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\(^1\) (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 \((1++)\)\(^2\)\(^-\)\(^6\). However, the mortality reduction attenuates markedly the longer that treatment is delayed after the onset of infarction \((1++)\)\(^3\)\(^-\)\(^5\),\(^\,7\) Several studies have demonstrated the feasibility and safety of pre-hospital assessment and initiation of fibrinolysis in the community \((1++)\)\(^2\)\(^-\)\(^16\). 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,\(^17\) 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 \((2+)\)\(^4\). 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++)\(^5\). 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+).\(^7\) 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)\(^8\)\(^-\)\(^15\) 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-),\(^10\) 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+).\(^9\) 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.\(^18\) 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

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>Time difference</th>
<th>Pre-hospital thrombolysis</th>
<th>In-hospital thrombolysis</th>
<th>Reduction ± standard deviation</th>
<th>Odds ratio and 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITI</td>
<td>360</td>
<td>Alteplase (100 mg over 3 hours)</td>
<td>33 minutes</td>
<td>5.7%</td>
<td>8.1%</td>
<td>31 ± 35</td>
<td></td>
</tr>
<tr>
<td>EMIP</td>
<td>5,649</td>
<td>Anistreplase (intravenous bolus of 30 IU)</td>
<td>55 minutes</td>
<td>9.7%</td>
<td>11.1%</td>
<td>15 ± 8</td>
<td></td>
</tr>
<tr>
<td>GREAT</td>
<td>311</td>
<td>Anistreplase (intravenous bolus of 30 IU)</td>
<td>130 minutes</td>
<td>6.7%</td>
<td>11.5%</td>
<td>44 ± 30</td>
<td></td>
</tr>
<tr>
<td>Castaigne</td>
<td>100</td>
<td>Anistreplase (intravenous bolus of 30 IU)</td>
<td>60 minutes</td>
<td>6.0%</td>
<td>4.0%</td>
<td>-52 ± 114</td>
<td></td>
</tr>
<tr>
<td>McNeill</td>
<td>57</td>
<td>Alteplase (150 mg over 5 hours)</td>
<td>68 minutes</td>
<td>7.4%</td>
<td>10.0%</td>
<td>28 ± 80</td>
<td></td>
</tr>
<tr>
<td>Barbash</td>
<td>87</td>
<td>Alteplase (120 mg over 6 hours)</td>
<td>36 minutes</td>
<td>0.0%</td>
<td>6.8%</td>
<td>87 ± 50</td>
<td></td>
</tr>
<tr>
<td>Schofer</td>
<td>78</td>
<td>Urokinase (intravenous bolus of 2 million IU)</td>
<td>43 minutes</td>
<td>2.5%</td>
<td>5.3%</td>
<td>53 ± 83</td>
<td></td>
</tr>
<tr>
<td>McAleer</td>
<td>145</td>
<td>Streptokinase (1.5 million IU over 30 minutes)</td>
<td>34 minutes</td>
<td>11.6%</td>
<td>10.8%</td>
<td>-9 ± 61</td>
<td></td>
</tr>
<tr>
<td>Crude total</td>
<td>6,607</td>
<td></td>
<td></td>
<td>9.1%</td>
<td>10.7%</td>
<td>17 ± 8</td>
<td></td>
</tr>
</tbody>
</table>

Test for homogeneity: Chi square = 4.69.
Treatment effect: 2p = 0.023.

*With the exception of the Barbash trial, which used a 60-day mortality endpoint, most of these trials defined early mortality as death occurring in-hospital or within 30 days.
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 \((2+)\), 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 ≥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+). 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 ≥30 minutes of chest discomfort beginning ≤12 hours previously and consistent with ischaemic aetiology (1++, A).

2. An ECG showing ST-segment elevation measuring ≥1 mm in two or more inferior leads, or ≥2 mm in two or more contiguous anterior leads V₁ to V₃, or ≥1 mm in leads V₄, V₅, V₆ 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

Patient with chest pain 1-2 hours away from the nearest hospital reported via an emergency call to the ambulance service and/or GP.

- Assess patient and take a clinical history at the rural site.

- Administer 150 to 300 mg of aspirin.
- Administer pain relief and/or anti-nausea drugs if needed.

- Fax 12-lead ECG to cardiologist at nearest base hospital.

- Does the patient have any contraindications against fibrinolytic therapy?
  - Suspected aortic dissection.
  - History of stroke.
  - Head trauma or brain surgery within previous 6 months.
  - Recent lumbar puncture.
  - Known cerebral tumour.
  - Aneurysm.
  - Internal bleeding within previous 6 weeks.
  - Active bleeding or bleeding disorder.
  - Major surgery or trauma.
  - CPR within previous 3 weeks.
  - Oral anticoagulant therapy.
  - Systolic BP ≥180 mmHg or diastolic BP ≥110 mmHg.
  - Puncture of non-compressible blood vessel within previous 2 weeks.
  - Peptic ulcer disease.
  - Pregnancy.

- Administer bolus fibrinolytic agent (either reteplase or tenecteplase) in consultation with the cardiologist provided there are no contraindications.
- Administer enoxaparin or intravenous heparin.

- Does the patient require admission to hospital?

- Transport to hospital by road or air once stabilized.

- Assess for other causes of chest pain.
- Administer appropriate treatment.

- Assess patient and take a clinical history at the rural site.

- Transport to hospital by road or air once stabilized.

- Apply defibrillator.
- Administer adrenaline and atropine.
- Administer pain relief and anti-nausea drugs if needed.

- Decide to refer specialist.

- Has cardiac arrest occurred?

- Administer bolus fibrinolytic agent (either reteplase or tenecteplase) in consultation with the cardiologist provided there are no contraindications.
- Administer enoxaparin or intravenous heparin.

- NO

- YES

- Apply defibrillator.
- Administer adrenaline and atropine.
- Administer pain relief and anti-nausea drugs if needed.

- NO

- YES

- Refer to specialist.

- Has cardiac arrest occurred?

- Administer bolus fibrinolytic agent (either reteplase or tenecteplase) in consultation with the cardiologist provided there are no contraindications.
- Administer enoxaparin or intravenous heparin.

- NO
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).


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).


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 ≥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). 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). In patients aged ≥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


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.

   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

   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
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 System¹

**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.
Grades of recommendation

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

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

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

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