	P value
Cardiovascular (CV) death, MI, stroke (primary endpoint)	11.47 per cent	9.28 per cent	0.0005
CV death	5.4 per cent	5.06 per cent	not available
MI	6.68 per cent	5.19 per cent	<0.001
Stroke	1.4 per cent	1.2 per cent	not available
Non-CV death	0.70 per cent	0.67 per cent	not available

The optimal dose of UFH has not been established, but a weight-adjusted regimen with frequent monitoring to maintain the activated partial thromboplastin time (aPTT) to 1.5–2 times the control is the most established regimen.

Recently, the trend has been towards an increased preference for low molecular weight heparins (LMWHs). Unfractionated heparin has a variable dose-response curve because it binds competitively to plasma proteins other than antithrombin. In addition, the risk of heparin-induced thrombocytopenia is higher with UFH than with antithrombin agents.<sup>9</sup>

LMWHs have significant advantages over UFH, such as the ease of subcutaneous administration and the avoidance of aPTT monitoring. Subcutaneous enoxaparin therapy was compared with UFH in the TIMI-11B trial,<sup>10</sup> where patients with ACS were compared for the outcomes of death, MI and urgent revascularisation. Mortality at eight days from all causes was 14.5 per cent for patients in the UFH group compared with 12.4 per cent in the enoxaparin group ( $P = 0.048$ ). These findings were similar in the ESSENCE trial,<sup>11</sup> where enoxaparin was found to be more effective than UFH at reducing the incidence of death, MI and recurrent angina.

In the FRISC-II trial, dalteparin and aspirin treatment was associated with a 6.2 per cent risk of death or MI in ACS patients after one month compared with 8.4 per cent with aspirin alone ( $P = 0.048$ ).<sup>12</sup> Aspirin, in addition to dalteparin or placebo therapy was continued for three months, after which time the difference in the rates of death, MI or revascularisation was statistically significant (29.1 per cent with dalteparin, 33.4 per cent with placebo;  $P = 0.031$ ).

Several trials, including the FRIC trial<sup>13</sup> compared different types of UFH and LMWH and have shown equivalence between the two strategies, making overall meta-analyses between UFH and LMWH comparable in clinical terms. However, the ease of administration and reliability of efficacy of LMWH can offset much of the cost differences between the two types of heparin.

**$\beta$ -Blockers** In the absence of contraindications (see Panel 1),  $\beta$ -blockers are considered to be the first line agents for stable and unstable angina<sup>14</sup> and have been shown to reduce the incidence of subsequent MI and recurrent ischaemia.

$\beta$ -Blockers act on the  $\beta_1$  (cardiac) and  $\beta_2$  (bronchial and smooth muscle) receptors. They selectively block the effects of nor-adrenaline and adrenaline on the  $\beta$ -receptors. This leads to:

- reduced cardiac output and venous return
- coronary vasodilation and enhanced coronary artery blood flow
- reduced myocardial oxygen demand due to reduced heart rate and blood pressure
- reduced force of ejection in systole

In patients with no concomitant diseases, the choice of  $\beta$ -blocker is less important. However, in patients with impaired left ventricular function, cardioselective  $\beta$ -blockers (bisoprolol, carvedilol, metoprolol) have clear evidence of benefit.<sup>15</sup>

Common side effects of  $\beta$ -blockers include fatigue or lethargy, masking of signs of hypoglycaemic attack, cold in the extremities of the body, bradycardia, heart block and impotence.

Sudden withdrawal of a  $\beta$ -blocker can cause angina to be exacerbated, since during treatment,  $\beta$ -receptors available for stimulation increase and are exposed when the agent is removed. Phased withdrawal allows for a gradual reduction in the number of these additional  $\beta$ -receptors.<sup>16</sup>

*Panel 1: Contraindications to the use of  $\beta$ -blockers*

- Asthma
- Chronic obstructive pulmonary disease (unless stable mild or moderate)
- Peripheral vascular disease (severe or Raynaud's)
- Cardiac conduction abnormalities (heart block)

Agents such as atenolol, bisoprolol, carvedilol and metoprolol are relatively selective for  $\beta_1$  receptors if given in low doses: that is, cardioselectivity decreases as the dose is increased. Bisoprolol is thought to be the most selective  $\beta$ -blocker.<sup>15</sup> No  $\beta$ -blocker is completely safe in patients at risk of asthma and severe chronic obstructive pulmonary disease, and should only be used under expert care and withdrawn if any exacerbation occurs.

**Calcium channel blockers** Calcium antagonists, on their own, have not been shown in randomised trials of ACS patients to have mortality benefits and therefore their use is mainly as an add-on agent to  $\beta$ -blockers for the reduction of ischaemic symptoms. These agents should not be used alone in patients with impaired left ventricular function where there are concerns of pro-arrhythmic risks.

There are two main groups of calcium channel blockers: dihydropyridines, including nifedipine and amlodipine, and non-dihydropyridines, including benzothiazepines (eg, diltiazem) and phenylalkylamines (eg, verapamil). There is an overlap in the mechanisms of action of these agents.

The main actions of the calcium channel blockers are vasodilation of the coronary and peripheral arterioles, reduction of myocardial contractility and depressed conduction of the sinoatrial and atrioventricular nodes.<sup>16</sup>

The short-acting nifedipine preparations have been shown to be associated with a 16 per cent increased risk of MI or recurrent angina by causing reflex tachycardia and increased oxygen demand in patients with unstable angina who are not receiving beta-blockers. A combination of nifedipine and  $\beta$ -blocker, however, is associated with a 20 per cent lower incidence of these events.<sup>17</sup>

The pharmacokinetics of the available agents vary between the classes and the sustained-release preparations or brands available. Changes in preparations for patients can lead to altered effectiveness and should be avoided.

**Nitrates** Nitrates are widely used in the management of angina. However, to date, evidence confirming their efficacy at reducing rates of cardiac events is lacking. Since nitrates are inexpensive and no longer under patent, trials assessing this issue may never be performed.

The major beneficial effects of glyceryl trinitrate (GTN) or other organic nitrates, such as isosorbide dinitrate or mononitrate, are reductions in pre-load and after-load. These result in a reduction in myocardial work and oxygen demand. Mononitrates enter the walls of veins and arteries, combine with sulphhydryl groups and form nitric oxide. Nitric oxide activates guanylate cyclase to produce cyclic guanosine

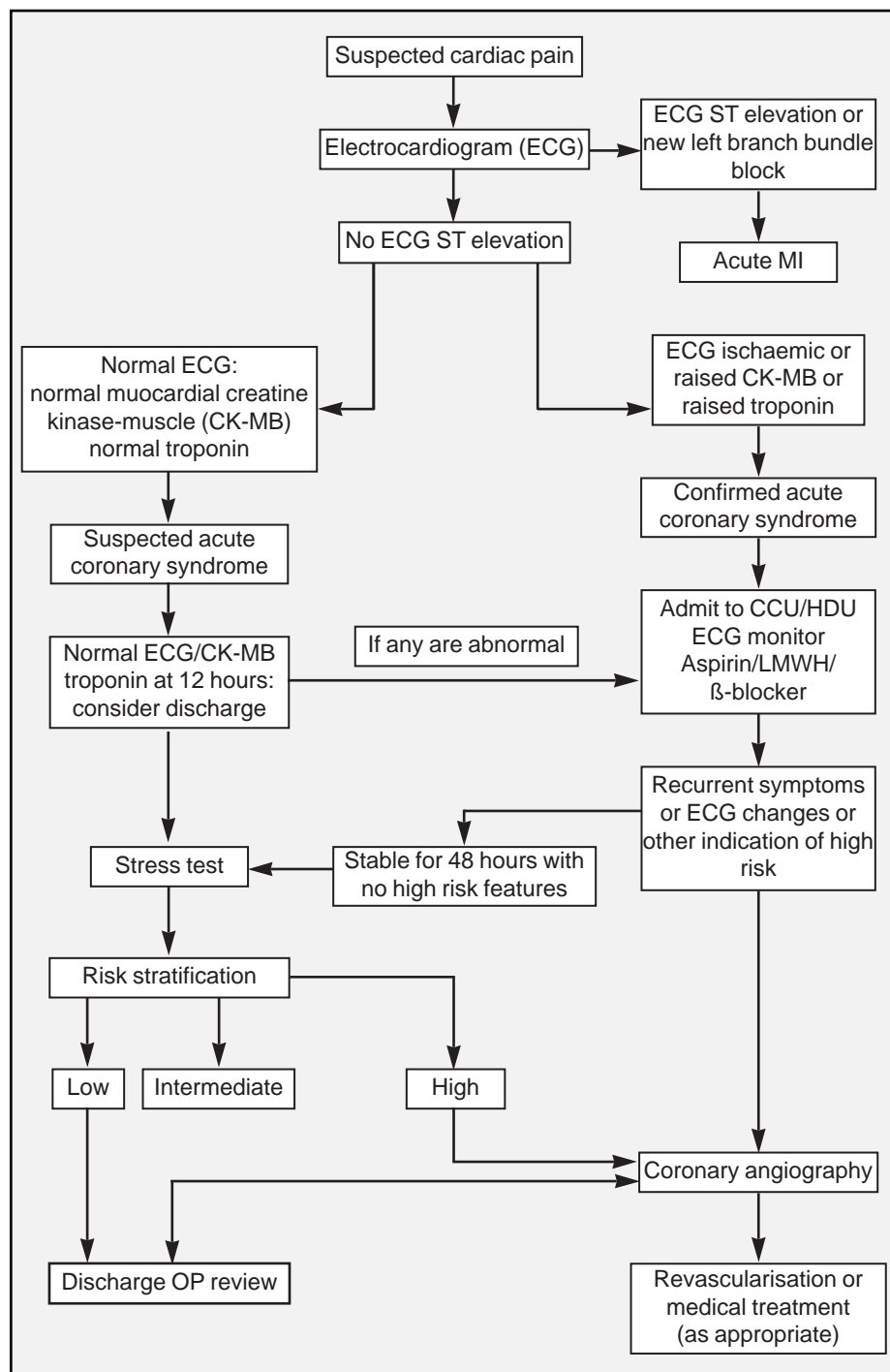


Figure 1: British guidelines on management of patients with ACS without ST elevation<sup>3</sup>

monophosphate, causing relaxation of vascular smooth muscles with maximal dilation of veins and some dilation of arteries. Decrease in intramural pressure allows better perfusion of the deeper layers of myocardial tissue.<sup>18,19</sup>

Nitrates have also been shown to have substantial antiplatelet effects.<sup>20</sup>

Organic nitrates can be administered via a number of routes or formulations. These include sublingual, buccal, oral, topical and intravenous infusion.

Sublingual GTN tablets and spray abort established anginal attacks and prevent the incidence of others.

Intravenous GTN should be used early in the treatment of ACS patients for the relief

of anginal symptoms. It is important that GTN infusions should be administered using giving sets that do not contain PVC (polyvinyl chloride). This is because GTN injection is incompatible with PVC: 40 to 80 per cent of the final dilution for infusion is absorbed by the PVC tubing and intravenous giving sets.

Long acting nitrates are more prone to tolerance. The mechanism responsible for this remains poorly understood, but probably involves intrinsic abnormalities of the vasculature, including enhanced vascular superoxide and endothelin production. Mononitrates need to be given in the morning and at midday so that a nitrate-free interval is achieved.

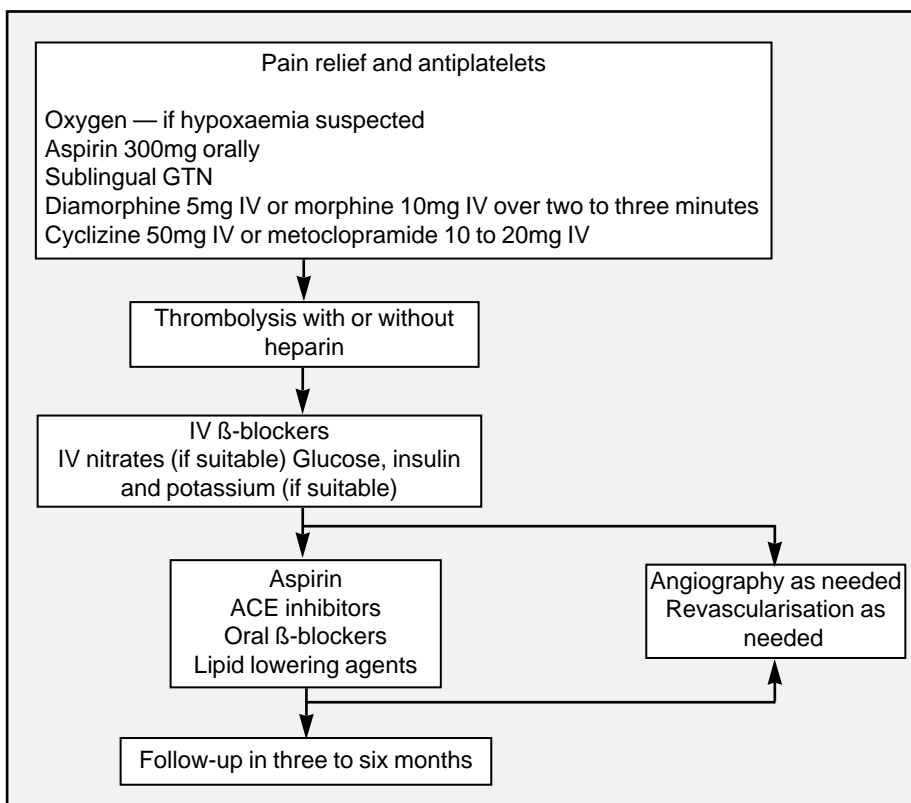


Figure 2: Treatment guidelines for patients with acute MI (immediate management)

Dinitrates are usually given three times a day.

Recent studies have suggested that the supplemental use of antioxidants, such as vitamin C, can reduce nitrate tolerance.<sup>21</sup>

Tachycardia, dizziness, flushing and headaches (intolerable in about 25 per cent of patients) are some of the side effects of nitrates.

**Potassium channel activators** Nicorandil is a nicotinamide nitrate which activates adenosine triphosphate-dependent channels and increases the efflux of potassium ions, dilating large coronary arteries and reducing both the pre-load and after-load. Nicorandil has similar efficacy to other anti-anginal drugs (nitrates and calcium channel blockers) in controlling symptoms, but as yet there is limited evidence about its efficacy, particularly in combination with other agents. However, when added to maximal therapy with other anti-anginal agents in refractory cases, it may produce additional benefit. This is under evaluation in a large European trial.<sup>22</sup>

#### Glycoprotein IIb/IIIa antagonists

Unlike antiplatelet agents that target only one of many individual pathways involved in platelet aggregation, glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors inhibit the final common pathway involved in platelet aggregation. Three intravenous agents are used in clinical practice: a murine-human chimeric antibody (eg, abciximab), a synthetic peptide form (eptifibatide) and a synthetic non-peptide form (tirofiban). The

last two agents are much smaller “designer” molecules. All three agents have a rapid onset of antiplatelet activity and provide over 80 per cent platelet inhibition. The reversal of platelet inhibition after discontinuation of infusion is more rapid with eptifibatide and tirofiban (two to four hours) than abciximab (three to 10 days).<sup>23</sup>

#### Unstable angina or non-ST elevation MI

The use of intravenous GP IIb/IIIa inhibitors in ACS patients has been extensively investigated. Studies have consistently shown a reduction in the 30-day risk of the composite end point of death, myocardial infarction or the need for repeated revascularisation by 22 to 56 per cent when administered with unfractionated heparin and aspirin.<sup>24-27</sup> However, the trials have not been large enough to demonstrate a significant mortality benefit. The third part of this month’s special feature gives an overview of the results of the clinical trials.

Figure 1 (p127) shows current guidelines on the management of patients with ACS without ST elevation.

### MYOCARDIAL INFARCTION

Approximately 300,000 people in the UK suffer an MI each year. The National Service Framework for Coronary Heart Disease (standard six) states that “people thought to be suffering from a heart attack should be assessed professionally and, if indicated, receive aspirin. Thrombolysis should be given within 60 minutes of calling for professional help.”<sup>21</sup>

At least 300mg of aspirin should be given at the onset of MI (see Figure 2). This reduces the risk of death by about 25 per cent. Thrombolytics, in addition to aspirin, can further reduce this risk by 20 to 25 per cent, with the largest benefit seen when given early. Aspirin, β-blockers and cholesterol-lowering therapies reduce the risk of further MI or cardiovascular death.

ACE inhibitors are indicated for high-risk patients or those with left ventricular failure.

During the acute phase of an MI, glucose levels must be meticulously controlled in patients with diabetes.

The NSF has set a target that by April, 2002, 75 per cent of eligible patients receive thrombolysis within 30 minutes of hospital arrival and that 80 to 90 per cent of patients are discharged from hospital after an MI taking aspirin, β-blockers and statins.

**Aspirin and clopidogrel** For every 1,000 MI patients treated with aspirin within the first 24 hours of the onset of symptoms, 40 vascular events in the first month and 40 more in the next two years can be prevented.

The ISIS-2 trial<sup>28</sup> clearly established the large benefits of aspirin therapy in acute MI: aspirin alone reduced 35-day mortality by 23 per cent and when combined with streptokinase, this mortality was reduced by 42 per cent. Long-term aspirin reduces the risk of vascular mortality by 13 per cent, non-fatal MI by 31 per cent, non-fatal stroke by 42 per cent and all vascular events by 25 per cent.

No definitive data have been produced for the optimal dose but lower doses are associated with less bleeding.<sup>29</sup> A maintenance dose of 75mg to 325mg daily has been suggested.<sup>30</sup>

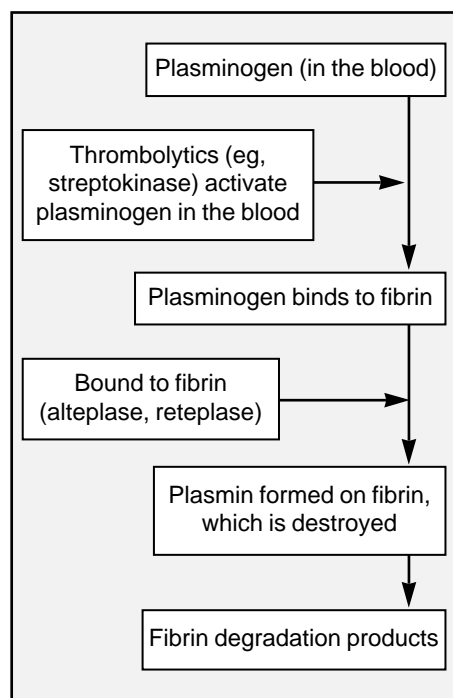


Figure 3: Mechanism of action of thrombolytics

Table 2: ACC/AHA guidelines for use of heparin in acute MI<sup>38</sup>

Patients treated with:	Unfractionated heparin	LMWH (enoxaparin)
Alteplase	IV if ST elevation	Pending data
Streptokinase	IV if high risk for systemic emboli SC if not high risk	Pending data
No thrombolytic (non-ST elevation)	IV if high risk for systemic emboli SC if not high risk	SC

Clopidogrel is a good alternative for patients allergic to, or unable to take aspirin. Ticlopidine has an increased risk of neutropenia associated with it. The CAPRIE trial<sup>31</sup> compared the effects of clopidogrel 75mg daily with those of aspirin 325mg daily, in patients with atherosclerotic cardiovascular disease. The annual event rate of myocardial infarction was 5.03 per cent with clopidogrel and 4.84 per cent with aspirin ( $P = 0.66$ ). Long-term therapy with clopidogrel was more effective than aspirin in reducing the combined risk of myocardial infarction and vascular death, especially in patients with peripheral artery disease. Clopidogrel was also shown to be as safe and as well tolerated as aspirin.

**Thrombolytics (fibrinolytics)** The mechanism of action of thrombolytics is illustrated in Figure 3 (p128).

The re-establishment of coronary blood flow within 90 minutes in an artery threatened by thrombotic occlusion correlates with a substantial mortality reduction at 30 days.<sup>29</sup> For every thousand MI patients presenting within an hour of chest pain onset, prompt therapy with thrombolysis prevents at least 39 and up to 65 deaths compared with 20 deaths for those treated within seven to 12 hours. Results from the MITI trial, where alteplase and aspirin were started either at home or in hospital as soon as possible, showed that reperfusion within 70 minutes reduced the death rate from 8.7 to 1.2 per cent as well as reducing infarct size.<sup>32</sup>

A number of trials have been carried out comparing alteplase (tPA) to streptokinase.<sup>33-36</sup> These have concluded that the choice of agent is less important than the time between onset of symptoms and administration of agent. Alteplase appears to exhibit greater specificity for clot fibrin than does streptokinase, which has a greater propensity to induce a systemic lytic state. This has not, however, been shown to have a significant influence on the overall mortality rates of patients taking the two agents. Economic considerations may therefore weigh heavily in favour of streptokinase.

Antibody response to streptokinase develops after four days of administration and may persist for up to 12 months.<sup>37</sup> This may result in resistance to streptokinase readministration. During this time, another infusion of streptokinase may be ineffective and an alternative such as alteplase or reteplase should be given.<sup>38,39</sup> Patients with high antibody titres given streptokinase experience more adverse reactions, for example, hypotension and serum sickness.

**Heparins** UFH has an established place in the treatment of MI when thrombolysis is given to a patient with ST-elevation MI.<sup>29,30,40</sup> The American College of Cardiology/American Heart Association (ACC/AHA) guidelines<sup>40</sup> recommend that intravenous UFH should be given to patients undergoing reperfusion therapy with alteplase (Table 2). It should be used for the initial 24 to 48 hours to prevent further thrombin production and to reduce the risk

of reocclusion. The dose should be adjusted to keep the aPTT to between 60 and 80 seconds. The duration of therapy is uncertain; in patients with larger anterior infarctions and patients with atrial fibrillation who are at high risk of embolism, intravenous administration should be for about five to seven days, or until they are ambulatory.

## Panel 2: Profile of ACE inhibitors

### Commonly used agents

Captopril  
Lisinopril  
Ramipril  
Trandolapril

### Actions

Vasodilation  
Reduction of ventricular stress  
Reduction of LV enlargement  
Reduction of blood pressure

### Side effects

Cough (common, 6 to 14 per cent)  
Hypotension  
Deterioration of renal function and renal failure  
Angioedema  
Hyperkalaemia  
Skin reactions

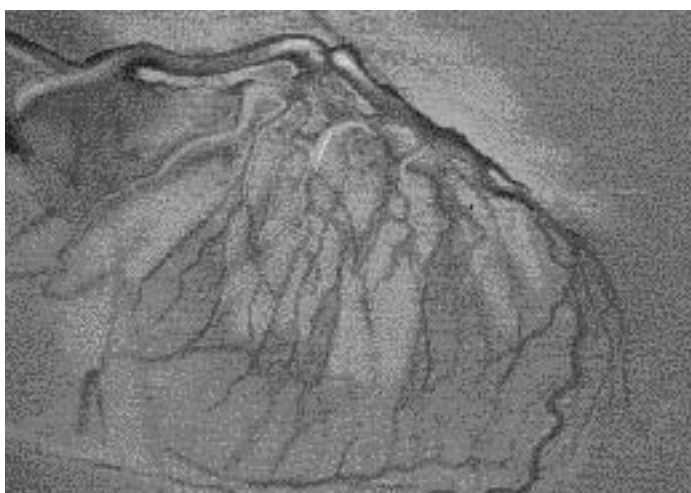
### Contraindications

Severe renal failure  
Bilateral renal artery stenosis  
Pre-existing hypotension  
Severe aortic stenosis  
Obstructive cardiomyopathy  
Pregnancy

Heparin is administered with streptokinase if the patient is at high risk of systemic emboli (large anterior MI, atrial fibrillation, previous emboli or known intravenous thrombus).

Data for the use of direct thrombin inhibitors in the treatment of acute MI are currently limited. Lepirudin was compared to subcutaneous UFH in patients treated with streptokinase after ST-elevation MI in the HIT-4 trial.<sup>41</sup> It did not significantly improve the restoration of blood flow in the infarcted vessel but it did reduce ST segment elevation at 90 minutes (not significant at 180 minutes). In the HERO trial,<sup>42</sup> the use of bivalirudin was more effective at producing early patency than UFH in patients receiving streptokinase for acute MI, without increasing the risk of bleeding. However, this did not translate into significant clinical benefits and more evidence is needed before the use of these agents becomes routine.

**β-Blockers** The ACC/AHA guidelines recommend that β-blockers should be administered to all patients in whom they are not contraindicated within a few days of the MI if not already administered in the acute phase, and should be continued indefinitely.<sup>40</sup> β-Blockers have been shown to prolong life following MI by reducing the risk of reinfarction, infarct size, cardiac rupture, supraventricular and ventricular arrhythmias, and sudden death, when insti-



Coloured angiogram showing a narrowed coronary artery, showing as the pinched part of the artery at the top

tuted within hours to several weeks of an infarction and continued for at least three years, perhaps indefinitely.

The ISIS-I study showed that administration of an intravenous  $\beta$ -blocker in acute MI can prevent six deaths over the next seven days for every thousand patients treated.<sup>43</sup> A cardioselective agent should be used long term with a once-daily dosing regimen.<sup>16</sup> It is not known if the protective effect of  $\beta$ -blockers continues throughout life, but withdrawal can cause rebound worsening of myocardial ischaemia.

$\beta$ -Blockade added to angiotension converting enzyme (ACE) inhibitor therapy can also reduce total mortality and progression to severe heart failure. The effects are additive and reduce post-infarction mortality in patients with reduced ejection fractions, therefore producing a 40 per cent reduction in mortality.<sup>44-46</sup>

**ACE inhibitors** ACE inhibitors act on the renin-angiotensin system to inhibit vasoconstriction as well as affecting bradykinin breakdown to produce vasodilatory nitric oxide and prostacyclin.<sup>47</sup> By reducing preload and afterload, they reduce ventricular stress and enlargement (see Panel 2).

After an MI, the degree of ventricular dilatation is inversely proportional to survival: that is, the greater the degree of ventricular enlargement, the worse the prognosis. ACC/AHA guidelines recommend the use of ACE inhibitors within the first 24 hours of a suspected acute MI with ST segment elevation or heart failure, in the absence of hypotension, or any other contraindication.<sup>40</sup>

ACE inhibitors attenuate left ventricular remodelling and reduce the risk of subsequent MIs (Figure 4). Although they should be started within 24 hours of the MI, beneficial effects are still seen if initiated within 7

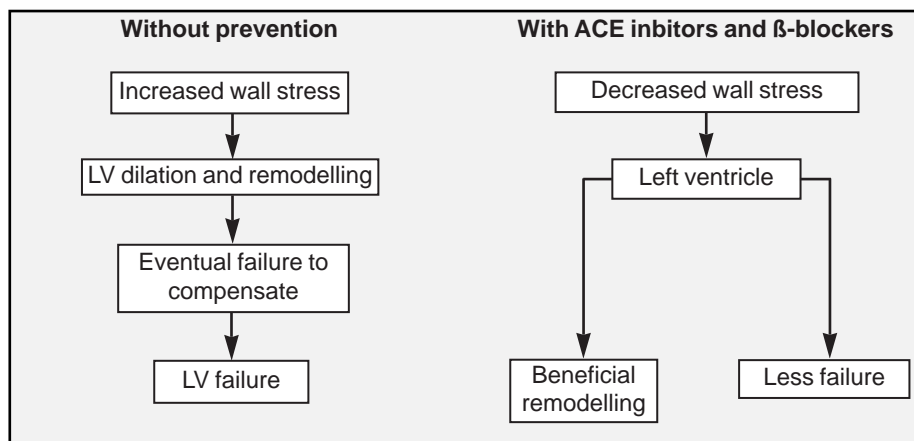


Figure 4: Effects of ACE inhibitors and  $\beta$ -blockers on the left ventricle

days.<sup>47</sup>

A number of trials have demonstrated the usefulness of and improved survival with ACE inhibitor therapy post-MI, especially in patients with left ventricular dysfunction. Therapy should be continued long term for all high-risk patients.

The findings of the HOPE trial<sup>48</sup> indicate that ramipril substantially lowers the risk of death, heart attack, stroke, coronary revascularisation, heart failure and complications related to diabetes mellitus in high-risk patients. There are two large, ongoing trials similar to the HOPE study: PEACE (Prevention of Events with ACE inhibition study) and EUROPA (European trial of reduction of cardiac events with perindopril in stable coronary artery disease). These should answer the question of whether all post-MI patients with coronary artery disease, regardless of LV function, will benefit from ACE inhibitors.

**Insulin** The concept of using glucose-insulin-potassium (GIK) infusions after acute MI has been a topic of discussion since 1962.<sup>49</sup> High concentrations of free fatty acids (FFAs) can increase myocardial oxygen demand and depress myocardial mechanical activity and contraction. FFAs affect calcium homeostasis, which in turn leads to electrical instability and arrhythmias. Insulin lowers plasma FFA concentrations by inhibition of lipolysis.

GIK infusions may also:

- improve myocardial performance with lower oxygen consumption
- protect ischaemic coronary vasculature
- restore intracellular potassium
- promote wound healing and reduce tissue oedema
- facilitate spontaneous thrombolysis

GIK was initially advocated for the treatment of acute MI as a polarising agent to promote electrical stability and provide metabolic support. A mixture of glucose 30 per cent, 50 units of insulin and 80mmol of potassium in one litre given at a rate of

1.5ml per kg per hour was demonstrated to suppress sufficiently the plasma concentrations of harmful free fatty acids.<sup>50</sup> Trial data for GIK are still relatively limited.

The ECLA study<sup>51</sup> compared high dose GIK infusions to low dose GIK infusions and usual care. The high dose (25 per cent glucose, 50 units of insulin and 80mmol potassium in 1 litre given at a rate of 1.5ml per kg per hour over 24 hours) was associated with a significant reduction in the composite end point of death, non-fatal severe congestive heart failure and non-fatal ventricular fibrillation. A randomised, placebo-controlled trial of GIK in 620 diabetic patients with acute MI (DIGAMI study)<sup>52</sup> used subcutaneous insulin four times a day after the initial GIK infusion. After a mean follow-up of 3.4 years, fewer deaths (33 per cent) occurred in the GIK group compared with 44 per cent in the placebo group. Seventy-five per cent of the infusion group and less than 50 per cent of the controls were still using insulin after 12 months, with continuing improvement in glycaemic control. The data currently available support the routine use of modified GIK for diabetic patients but data are still awaited to establish whether all MI patients would benefit.

**Magnesium** The role of magnesium in the treatment of MI is uncertain. The LIMIT-2 study<sup>53</sup> suggested the benefits of intravenous magnesium given before thrombolysis, but these effects were not seen in the much larger ISIS-4 study.<sup>54</sup> Therefore, intravenous magnesium is not currently used routinely in the treatment of MI, but may be useful in patients with documented deficiencies of magnesium, especially if they were receiving diuretics before the onset of the MI.

**Statins** Large, prospective trials have established that cholesterol reductions in patients at only moderate risk of coronary artery disease, decrease future coronary events.<sup>55</sup>

In England, only 30 per cent of patients with coronary heart disease and raised serum lipids and less than 4 per cent of patients eligible for primary prevention are undergoing lipid-lowering therapy. Of

those that are undergoing therapy, less than 50 per cent have achieved their target cholesterol concentrations.

Statins (HMG-CoA reductase inhibitors) act by decreasing hepatic cholesterol synthesis due to inhibition of HMG-CoA reductase. They are highly effective in reducing total cholesterol and LDL cholesterol as well as modestly increasing HDL cholesterol.

The absolute coronary heart disease risk can be estimated by weighting and collating the influence of all major risk factors using an epidemiology-derived risk function. The National Service Framework for Coronary Heart Disease<sup>1</sup> states that the following methods are appropriate for risk stratification:

- Sheffield tables<sup>56</sup>
- coloured charts,<sup>57</sup> for example, those of the European coronary risk score, New Zealand risk assessment tool and Joint British Societies coronary risk prevention<sup>58</sup>

However, these methods are based on the Framingham risk equation which was carried out in high-risk, middle-aged, largely white North Americans. It therefore does not accurately predict the risk for other populations, such as British Asians or patients with strong familial histories of premature coronary heart disease.

The NSF on coronary heart disease states that statins should be given to lower serum cholesterol concentrations to either below 5mmol per litre (LDL cholesterol to below 3mmol per litre) or by 30 per cent (whichever is greater). The guidelines are unclear as to whether statins should be started immediately or on discharge. In practice, however, statins should be started on admission as evidence shows that prescription rates decrease following discharge.<sup>2</sup>

Pravastatin and simvastatin have long-term safety and efficacy data and are currently licensed for secondary prevention of coronary heart disease. The dose required to lower LDL-cholesterol varies between the drugs, although atorvastatin appears to be the most effective, followed by simvastatin, cerivastatin, pravastatin and fluvastatin in that order.<sup>59</sup> Atorvastatin and simvastatin have similar effects on lowering triglycerides.

Currently, simvastatin or pravastatin should be used as routine first line therapy for the prevention of CHD events, on the basis of long-term clinical outcome data.

## CONCLUSION

Numerous treatment options for patients with unstable angina or myocardial infarction are available and effective. However, prescribing of these agents is sub-optimal.<sup>2</sup> In post-MI patients, 85 per

cent were prescribed an anti-platelet therapy, 72.3 per cent  $\beta$ -blockers, 50.6 per cent ACE inhibitors and 58.6 per cent statins. Results from the recent EUROASPIRE II study<sup>60</sup> showed that only 62.9 per cent of patients with high cholesterol were on lipid lowering therapy and of these only 41 per cent had reached target cholesterol levels. Rates of prescription of other agents barely changed compared with those seen in EUROASPIRE I performed five years earlier. The challenge therefore remains to collate and summarise the evidence, create up-to-date and clear guidelines and finally to implement these guidelines fully, to maximise the benefit to patients at high risk of MI.

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