

# Ischaemic Heart Disease/Chest Pain

## Part 1: Acute chest pain

**Author:** Dr John Hester (former Top End DMO)

**Topic Reviewers:** Dr Steve Brady (ASH); Central Australian DMOs; Kenna Bistani (RAN, Pine Creek); Monica Ostigh (RAN, Jabiru); Angela Peermen (RAN, Oenpelli Clinic); Kaz Knudsen (RAN, WA); Patrick and Anne Cashman (RANs, Mt Liebig Clinic); Dy Kelaart (RAN, Yuendumu Clinic)

Cardiovascular disease is Australia's largest health problem. It kills more people than any other disease and generates enormous costs for the Australian health care system. The major types of cardiovascular disease are ischaemic heart disease (IHD), cerebrovascular accident (CVA), peripheral vascular disease (PVD) and congestive heart failure (CHF). Rheumatic fever and rheumatic heart disease are also very important and are encountered frequently in the Aboriginal and Torres Strait Islander peoples.

IHD results in a heavy physical and emotional burden upon individuals and families. In 1996 it accounted for 13% of the total disease burden in the country, 19% of premature mortality and 5% of years of equivalent 'healthy' life lost through disease, impairment or disability.<sup>1</sup>

In 1998–99 there were 437,717 hospitalisations in Australia where cardiovascular disease was the principal diagnosis (7% of all hospitalisations). Of these, IHD accounted for 158,131 of them. Acute myocardial infarction then accounted for 33,908 of the 158,131 figure. Further sobering information is that, during the same time, there was a total of 27,825 deaths from IHD, both in and out of hospital.<sup>1</sup>

Trends in the rate of fatal and non-fatal myocardial infarction among males and females aged 35–64 years of age have been monitored in Newcastle (NSW) and Perth (WA) as part of the World Health Organization's multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project. Analysis of the data reveals that the rates of non-fatal heart attack have fallen by between 2.5% and 3.7% per year during the period 1984–93. Similarly IHD death rates have also declined by 4.3% per year among males and 4.1% per year among females for the period 1987–98. Such declines have resulted in a total decline of 39% among males and 38% among females during this 12 year period.

However, the above figures are for all Australians. Deaths from IHD were twice as high among Indigenous Australians as among non-Indigenous Australians in 1996–98. In fact, the ratio increases to six to eight times for those in the 25–64 age group.<sup>1</sup> IHD is a major health issue in Indigenous communities and the appropriate treatment of ischaemic chest pain is vital.

### Definition

According to the American College of Cardiology (ACC) and the American Heart Association (AHA), ischaemic heart pain is defined as chest discomfort that is:

- usually in the centre of the chest
- can feel like uncomfortable pressure, squeezing or fullness
- can involve one or both arms, the back, the neck and the jaw
- can be associated with dyspnoea, sweating, nausea or light-headedness<sup>2</sup>.

Such a situation needs an immediate response due to the possibility of myocardial infarction. As a preliminary step, the National Heart Foundation of Australia (NHFA), The Cardiac Society of Australia and New Zealand (CSANZ), the ACC and the AHA all stress prompt presentation to a medical service for review. However, especially in Australian Indigenous communities, this may be a problem. According to Ong & Weeramanthri<sup>3</sup> the foremost problem is a person presenting to the emergency department (ED) of a hospital. In both urban and rural areas Indigenous patients (I) presented significantly later than non-Indigenous patients (N/I) (10 hrs 00 mins vs 3 hrs 26 mins).

However, if only rural Indigenous patients are considered, no statistically significant delay can be found when comparisons are made with rural non-Indigenous patients for time to primary presentation, ED presentation, first ECG or time of thrombolytic therapy. A caveat on these statements is that many Indigenous patients cannot (or may not) accurately state when their pain began. As such there may be a significant delay in Indigenous presentation to the health clinic, but no study has yet confirmed this fact.

Unfortunately, no additional statistical comparison between rural and urban people was made in the above-mentioned study.<sup>3</sup> However, the raw figures indicate that the delay in presentation to an ED (10 hrs 23 mins vs 6 hrs 00 mins (I) & 7 hrs 48 mins vs 2 hrs 48 mins (N/I)) and the delay in provision of thrombolytic therapy (7 hrs 45 mins vs 2 hrs 45 mins (I) & 6 hrs 2 mins vs 3 hrs 3 mins (N/I)) are definitely areas that need improvement. Statistical significance regarding the figures in this study would not be likely, but any delay greater than six hours compromises the effectiveness of a thrombolytic agent.<sup>4</sup> Improving patient knowledge regarding when one should go to the clinic will have its benefits. However, it is the provision of therapy earlier that will have the greatest benefit.

The management of ischaemic heart pain is an evolving process. Initial treatment with rest, oxygen, aspirin and nitrates has been endorsed by the NHFA and the CSANZ in their document Management of Unstable Angina Guidelines 2000<sup>5</sup> and the ACC/AHA document Guidelines for the management of patients with Acute Myocardial Infarction: Executive Summary and Recommendations 1999 Update.<sup>2</sup>

However, it is the utility of other agents that is generating much interest. The pathophysiology of the acute coronary syndromes essentially involves thrombus critically obstructing blood flow down a coronary blood vessel. Thrombus formation is secondary to plaque rupture. Plaque is the material lining such vessels. It contains extracellular and intracellular lipid, collagen, connective tissue matrix proteins and inflammatory cells. Foam cells are also present in plaque and produce a large number of cytokines and inflammatory mediators. This inflammation is in response to modification (probably oxidation) of low-density lipoproteins in the subendothelial space and to local monocyte adhesion and migration. The basic sequence of events is that the collagen cap overlaying the plaque is infiltrated by inflammatory cells and therefore broken down. (Rupture of a plaque is most likely if it is eccentrically shaped and has a shallow, lipid-rich centre.) Exposure of plaque contents or the development of eddy currents then activates various arms of the coagulation pathway.

Unstable angina pectoris (UAP), non-ST elevation myocardial infarction (non-STEMI) and ST elevation myocardial infarction (STEMI) comprise the acute coronary syndromes. As such all are part of a continuum of escalating myocardial damage. Whether one has the more mild UAP or the more severe STEMI relates to the extent of platelet aggregation, vasospasm and distal platelet micro-embolization following plaque rupture. The quality of collateral flow to jeopardised myocardium also determines how much damage is done. Currently it is thought that patients with UAP or non-STEMI have a platelet-rich non-occlusive thrombus on a fissured or ruptured atherosclerotic plaque, whereas those with STEMI usually have occlusive thrombus principally made up of fibrin containing trapped erythrocytes.<sup>6</sup>

## Evidence for individual medical therapies

### Oxygen

Supplemental oxygen is usually given to all patients with an acute coronary syndrome. This is especially indicated if the arterial saturation is less than 95%. Although there is no data on morbidity or mortality reduction, experimental results suggest that ST elevation and ischaemic injury are reduced.<sup>7,8</sup> The reason for its use is that even uncomplicated patients can initially be somewhat hypoxic due to ventilation-perfusion mismatch and the presence of extra pulmonary fluid.<sup>9</sup>

### Aspirin

Aspirin irreversibly inhibits cyclo-oxygenase, preventing platelet synthesis of thromboxane A<sub>2</sub>, a potent vasoconstrictor and stimulator of platelet aggregation. The value of this anti-inflammatory action, which acts to decrease the amount of plaque rupture and its sequelae, has been clearly proven by several studies.<sup>7,10</sup> It also reduces the rate of death or completed myocardial infarction by about 50%.<sup>11</sup> Unfortunately up to a third of patients are non-responder, but as a general rule aspirin should be given to all patients unless there is an established allergy.

### ADP-receptor antagonists

Clopidogrel is an ADP-receptor antagonist and is an option for those intolerant of aspirin. Its chronic use has been evaluated in patients with UAP in the CURE Trial.<sup>12</sup> It has none of the neutropenia associated with the ticlopidine (no longer used) and less gastrointestinal bleeding than that associated with aspirin. However, its high cost precludes it from replacing aspirin at the moment.

*[Editor: Dr Steve Brady adds; It is used in combination with aspirin in high-risk patients (CURE Trial).]*

### Nitrates

All the nitrates have systemic and coronary effects. The systemic effects include venous pooling, which reduces left ventricular preload and end-diastolic pressure, as well as causing a slight decrease in afterload. The coronary effects include vasodilatation of normal and atherosclerotic coronary arteries, an increase in coronary artery collateral flow and redistribution of flow from subepicardial to subendocardial regions. As such they are ideally suited to managing acute coronary syndromes.

There is both clinical and experimental evidence that nitrate therapy reduces infarct size, improves regional wall motion and may prevent the left ventricular remodelling that occurs after a large infarct.<sup>13,14</sup> Combined data from randomized controlled trials of nitrate use in acute myocardial infarction have also demonstrated a small but statistically significant reduction in mortality.<sup>15</sup> Nitrate therapy is contra-indicated when the systolic blood pressure is less than 90mmHg or when the heart rate is less than 60 beats/min. It is important to note that nitrates should be used with extreme caution in patients with suspected right ventricular infarction. These patients depend especially on ventricular preload to maintain cardiac output and so can be made very hypotensive if nitrates are given.

### β-blockers

β<sub>1</sub> receptor blockade in the heart results in decreased cardiac work and myocardial oxygen demand. Several clinical trials have demonstrated a reduction in recurrent ischaemia, re-infarction and mortality when they have been used in the first hours of a myocardial infarct.<sup>16,17</sup> However, there are relative contra-indications to the use of β-blockers and so their use in acute coronary syndromes is not automatic. These relative contra-indications are a heart rate <60 beats/min, systolic blood pressure <90mmHg, prolonged first degree or higher atrio-ventricular block, severe chronic obstructive airways disease, asthma, severe peripheral vascular disease or diabetes mellitus.

## Calcium channel blockers

Calcium channel blockers have not been shown to decrease mortality in acute myocardial infarction and may even be harmful to certain patient subsets.<sup>18</sup> A  $\beta$ -blocker is a more appropriate option for most patients. However, if  $\beta$ -blockers are contra-indicated and if there is no evidence of heart failure or heart block, a heart-rate-slowing calcium channel blocker (diltiazem or verapamil) may be used.<sup>5</sup>

## Intervention

The primary goal of treatment in acute coronary syndromes is reperfusion of the infarct-related artery in as short a time as possible. Swift reperfusion has been demonstrated to decrease mortality<sup>19,20,21,22,23</sup> and to preserve left ventricular function.<sup>24</sup> Present strategies for acute reperfusion include the use of thrombolytic agents and a variety of catheter-based interventions.

Thrombolytic therapy is the most widely used method to achieve acute reperfusion, and when given within the first 12 hours from the onset of symptoms reduces mortality by approximately 30%.<sup>19,20,21,22,23</sup> Further breakdown of the first 6 hours shows a relative mortality reduction of 30% between 0 and 1 hour, 25% between 2 and 3 hours and 18% between 4 and 6 hours. Data regarding use after 12 hours is limited and not encouraging, so the current recommendation remains at use before 12 hours.

Having established that thrombolytics can save lives, the GUSTO IIB Trial<sup>25</sup> attempted to establish which is the superior treatment: coronary angioplasty or thrombolytic therapy. Figures from the trial indicated that angioplasty was more successful than thrombolysis. However Practice Registers in the USA suggest that outside of clinical trials, angioplasty is equal to and not necessarily better than thrombolytic therapy.

These facts then behave us to seek the most effective and available treatment for persons in remote areas who require treatment for their evolving myocardial infarct. Portable cardiac catheter theatres or cardiovascular surgery units are not a possibility in rural and remote Australia. Furthermore, any trained healthcare worker who can give an intravenous antibiotic can give a thrombolytic agent. Hence, thrombolytic therapy is the only sound and ethically responsible treatment for those who meet the indications for such intervention.

## Indications for thrombolysis:<sup>2,4,26</sup>

1. A >20 minute history of chest pain fitting ACC/AHA criteria
2. ST elevation in two or more contiguous leads (>1mm in limb leads or >2mm in chest leads) or new Bundle Branch Block formation
3. Time to therapy is <12 hours

## Contra-indications for thrombolysis

Much debate exists in the literature regarding which contra-indications are absolute and which ones are relative. Only discussion with a relevant specialist at the time of a patient's presentation will clarify the situation.

Current contra-indications are:<sup>4</sup>

- Recent (<10 days) prolonged and vigorous external heart massage
- Known haemorrhagic diathesis
- Patients with current concomitant therapy with oral anticoagulants e.g. Warfarin
- Intracranial neoplasm, arteriovenous malformation or aneurysm
- Neoplasm with increased bleeding risk
- History of cerebrovascular accident
- Severe uncontrolled hypertension (>160mmHg Systolic and >100mmHg Diastolic) (Severe hypertension on presentation can be treated with sub-lingual or oral nitrates.)
- Active peptic ulceration

- Portal hypertension (oesophageal varices)
- Severe liver or renal dysfunction
- Acute pancreatitis, pericarditis, bacterial endocarditis
- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions
- Within three months of severe bleeding, major trauma or major surgery (e.g. coronary artery bypass graft, intracranial or intraspinal surgery or trauma), obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels.

Intracranial haemorrhage is the most feared outcome in all studies. The incidence of such a haemorrhage following a thrombolytic agent increases with age, particularly in patients with a systolic BP >170, diastolic BP >95 or both, or if recombinant plasminogen activator r-PA has been used.<sup>27</sup>

## Thrombolytics

There are currently three fibrinolytic agents available in Australia: Streptokinase; tissue plasminogen activator t-PA (Alteplase); and recombinant plasminogen activator r-PA (Retepase).

### Streptokinase

Streptokinase was the first available fibrinolytic agent and has been shown to reduce mortality in acute myocardial infarction. It saves approximately 25 lives per thousand patients treated<sup>21</sup> and is associated with an average risk of non-fatal intracerebral bleeding of about 3/1000. Streptokinase decreases infarct mortality by 25% and is more efficacious the earlier that it is given. Usually it is given as an infusion of 1.5 million units intravenously over 60 minutes. Of particular importance is the fact that Streptokinase is a naturally occurring product of the streptococcus bacteria and will induce antibody production.

Clinical problems related to Streptokinase include:

1. Hypotension due to vasodilatation. This may occur in up to a third of patients and is partly dependent upon the speed of the infusion. Slowing the infusion or giving intravenous fluids corrects the situation.
2. Rash or hives often occur. Also true anaphylaxis is always a possibility.
3. Antibodies develop within five days, peak at 14 days and can still be at a level that will neutralize a standard dose of Streptokinase up to four years after the initial administration.<sup>28</sup>
4. Of major importance in Indigenous communities is the fact that a high rate of exposure to streptococcal infections will lead a large number of people having antibodies. The levels of anti-streptokinase IgG and streptokinase resistance in a subset of Aboriginal and non-Aboriginal persons in the Northern Territory has been investigated by Urdahl et al.<sup>29</sup> This study demonstrated that Aboriginal adults exhibited levels of anti-streptokinase IgG and streptokinase resistance that respectively were almost 20 and 15 times greater than the values for non-Aboriginal adults. Furthermore, at any one time at least 23% of Aboriginal adults had sufficiently high enough levels of streptokinase resistance to neutralize a standard 1.5 million unit dose of Streptokinase. Thus Streptokinase is not recommended for use in Indigenous communities.

### Tissue plasminogen activator

t-PA is a recombinant form of tissue plasminogen. It has been shown to achieve improved re-perfusion rates compared to Streptokinase. This then results in an extra 10 lives per thousand patients treated being saved.<sup>30</sup> However, it is also associated with a slightly higher rate of intracranial haemorrhage producing one extra disabling stroke per thousand patients treated.<sup>30</sup> It is also very expensive. It is given as a 100mg dose infusion over 90 minutes.

### Recombinant plasminogen activator

r-PA is a variant of t-PA produced by further genetic engineering. Basically it is non-glycosylated and lacks three N-terminal domains in comparison to t-PA. As a result of these structural changes it has a longer half-life (18 mins) compared to t-PA (four minutes). Also it has fibrin specificity

without fibrin binding. This characteristic allows superior penetration into a thrombus and slightly faster thrombolysis compared to t-PA. (In contrast t-PA binds very tightly to fibrin at the surface of a thrombus.) The main advantage of r-PA is that it can be given as a double bolus of 10 units 30 minutes apart. On the down side, it has been demonstrated that the incidence of haemorrhagic strokes is increased with the use of r-PA, especially in those over the age of 75 years or hypertensive.

### **Choice of agent**

For most of Australia Streptokinase is the thrombolytic agent of first choice. However, the widespread occurrence of streptococcal infection in Indigenous populations, the need for possible repeat treatments in the future and its simpler bolus delivery method make r-PA the preferred option for Indigenous people.

*[Editor: Dr Steve Brady (ASH) adds that Tenectaplastase (Tnk-tPA) is another thrombolytic agent that may become the treatment of choice (single injection and probably lower rate of intracranial haemorrhage than other tPAs — similar to historic levels with SK — see ASSENT 2 trial).]*

### **Heparin**

Heparin is an agent that binds with antithrombin, increasing its ability to inactivate factor Xa and thrombin. Evidence of benefit from the use of unfractionated heparin alone for the treatment of acute coronary syndromes is weak. A meta-analysis in 1996 of six previous randomized short-term trials assessed the value of the addition of unfractionated heparin to aspirin for the treatment of UAP in 1352 patients.<sup>31</sup> There was a trend towards reduced death and myocardial infarction in the patients receiving heparin. However, only four of the studies reported results to 12 weeks and by then most of the benefit had been attenuated. It should be noted that heparin-induced thrombocytopenia syndrome (HITS) occurs in approximately 1–3% of patients.<sup>31</sup>

The use of heparin in combination with thrombolytics has been investigated in ISIS III and GUSTO. In ISIS III<sup>32</sup> there was no benefit of subcutaneous heparin in comparison to no heparin with either streptokinase or t-PA. In GUSTO<sup>20</sup> there was no advantage in intravenous over subcutaneous heparin with streptokinase at either 30 days or one year. Thus, it can be postulated that there is no advantage of using heparin with streptokinase.

Interestingly, the data for heparin with r-PA is similar. The 90 minute patency is similar with or without heparin.<sup>33</sup> However, the use of heparin with r-PA has been due to the HART study<sup>34</sup> which demonstrated decreased coronary patency at 18 hours in patients not given heparin. The European Co-operative Study by Rapold et al.<sup>35</sup> was also influential because it demonstrated heparin's ability to completely prevent the creation of the cleavage peptide Fibrinopeptide A (a marker of the action of thrombin on fibrin formation) that always occurs when r-PA is used alone.

The current ACC/AHA guidelines<sup>2</sup> recommend an initial bolus of 60 units/kg (maximum of 5000 units) and an initial infusion of 12 units/kg per hour. An APTT of 50–70 seconds is ideal and adjustment of the infusion rate may be required. Heparin should be used for a minimum of 24 hours.

### **Low molecular weight heparin**

Low molecular weight heparins (LMWH) are created by the depolymerization of unfractionated heparin. LMW heparins have several advantages over unfractionated heparin. These include a greater activity against factor Xa than thrombin and a lesser degree of binding to plasma proteins and endothelial cells. This then results in a more predictable dose-response relationship. Also, the long half-life of approximately four hours after subcutaneous injection allows twice-daily treatment. A further advantage is that the rate of HITS is lower when LMW heparins are used. To date some trials have promoted LMWH over UFH<sup>36</sup>, but a definitive recommendation can not yet be made.

*[Editor: Dr Steve Brady (ASH) adds LMWH enoxaparin but not other LMWH is the treatment of choice based on ease of administration and two trials showing efficacy over unfractionated heparin. Post TnK-tPA enoxaparin has shown at least similar and probably superior efficacy to unfractionated heparin, and again may become treatment of choice due to ease of administration (ASSENT 3 trial).]*

## **Other agents**

### *Glycoprotein IIb/IIIa receptor Antagonists*

Platelet aggregation is a central component of coronary thrombosis. The aggregation can be stimulated by a variety of substances, but the final common mechanism is activation of the glycoprotein IIa/IIIb receptor that is the platelet membrane receptor for fibrinogen.

Currently there are eight different glycoprotein IIa/IIIb receptor antagonists on the Australian market. The agents most widely known are:

- abciximab (a monoclonal antibody that is an irreversible blocker)
- eptifibatid (a peptide)
- tirofiban (a non-peptide small molecule).

Results of studies involving these receptor antagonists have been variable. The use of tirofiban in combination with aspirin and heparin vs aspirin and heparin alone in the PRISM-Plus study<sup>37</sup> has demonstrated a significant reduction in the endpoints of death and non-fatal infarction at seven days and 30 days, but not at six months. Further studies are awaited.

## **Antibiotics**

In a study by Gupta et al in 1997<sup>38</sup> serological evidence was found that Chlamydia pneumoniae is associated with atherosclerosis. In fact, it was found that C. pneumoniae would localize in coronary plaque and promote LDL-cholesterol oxidation. Leading on from this study, two reports on the use of roxithromycin in patients with unstable angina revealed a decrease in ischaemic events at 30 days<sup>39</sup> and six months<sup>40</sup>. Given the prevalence of other chlamydial diseases in non-Indigenous and Indigenous communities, this will be a topic of much interest during the years ahead.

*[Editor: A number of reviewers were concerned about giving thrombolytics without having facilities to monitor (and defibrillate) the patients ECG for reperfusion arrhythmias. We put this question to Dr Marcus Ilton, RDH cardiologist, who also put it to a large conference of cardiologists in Sydney in 2001. He reports that no cardiologist could think of a reason to withhold thrombolytic treatment just because there was no cardiac monitor. They were clear in their view that if you are confident that it is an acute coronary syndrome, there was more danger of fatal arrhythmia from withholding thrombolysis than from giving it.*

*The protocol stresses that thrombolysis should only be done if the clinic staff and consulting doctor are confident/ comfortable with the procedure.*

*Some indication of magnitude of benefit from thrombolysis (within six hours compared to no thrombolysis) is provided in the summary of evidence in Clinical Evidence\*. Fifty-six people would have to be treated in the acute phase to prevent one additional death (NNT = 56). The benefit is even greater in those with anterior infarcts. The benefits persist, and possibly become greater over long-term follow up (possibly through less heart failure from preserved myocardium). One RCT (n = 219) showed a 15% absolute risk reduction for death at 12 years follow up (NNT = 7). The absolute benefit was about one third less in those given thrombolysis 7–12 hours after onset of pain compared to <6 hours from onset.*

*There is an increased risk of stroke with thrombolysis. The estimated number needed to harm (NNH) for one extra stroke was 250. The NNH for other major bleeding was 143.*

*\*Shamir M, Urban P, De Benedetti E. Acute myocardial infarction in Clinical Evidence. BMJ Publishing Group, 2001.]*

## References

1. Australian Facts 2001. Heart, stroke and vascular diseases. Publisher: Australian Institute of Health and Welfare, National Heart Foundation of Australia and National Stroke Foundation of Australia. April 2001.
2. 1999 Update: ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction: Executive Summary and Recommendations. *Circulation* 1999; 100:1016–30.
3. Ong M, Weeramanthri. Delay times and management of acute myocardial infarction in Indigenous and non-Indigenous people in the Northern Territory. *Medical Journal of Australia* 2000; 173:201–4.
4. Rapilysin Questions and answers. Information for Healthcare Professionals. Product Information. Roche Pharmaceuticals.
5. Management of Unstable Angina Guidelines — 2000. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. *Medical Journal of Australia* 2000; 173(supplement): S65–S88.
6. Aroney C. Management of the acute coronary syndromes. *Australian Prescriber* 2001; 24(3):56–8.
7. Madias J, Hood W. Reduction of precordial ST-segment elevation in patients with anterior myocardial infarction by oxygen breathing. *Circulation* 1976; 53(supplement):198–200.
8. Maroko P, Radvany P, Braunwald E et al. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. *Circulation* 1975; 52:360–8.
9. Fillmore S, Shapiro M, Killip T. Arterial oxygen tension in acute myocardial infarction: Serial analysis of clinical state and blood gas changes. *American Heart Journal* 1970; 79:620–9.
10. Lincoff A, Topol E. Illusion of reperfusion: Does anyone achieve optimal reperfusion during acute myocardial infarction? *Circulation* 1993; 87:1792–805.
11. Lewis H, Davis J, Archibald D, Steinke W et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration cooperative study. *New England Journal of Medicine* 1983; 309:396–403.
12. Yusuf S, Fox K, Tognoni G et al. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *New England Journal of Medicine* 2001; 345(7):494–502.
13. Jugdutt B, Warnica J. Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications: Effect of timing, dosage, and infarct location. *Circulation* 1988; 78:906–19.
14. Yusuf S, Collins R, MacMahon S et al. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomized trials. *Lancet* 1988; 1:1088–92.
15. A randomized factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction: ISIS-4. *Lancet* 1995; 345:669–85.
16. First International Study of Infarct Survival Collaborative Group: Randomized trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet* 1986; 2:57–66.
17. The MIAMI Trial research Group: Metoprolol in acute myocardial infarction: Patient population. *American Journal of Cardiology* 1985; 56(SupplementG):1–57.
18. Furberg C, Psaty B, Mayer J. Nifedipine: Dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995; 92:1326–31.
19. Gruppo Italiano per lo Studio Della Sopravvivenza nell'Infarto Miocardico (GISSI): Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; 1:397–402.
20. The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *New England Journal of Medicine* 1993; 329:673–82.
21. Second International Study of Infarct Survival Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction. ISIS-2. *Lancet* 1988; 2:349–60.
22. Wilcox R, von der Lippe G, Olsson C et al. Trial of tissue plasminogen activator (t-PA) for mortality reduction in acute myocardial infarction: The Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet* 1988; 2:525–30.

23. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet* 1994; 343:311–22.
24. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction and improved survival: Should the paradigm be expanded? *Circulation* 1989; 79:441–4.
25. The GUSTO IIb Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty and tissue plasminogen activator for acute myocardial infarction: the Global use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes. *New England Journal of Medicine* 1997; 336:1621–8.
26. Ellis C, French J, White H. Thrombolytic eligibility. *Australian and New Zealand Journal of Medicine* 1998; 28:518–24.
27. Simmons M, Maggioni A, Knatterud G et al. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet* 1993; 342:1523–8.
28. Elliott J, Cross D, Cederholm-Williams S, White H. Neutralizing antibodies to streptokinase four years after intravenous thrombolytic therapy. *American Journal of Cardiology* 1993; 71:640–5.
29. Urdahl K, Mathews J, Currie B. Anti-streptokinase antibodies and streptokinase resistance in an Aboriginal population in northern Australia. *Australian and New Zealand Journal of Medicine* 1996; 26:49–53.
30. Aylward P, Hunt D et al. Reperfusion Therapy for Acute Myocardial Infarction – Guidelines. National Heart Foundation of Australia, December 2000.
31. Oler A, Whooley M, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *Journal of the American Medical Association* 1996; 276:811–15.
32. Third international study of infarct survival. ISIS-III. *Lancet* 1992; 339(8796):753–70.
33. Topol E, George B, Kereiakes D et al. A multi-center randomised controlled trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. *Circulation* 1989; 79:281–6.
34. Hsia J, Hamilton W, Kleiman N et al. The Heparin-Aspirin Reperfusion Trial (HART) Investigators. A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. *New England Journal of Medicine* 1990; 323:1433–7.
35. Rapold H, de Bono D, Arnold A et al for the European Cooperative Study Group. Plasma fibrinopeptide A levels in patients with acute myocardial infarction treated with alteplase. Correlation with concomitant heparin, coronary artery patency and recurrent ischaemia. *Circulation* 1992; 85:928–34.
36. Cohen M, Demers C, Gurfinkel E et al for the ESSENCE Study Group. A comparison of low-molecular weight heparin with unfractionated heparin for unstable coronary artery disease. *New England Journal of Medicine* 1997; 337:447–52.
37. Platelet Receptor Inhibition in Ischaemic Syndrome Management in Patients limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *New England Journal of Medicine* 1998; 338:1488–97.
38. Gupta S, Leatham E, Carrington D et al. Elevated Chlamydia pneumoniae antibodies, cardiovascular events and azithromycin in male survivors of myocardial infarction. *Circulation* 1997; 96:404–7.
39. Gurfinkel E, Bozovich G, Daroca A et al. Randomised trial of roxithromycin in non-Q-wave coronary syndromes: ROXIS Pilot Study. ROXIS Study Group. *Lancet* 1997; 350:404–7.
40. Gurfinkel E, Bozovich G, Beck E et al. Treatment with the antibiotic roxithromycin in patients with acute non-Q-wave coronary syndromes. The final report of the ROXIS Study. *European Heart Journal* 1999; 20:121–7.

## APPENDIX

Evidence Summary: Immediate use of  $\beta$ -blockers in acute myocardial infarction

### Question

In people with acute myocardial infarction, does immediate use of  $\beta$ -blockers — compared to delayed use of  $\beta$ -blockers — affect death or re-infarction rates?

### Rationale for question

When people are treated for AMI in the community with thrombolysis we are uncertain as to whether we should give  $\beta$ -blockers at the same time or delay it until they reach hospital.

### Inclusion criteria for studies reviewed

Randomised trials or systematic reviews comparing immediate (intravenous)  $\beta$ -blockers with delayed  $\beta$ -blockers

### Search strategy

(Acute and myocardial and infarction) and ( $\beta$ -blockers} or  $\beta$ -near-blockers}) and intravenous.

## Results

### Studies (quality and size)

No systematic review of this topic found in Cochrane or Pubmed. Only One RCT found. This trial had been extensively referred to in all secondary sources.

The trial was ‘Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, Smith HC et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. *Circulation*. 1991; 83(2): 422–437.’

This was a randomized controlled trial in which the assessors were blinded comparing an international group of 720 participants and 714 controls. Participants were given immediate intravenous metoprolol followed by oral treatment whereas the controls had oral metoprolol commenced at six days. The primary endpoint was global ejection fraction at discharge, and this did not differ between groups. Secondary analyses included a combined end point of death and re-infarction at six weeks. There was no significant difference between the groups with 7.2% of the participants and 9.6% of the control group attaining this endpoint at six weeks.

### Conclusion (estimated absolute effect size)

No differences between the groups were seen.

### Comments

Death and re-infarction were secondary endpoints in this trial. The study size was calculated based upon the primary endpoint rather than the secondary endpoints. However, this was a large trial, and since there were more than 50 events in the control groups, this suggests that there would have been more than an 80% chance of picking up a 50% difference in outcomes.

### Implications for CARPA STM 4th edition

Recommend that there is no need for urgent commencement of  $\beta$ -blockers and this can be instituted during ongoing therapy at the hospital.

## Reference

Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, Smith HC et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. *Circulation* 1991; 83(2):422–37.