

# **Guidelines for pre-hospital administration of fibrinolytic therapy by New Zealand general practitioners**

The Pre-Hospital Fibrinolysis Guidelines Working Party\*

\*(See Appendix A).

**Correspondence:** Honorary Professor Harvey White

Cardiology Department

Auckland City Hospital

Private Bag 92024

Auckland 1030

New Zealand

**Telephone:** 0-9-630 9992

**Fax:** 0-9-630 9915

**Email:** HarveyW@adhb.govt.nz

## Introduction

These guidelines have been developed in consultation with the Ministry of Health to ensure equity of access to fibrinolytic therapy (previously known as thrombolytic therapy) throughout New Zealand. There are many rural areas of the country where patients with acute myocardial infarction currently do not receive fibrinolytic therapy in a timely manner because of the time and distance involved in transporting them to hospital.

The guidelines have been written after wide consultation with various groups and a series of discussions between the members of the Pre-Hospital Fibrinolysis Guidelines Working Party (Appendix A). The search strategy for evidence included a Medline search. The recommendations listed in the guidelines are based on the evidence and on the consensus of the Working Party. The levels of evidence are graded according to the Scottish Intercollegiate Guidelines Network (SIGN) method<sup>1</sup> (Appendix B) to differentiate between those based on strong evidence and those based on weak evidence. The grading does not signify the importance of the recommendation, but rather, the strength of the supporting evidence.

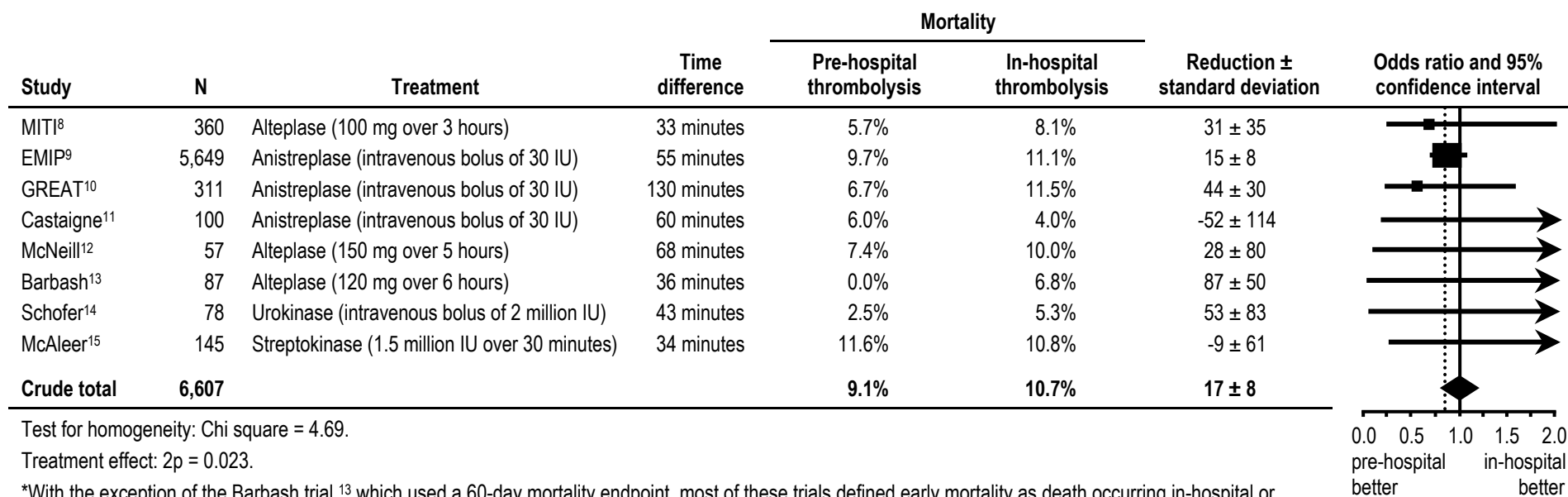
Over the past decade, it has been shown that fibrinolysis reduces mortality in patients suffering acute myocardial infarction **(1++)**.<sup>2-6</sup> However, the mortality reduction attenuates markedly the longer that treatment is delayed after the onset of infarction **(1++)**.<sup>3-5,7</sup> Several studies have demonstrated the feasibility and safety of pre-hospital assessment and initiation of fibrinolysis in the community **(1++)**.<sup>2,7-16</sup> The greater the distance from a hospital with fibrinolytic facilities, the greater the potential for myocardial salvage by pre-hospital fibrinolysis. This is because myocyte necrosis progresses rapidly over time,<sup>17</sup> and many more lives are saved when patients are treated very early in the course of infarction than when they are treated later. A retrospective analysis of the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-1) Study revealed that patients who received treatment within 1 hour had a 51% reduction in mortality at 21 days **(2+)**.<sup>4</sup> This

was a hypothesis-generating analysis and must be interpreted cautiously, but it does demonstrate the potential benefit of very early treatment.

In the Fibrinolytic Therapy Trialists' (FTT) overview of 58,600 randomized patients, the calculated mortality reduction for every hour of delay avoided was 1.6 lives saved per 1,000 patients treated with fibrinolysis, with a 30% mortality reduction at 1 hour, 25% at 2 to 3 hours, and 18% at 4 to 6 hours **(1++)**.<sup>5</sup> Another analysis, which excluded some of the studies in the FTT overview because they included patients with unstable angina, reported even greater mortality reductions with earlier treatment (48% at 1 hour, 44% at 2 hours, and 20% after 3 hours) **(1+)**.<sup>7</sup> The implied benefit of earlier treatment in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-I) Trial was five lives saved for every hour of delay avoided per 1,000 patients treated **(2+)**. It is acknowledged that all of these analyses were observational, as none of the studies purposely randomized patients to receive fibrinolytic therapy at different timepoints, and it should be borne in mind that patients who present later may have different baseline characteristics from those who present earlier, e.g. those presenting late are more likely to be elderly, female or diabetic.

There have been eight randomized trials comparing pre-hospital fibrinolysis with in-hospital fibrinolysis. A meta-analysis of these trials (Figure 1)<sup>8-15</sup> showed that there was an overall 17% reduction in mortality, with 16 lives saved per 1,000 patients treated with pre-hospital fibrinolysis (P=0.02) **(1++)**. Of note, there was a 44% mortality reduction in the Grampian Region Early Anistreplase (GREAT) Trial **(1-)**,<sup>10</sup> in which there was a 2-hour treatment delay, while in the European Myocardial Infarction Project (EMIP), there was only a 15% mortality reduction despite a shorter treatment delay of only 55 minutes **(2+)**.<sup>9</sup> In another recent trial, pre-hospital administration of tissue plasminogen activator (TPA) was shown to be equivalent to primary angioplasty in reducing the combined risk of death, reinfarction and stroke.<sup>18</sup> Follow-up at 2½ years showed that the mortality rates were 6.7% in patients treated with pre-hospital fibrinolysis versus 8.8% in those treated with primary angioplasty (P=0.05 for patients treated within 2 hours of symptom onset) **(1+)**.

Figure 1: Results of trials comparing pre-hospital and in-hospital fibrinolysis, showing the relative risk of early mortality\*



Fibrinolysis carries a small risk of intracranial haemorrhage, but this is offset by a reduction in the risk of ischaemic stroke, and as some of the strokes are fatal, they are already counted in the mortality benefit. The overall benefit/risk ratio of fibrinolysis is 16 lives saved at the cost of causing one nonfatal disabling stroke per 1,000 patients treated with fibrinolysis.

The likelihood of ventricular fibrillation is greater when fibrinolytic therapy is administered very early after the onset of symptoms **(2+)**,<sup>19</sup> but other complication rates are similar to those seen with in-hospital fibrinolysis. It is therefore recommended that communities more than 1 hour away from the nearest hospital with fibrinolytic facilities should initiate programmes to administer pre-hospital fibrinolysis.

## Recommendations

**Programme implementation:** Before pre-hospital fibrinolysis programmes can be commenced, it is desirable that all medical practitioners involved should receive adequate training in collaboration with the central supporting service. Practice nurses, community hospital nurses and ambulance officers would also benefit from training. The training should include information on:

- Interpretation of electrocardiograms (ECGs).
- The particular fibrinolytic agent chosen **(4)**.
- Indications for and contraindications against fibrinolytic therapy **(4, D)**.
- Management of the potential side-effects of fibrinolytic therapy.
- Use of defibrillators **(4, D)**.

An ongoing audit should be maintained, with regular reviews to assess the accuracy of infarct diagnosis, the timing of fibrinolytic administration, and patient outcome.

## Principles for pre-hospital administration of fibrinolytic therapy

1. All general practitioners administering fibrinolytic therapy must have a well maintained defibrillator available at the time of fibrinolysis **(4, D)**.
2. Fibrinolysis should be considered in all patients who: (a) meet the diagnostic criteria for acute myocardial infarction; and (b) present within 12 hours of symptom onset; and (c) are  $\geq 1$  hour away from the nearest hospital with fibrinolytic facilities **(4, D)**. The treatment algorithm is outlined in Figure 2 and discussed in detail below.
3. The diagnosis of acute myocardial infarction must be confirmed by a 12-lead ECG **(1++ , A)**, and approval for pre-hospital fibrinolysis must be obtained from the supervising hospital **(4, D)**.
4. The ECG should be faxed or transmitted via a modem to the supervising hospital. While it is recognized that digitally transmitted ECGs are clearer and require less processing, budgetary constraints may mean that faxing is the preferred option. This decision will need to be made on a local basis **(4, D)**.
5. Every effort should be made to minimize the delay between the diagnosis of infarction and the administration of fibrinolytic therapy **(1+ , A)**. A bolus fibrinolytic agent such as reteplase (RPA) or tenecteplase (TNK-TPA) should be administered as soon as possible after the diagnosis of myocardial infarction is confirmed. Currently, reteplase is the bolus fibrinolytic agent most commonly used for pre-hospital fibrinolysis in New Zealand. Tenecteplase has been shown to be associated with less systemic bleeding than tissue plasminogen activator **(1+)**.<sup>20</sup> Streptokinase is not recommended for pre-hospital fibrinolysis because it requires an infusion pump, is difficult to administer, and frequently causes hypotension. Tissue plasminogen activator is not recommended either because it too requires an infusion pump, and has a complex dosage regimen **(4, D)**.

6. The patient may be transported to hospital by road or air depending on the clinical stability of the patient, the distance involved, and the road and weather conditions. The transport policy will need to be assessed on a regional basis **(4, D)**.

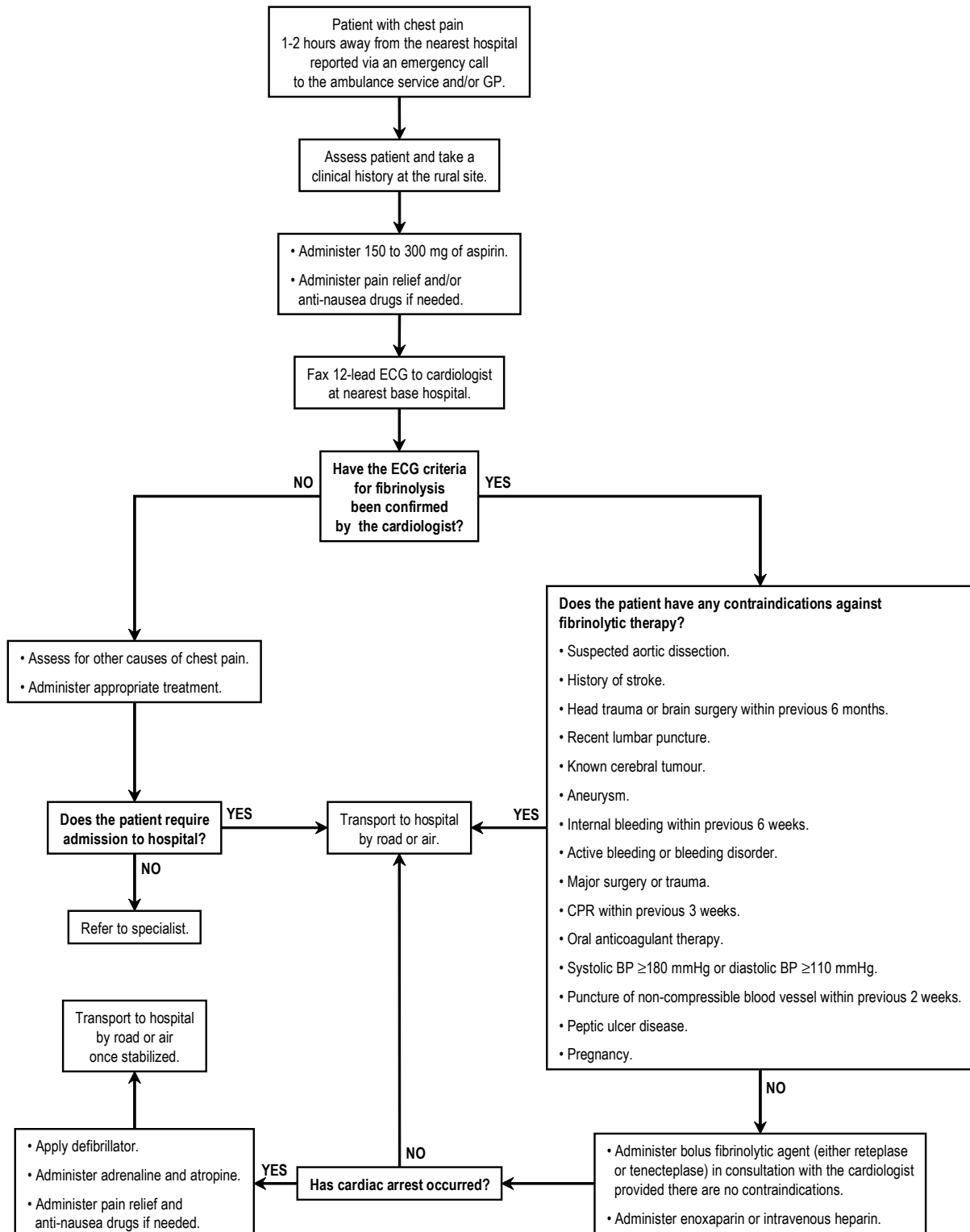
### **Indications for fibrinolysis**

1. A clinical history of  $\geq 30$  minutes of chest discomfort beginning  $\leq 12$  hours previously and consistent with ischaemic aetiology **(1++, A)**.
2. An ECG showing ST-segment elevation measuring  $\geq 1$  mm in two or more inferior leads, or  $\geq 2$  mm in two or more contiguous anterior leads  $V_1$  to  $V_3$ , or  $\geq 1$  mm in leads  $V_4$ ,  $V_5$ ,  $V_6$  or AVL **(1++, A)**.
3. A left bundle branch block pattern that is not known to be pre-existing **(1+, A)**.
4. Absence of contraindications against fibrinolysis **(4, D)**.

### **Contraindications against fibrinolysis**

1. Suspected aortic dissection **(4, D)**.
2. Any previous history of haemorrhagic stroke, or a suspected previous stroke in which haemorrhage was not excluded by scanning **(1+, A)**.
3. History of non-haemorrhagic stroke or central nervous system damage within 1 year **(1+, A)**.
4. Head trauma **(1+)** or brain surgery **(4, D)** within 6 months, recent lumbar puncture, known cerebral tumour or aneurysm **(1+, A)**.

Figure 2: Algorithm for pre-hospital administration of fibrinolytic therapy



5. Internal bleeding within 6 weeks **(4, D)**.
6. Active bleeding or known bleeding disorder **(4, D)**.
7. Major surgery, trauma or bleeding within 6 weeks **(1+, A)**.
8. Traumatic cardiopulmonary resuscitation within 3 weeks **(4, C)**.
9. Oral anticoagulant therapy **(3, C)**.
10. Persistent hypertension (systolic blood pressure of >180 mmHg or diastolic blood pressure of >110 mmHg) **(1+, A)**.
11. Puncture of a non-compressible blood vessel within 2 weeks **(4, D)**.
12. Peptic ulcer disease documented by endoscopy with symptoms occurring within the previous 3 months **(4, D)**.
13. Pregnancy **(4, D)**.

The indications for fibrinolysis and the absence of contraindications should be discussed fully with the hospital before an expeditious decision is made as to whether or not fibrinolytic therapy should be administered.

### **Dosage regimens**

- Reteplase should be administered intravenously as a 10 IU bolus over 2 minutes, and repeated 30 minutes later.
- Tenecteplase should be administered intravenously over 10 seconds in a weight-adjusted regimen (30 mg for patients weighing <60 kg, 35 mg for those weighing 60 to 69 kg, 40 mg for those

weighing 70 to 79 kg, 45 mg for those weighing 80 to 89 kg, or 50 mg for those weighing  $\geq 90$  kg) **(1++, A)**.

### Adjunctive therapy

1. All patients should receive 150 to 300 mg of soluble or sublingual aspirin to chew as soon as the possibility of acute myocardial infarction is considered **(1++, A)**.
2. If reteplase is chosen as the fibrinolytic agent, it should be followed immediately by unfractionated heparin administered intravenously in a dose of 4,000 IU for patients weighing  $>70$  kg or 3,500 IU for those weighing  $<70$  kg. Ideally, a heparin infusion should then be commenced at a rate of 12 IU/kg/hour (maximum 1,000 IU/hour) **(1-, B)**.<sup>21</sup> However, administration of an infusion may be impractical for logistical reasons, and so an alternative option is to administer a second heparin bolus after 90 minutes.
3. If tenecteplase is chosen as the fibrinolytic agent, it is recommended that enoxaparin be administered immediately as a 0.3 mL (30 mg) intravenous bolus followed by a 1 mg/kg subcutaneous injection **(1+, A)**.<sup>20,22</sup> In patients aged  $\geq 75$  years, the intravenous bolus should be omitted, and the subcutaneous dose should be increased to 0.75 mg/kg up to a maximum total dose of 75 mg. Alternatively, intravenous unfractionated heparin may be administered as detailed in item 2 above.
4. Medications such as adrenalin and atropine should be available in case of cardiac arrest.
5. Adequate medication for pain relief and nausea should be available.

**Equipment:** Advisory defibrillators should be available for immediate use during transportation.

**Indicators:** It is important that pre-hospital fibrinolysis services are audited, and so the following outcomes are to be documented along with patient demographics:

- Time from symptom onset to administration of fibrinolytic therapy.
- Time from first contact with emergency services (111 call), ambulance or primary healthcare services to administration of fibrinolytic therapy.
- Time from when the patient is first seen by a clinician to administration of fibrinolytic therapy.
- Time from administration of fibrinolytic therapy to start of transport.
- Time from administration of fibrinolytic therapy to arrival at hospital.
- Complications following acute myocardial infarction: bleeding, arrhythmia, cardiogenic shock, stroke, death.
- Death within 30 days after acute myocardial infarction.
- Baseline ECGs to determine the accuracy of diagnosis.

## Summary

New Zealand is a rural country with many isolated regions that are distant from hospitals with fibrinolytic facilities. Pre-hospital fibrinolysis is thus the only way that rural patients can be efficiently managed with modern reperfusion therapy. These guidelines provide a framework for safe and appropriate administration of fibrinolytic agents in the New Zealand rural community. The guidelines will be updated 2 years after publication.

## References

1. Harbour R, Miller J, for the Scottish Intercollegiate Guidelines Network Grading Review Group. A new system for grading recommendations in evidence based guidelines. *Br Med J*. 2001;323:334-6.
2. White HD, Van de Werf FJJ. Thrombolysis for acute myocardial infarction. *Circulation*. 1998;97:1632-46.
3. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;ii:349-60.
4. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet*. 1986;i:397-402.
5. 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 randomised trials of more than 1000 patients. *Lancet*. 1994;343:311-22.
6. Wilcox RG, von der Lippe G, Ollson CG, et al. Trial of tissue plasminogen activation for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet*. 1988;ii:525-30.
7. Boersma E, Maas ACP, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet*. 1996;348:771-5.
8. Weaver WD, Cerqueira M, Hallstrom AP, et al. Prehospital-initiated vs hospital-initiated thrombolytic therapy. *JAMA*. 1993;270:1211-6.
9. The European Myocardial Infarction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *N Engl J Med*. 1993;329:383-9.

10. GREAT Group. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian Region Early Anistreplase Trial. *Br Med J.* 1992;305:548-53.
11. Castaigne AD, Hervé C, Duval-Moulin A-M, et al. Prehospital use of APSAC: results of a placebo-controlled study. *Am J Cardiol.* 1989;64:30A-33A.
12. McNeill AJ, Cunningham SR, Flannery DJ, et al. A double blind placebo controlled study of early and late administration of recombinant tissue plasminogen activator in acute myocardial infarction. *Br Heart J.* 1989;61:316-21.
13. Barbash GI, Roth A, Hod H, et al. Improved survival but not left ventricular function with early and prehospital treatment with tissue plasminogen activator in acute myocardial infarction. *Am J Cardiol.* 1990;66:261-6.
14. Schofer J, Büttner J, Geng G, et al. Prehospital thrombolysis in acute myocardial infarction. *Am J Cardiol.* 1990;66:1429-33.
15. McAleer B, Ruane B, Burke E, et al. Prehospital thrombolysis in a rural community: short- and long-term survival. *Cardiovasc Drugs Ther.* 1992;6:369-72.
16. Morrison LJ, Verbeek PR, McDonald AC, et al. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. *JAMA.* 2000;283:2686-92.
17. Reimer KA, Lowe JE, Rasmussen MM, et al. The wave-front phenomenon of ischemic cell death. I. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation.* 1977;56:786-94.
18. Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet.* 2002;360:825-9.
19. Boissel JP, Castaigne A, Mercier C, et al. Ventricular fibrillation following administration of thrombolytic treatment: the EMIP experience. European Myocardial Infarction Project. *Eur Heart J.* 1996;17:213-21.

20. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358:605-13.
21. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation*. 1999;100:1016-30.
22. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Plus randomized trial in acute myocardial infarction. *Circulation*. 2003;108:135-42.

## Appendix A

### Pre-Hospital Fibrinolysis Guidelines Working Party

These guidelines were initiated and endorsed by the New Zealand Regional Committee of the Cardiac Society of Australia and New Zealand. Roche Products (New Zealand) Limited provided financial support for two meetings of the Working Party, but the guidelines were developed independently of pharmaceutical industry funding. The members of the Working Party are:

- Sandy Dawson, Clinical Advisor, Ministry of Health, Wellington.
- Marg Eckhoff, Rural Nurse, Roxburgh.
- Dr Sharon Kletchko, Emergency Medicine Specialist, Tauranga Hospital, Tauranga.
- Dr Laura Lambie, Clinical Advisor, Ministry of Health, Wellington.
- Dr Glen Marriott, General Practitioner, Coromandel.
- Margaret Mohammed, Wellington.
- Dr Gary Nixon, Dunstan Hospital, Clyde.
- Dr Chris Nunn, Cardiologist, Waikato Hospital, Hamilton.
- Dr Keri Ratima, Senior Advisor, Maori Health, National Health Committee, Ministry of Health, Wellington.
- Honorary Professor Harvey White (Chairman) Cardiologist, Auckland City Hospital, Auckland.

None of the Working Party members has any conflict of interest in connection with this work.

## Appendix B

### Scottish Intercollegiate Guidelines Network (SIGN)

#### Revised Grading System<sup>1</sup>

##### Levels of evidence

**1++** High-quality meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a very low risk of bias.

**1+** Well conducted meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a low risk of bias.

**1-** Meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a high risk of bias.

**2++** High-quality systematic reviews of case-control or cohort studies, high-quality case-control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal.

**2+** Well conducted case control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal.

**2-** Case control or cohort studies with a high risk of confounding, bias or chance, and a significant risk that the relationship is not causal.

**3** Non-analytical studies, e.g. case reports or case series.

**4** Expert opinion.

20 **Grades of recommendation**

21 **A** At least one meta-analysis, systematic review or randomized controlled trial rated as **1++**, and  
22 directly applicable to the target population; or a systematic review of randomized controlled  
23 trials or a body of evidence consisting principally of studies rated as **1+**, directly applicable to  
24 the target population, and demonstrating overall consistency of results.

25 **B** A body of evidence including studies rated as **2++**, directly applicable to the target population,  
26 and demonstrating overall consistency of results; or extrapolated evidence from studies rated as  
27 **1++** or **1+**.

28 **C** A body of evidence including studies rated as **2+**, directly applicable to the target population,  
29 and demonstrating overall consistency of results; or extrapolated evidence from studies rated as  
30 **2++**.

31 **D** Evidence level **3** or **4**; or extrapolated evidence from studies rated as **2+**.