Pre-hospital thrombolysis: current status and future prospects

ABSTRACT—The impact of thrombolytic therapy in acute myocardial infarction has been such that it now constitutes standard therapy for patients who present to hospital with acute myocardial infarction. In an attempt to minimise the duration of ischaemia, and subsequent impairment of contractile function, trials of pre-hospital thrombolysis have been initiated. These reveal time gains of up to 60 minutes but convincing evidence of clinical benefit has not yet been forthcoming. This review examines the rationale for very early thrombolysis, in the context of the underlying pathophysiological mechanisms. It examines the impact of recent small scale studies on coronary patency, left ventricular function and infarct size and examines the potential risks. Large scale studies of pre-hospital thrombolysis are in progress and their findings will need to be interpreted in comparison with optimal 'fast-track' in-hospital treatment. The review highlights the need for co-ordinated policies for acute management of myocardial infarction involving primary care, the emergency medical systems and cardiac units. Enthusiasm for wide scale administration of thrombolytics by general practitioners, without electrocardiographic confirmation of the diagnosis, must be tempered by a clear analysis of the potential risks and benefits. Current evidence does not support such widespread clinical application, outwith the current evaluation studies. An urgent re-evaluation of hospital triage of patients with acute myocardial infarction is merited.

Inopi beneficium bis dat qui dat celeriter.

He gives the poor man twice as much good who gives quickly.

Publilius Syrus. 1st century BC [1]

Thrombolytic therapy represents the first major advance in the treatment of acute myocardial infarction since the introduction of acute coronary care a quarter of a century ago. The impact of thrombolytic therapy on mortality and morbidity has been such

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that, in the absence of contraindications, it now constitutes standard therapy. If such therapy could be given before the patient reached hospital, would this confer additional benefit, would the potential risks be predictable and manageable, and would pre-hospital thrombolysis be feasible on a national scale? This review assesses recent evidence and the likely impact of current studies of pre-hospital thrombolysis. Feasibility of pre-hospital thrombolysis was established in Jerusalem in 1985, when a series of patients were given intravenous streptokinase before their transfer to hospital [2]. This feasibility has been reaffirmed based upon a number of relatively small studies in specialised centres, and the early phases of major international trials are now underway.

Potential benefits of pre-hospital thrombolysis

The aims of pre-hospital thrombolysis are to minimise the duration of ischaemia and to limit the complications of infarction. What is the evidence to support this approach? Experimentally, earlier treatment results in a higher rate of recanalisation, earlier reperfusion, smaller infarction and less left ventricular dysfunction [3,4]. Clinically, there is evidence to support the same findings and a lower mortality and subsequent morbidity [5–11].

However, not all the major placebo-controlled trials of thrombolysis have come to the same conclusion [12]. Furthermore, although studies in animals suggested that reperfusion of an occluded coronary artery after 6 hours would not result in significant myocardial salvage [13], the ISIS 2 study demonstrated reduction in mortality in patients treated 12–24 hours following the onset of symptoms [10].

These apparent contradictions can be resolved. First, an abrupt total occlusion in an experimental animal puts a volume of myocardium at risk, critically dependent on the extent of collateral supply. Among species with poorly developed collaterals (eg the pig or the sheep) the majority of the risk region develops infarction, and progression to necrosis is rapid. However, in the presence of well developed collaterals very little or even no infarction may develop despite similar coronary artery occlusion (eg in the guinea pig or well collateralised canine).

The impact of collateral supply has been clearly demonstrated in man, even in the absence of thrombolysis. Improved mechanical function is seen in patients with infarction and well developed collaterals when compared with those without, and these patients suffer less myocardial damage [14].

Hypothesis. In patients without significant collateral perfusion, the time course of injury resembles the experimental animal without collaterals. In patients with pre-existent stenoses and collateral perfusion, a more insidious subacute coronary artery syndrome exists with intermittent ischaemia and delayed occlusion. Such patients present later in the natural history, suffer smaller infarcts and benefit from the apparently 'late' thrombolysis.

Thus, the disparity between the steep time relationship predicted by animal models and the shallow time relationship suggested by clinical trials may reflect two populations of patients presenting with myocardial infarction: those with poor collateral supply and an abrupt occlusion, and those with a range of collateral supply and intermittent occlusion. The former group might be expected to present earlier after coronary occlusion and with more clear-cut onset of infarction. In keeping with the animal model, they have most to gain from very early thrombolysis (within the first hour). In the latter group, onset of infarction is more insidious or intermittent, and as a result of collateral supply the time window of benefit is extended. Thus, they may sustain significant benefit from thrombolytic therapy but this may not reflect a longer duration of ischaemia *per se*. Furthermore, reperfusion after the first six hours may be associated with an excess early risk of death (on the first day) compared with placebo treatment (ISIS 2 database). Later reperfusion may be associated with accelerated injury to damaged, but perhaps viable myocardium, 'reperfusion injury'.

Studies of pre-hospital thrombolysis that include a majority of patients with chest pain of more than two hours duration will include some patients with abrupt coronary occlusion/poor collaterals, at a time which is too late to expect to show benefit. They will also include some patients with intermittent occlusion/ good collaterals in whom there is little chance of showing benefit compared with in-hospital treatment, because time delay is less critical in this group. We postulate that, for pre-hospital thrombolysis to be effective, it must not only reduce the total duration of ischaemia but must reduce the first 60–90 minutes of ischaemia. Although difficult, a trial of very early treatment (within the first hour) is merited.

The major mortality studies of thrombolysis have tested relatively late therapy and have failed to test very early treatment. In GISSI 1 the data from the first hour were derived from a retrospective analysis, and in ISIS 2 relatively few patients were treated within the first hour. Indeed, in the comparison of streptokinase (plus aspirin) and placebo there were only 36 deaths within the first hour. This is an insufficient basis to test very early treatment.

A further issue may be relevant. It is scientifically dangerous to assume that time delay is the only difference between those presenting 'early' and 'late'. Such patients have not randomised themselves with respect to time and there is evidence to suggest that the 'early' group have larger infarctions, more severe pain and

more abrupt onset [15]. This is the group most at risk of extensive injury.

There is an apparent discrepancy between the original epidemiological studies [16,17], describing the relationship between time delay and mortality risk, and the findings of the recent large scale thrombolysis studies. In the former, patients with the shortest delay to presentation in hospital had the highest risk, but the large scale mortality studies have shown little time relationship to mortality risk or increasing risk with time delay. Among control patients in the GISSI study, mortality was 12% for those presenting within three hours of the onset of symptoms, but 14.1% thereafter (up to nine hours). Similarly, for patients discharged alive, subsequent mortality showed the same pattern: lowest among those seen within three hours. Similar findings were true of the ISAM study, and the ISIS 2 study showed no difference in mortality risk for the control group for the 0–3 hours versus 3–6 hours presentations. In the placebo group of the ASSET study there was a trend towards higher mortality in the 0–3 hour group (10.9%) compared with >3 hours (8.65%).

The differences between the original epidemiological studies and the thrombolysis studies may be explained, in part, by the inclusion of early 'medically unattended' cardiac deaths in the former studies [17] and the exclusion of very early deaths from the thrombolysis studies. Furthermore, certain high risk patients have been excluded from the thrombolysis studies, for example those with cardiogenic shock, those following prolonged resuscitation and those that arrive *in extremis*. Thus, the differences may simply reflect the inclusion criteria for the respective studies.

Trials of pre-hospital thrombolysis

Patient numbers are small in the published trials of pre-hospital thrombolysis. Only a few studies have been blinded and placebo-controlled [18–22]. Important inter-trial variables comprise: criteria for inclusion; the median delay from the onset of symptoms to pre-hospital treatment; the thrombolytic agents; and the medical systems providing the pre-hospital care. These studies are too small to demonstrate differences in mortality. Rather, they have attempted to use surrogate end-points such as arterial patency [22–30], left ventricular function (global ejection fraction and regional infarct-related wall movement) [18,21,26,27, 31], or infarct size (QRS scores and cardiac enzyme release) [19,21,23,26,28].

Coronary patency (Table 1)

In a study from the Netherlands, 59 patients received 0.5 MU of streptokinase by infusion begun at home, and 37 patients started treatment in hospital, a mean of 50 minutes later [23]. Both groups proceeded directly to coronary angiography following admission and received intracoronary streptokinase and repeat

Table 1. Angiographic patency of infarct-related coronary artery

Study	Agent used	DOT (min)	Saving (min)	No. treated	Infarct-related coronary patency
Castaigne [18]	anis, 30 IU	131 (med)	49 (med)	57 (v36)	72% on admission No comparison in-hospital v. pre-hospital treatment
McNeill [19]	rt-PA, 150 mg	119	68	27 (v30)	79% of 24 in pre-hospital group } at day 11 64% of 25 in in-hospital group
Schofer [21]	Uro, 2 mU	85	40	40 (v38)	60% of pre-hospital group } at discharge 66.7% of in-hospital group
Sauval [24]	rt-PA, 100 mg	126	55	80	83% of 30 patients at 48 hours
Picart [25]	anis, 30 IU	?	50	42	83% at day 3
Roth [27]	rt-PA, 120 mg	94	43	74 (v44)	82% of 65 in pre-hospital group } at 72 hours 77% of 43 in in-hospital group
Bosker [28]	SK, 0.5 mU	75	50	59 (v37)	56% on admission/76% after i.c. SK in pre-hospital group 17% on admission/73% after i.c. SK in in-hospital group
Kokott [29]	rt-PA, 100 mg	102	?	110	77.4% on admission/90.6% after i.c. rt-PA
Hooghoudt [30]	anis, 30 IU	93	62	41 (v21)	79% of pre-hospital group } at 14 days 78% of in-hospital group

All times are means except for *Castaigne* [18] where times are medians.
anis = anistreplase; SK = streptokinase; Uro = urokinase
DOT = delay from onset of symptoms to treatment.
No. treated = patients receiving pre-hospital thrombolysis.
Figures in parentheses are patients receiving in-hospital thrombolysis used as a comparative group.
Those studies in italics are double-blind placebo-controlled trials.

angiography. Not surprisingly, the initial angiogram demonstrated patency of the infarct-related artery in 56% of the patients treated at home and in only 17% of those beginning treatment in hospital. However, by the time the intracoronary infusion was complete, there was no significant difference in patency rates: 76% in the former group, 73% in the latter.

In a study from Germany, a mobile intensive care unit was employed and rt-PA (alteplase) infusion initiated outside hospital in 110 patients, at a mean of 41 minutes before arrival in the cardiac catheter laboratory [29]. Patency of the infarct-related artery was seen in 77.4% of patients one hour after the start of the infusion. After additional intracoronary rt-PA the patency was 90.6%.

Sauval and colleagues reported 83% patency 48 hours after a pre-hospital infusion of rt-PA (100 mg/1.5 hours) in 80 patients beginning therapy a mean of 2.1 hours after the onset of symptoms [24]. An identical patency rate was reported 72 hours after pre-hospital treatment with APSAC (anistreplase 30 iu/5 min) given in 42 patients a mean of 1.5 hours from the onset of symptoms [25].

In a trial conducted in Jerusalem, 83% of infarct-related arteries were patent 6 days after pre-hospital streptokinase infusion (0.75 MU/30 min), but this was almost identical to the patency rates in those patients starting treatment in hospital, albeit 55 minutes later [26]. Another study from Israel used rt-PA infusion (120 mg/6 hours) and demonstrated no difference in 72 hour patency between the group of 74 patients treated outside hospital and the 44 patients randomly assigned to treatment in the coronary care unit. This was in spite of a saving of 43 minutes in the delay to treatment in the pre-hospital group [27]. Similarly, no difference in patency was demonstrated after pre-hospital bolus urokinase, compared with in-hospital treatment, despite 40 minutes time gain [22].

Hooghoudt and colleagues compared patency at two weeks in 41 patients given anistreplase (APSAC) at home by ambulance crew, after telephone consultation with a cardiologist, and 21 patients, recruited according to the same selection criteria, who were treated with anistreplase in hospital a mean of 1 hour later [30]. There was no difference in patency: 79% in the pre-hospital group and 78% in the hospital group.

Table 2. Assessment of left ventricular ejection fraction

Study	Agent used	DOT	Saving	No. treated	Estimate of left ventricular function
Castaigne [18]	anis, 30 IU	131 (med)	49 (med)	57 (v36)	EF 56.7% in pre-hospital group EF 53.4% in in-hospital group } on admission n.s.
McNeill [19]	rt-PA, 150 mg	119	68	27 (v30)	EF 41% in pre-hospital group EF 35% in in-hospital group } at day 11 n.s. Regional EF 41% in pre-hospital group Regional EF 28% in in-hospital group } $p<0.05$
Schofer [21]	Uro, 2 MU	85	40	40 (v38)	EF 50% in pre-hospital group EF 57% in in-hospital group } at discharge n.s.
Weiss [26]	SK, 0.75 MU	63	55	29 (v84)	EF 62% in pre-hospital group EF 55% in in-hospital group } at day 6, $p<0.005$
Roth [27]	rt-PA, 120 mg	94	43	74 (v44)	EF 45% in 63 of pre-hospital group EF 48% in 41 of in-hospital group } at 72 hours
Villemant [31]	SK, 1.5 MU	?	74	67 (v53)	EF 59% in pre-hospital group if reperfusion < 2 h EF 48% in hospital group if reperfusion < 2 h EF 51% in pre-hospital group if reperfusion > 4 h EF 49% in hospital group if reperfusion > 4 h

EF = ejection fraction; SK = streptokinase; Uro = urokinase; anis = anistreplase.
DOT = delay from onset of symptoms to treatment.
No. treated = those receiving pre-hospital thrombolysis; med = median.
Figures in parentheses refer to patients receiving thrombolysis in hospital used as comparisons.
Those studies in italics are double-blind placebo-controlled trials.

These trials have demonstrated that time delay to thrombolytic therapy can be reduced by about 40 minutes by pre-hospital treatment. Although significant differences in early patency have been revealed by the time gain, caution must be employed in the interpretation of the patency endpoint. Such an endpoint did not serve to predict the results of the major large scale mortality studies of thrombolytic agents. For example, the TIMI 1 study revealed clear advantages for rt-PA over streptokinase with respect to 90 minute coronary patency [32], but these differences have not been substantiated in the large scale comparisons of the two agents with respect to mortality [10, 11].

Left ventricular function (Table 2)

Weiss demonstrated a significant improvement in global left ventricular function, as measured by angiography six days after admission, in 29 patients given pre-hospital streptokinase (0.75 MU) compared with the group who received treatment on arrival in hospital (mean of 63 minutes after the onset of symptoms) (n = 84). The pre-hospital group received very early treatment and achieved a time gain of 55 minutes [26]. The differences in ventricular function were particularly marked in patients with anterior myocardial infarction.

However, other studies have, in general, failed to confirm improvements in global ejection fraction, whether measured by angiography or radionuclide methods. A placebo-controlled study from France employing anistreplase reported a trend (not statistically significant) towards greater admission ejection fractions in 57 pre-hospital treated patients (56.7%) compared with 43 patients who received a placebo injection at home (53.4%) [18]. Similarly, a placebo-controlled trial of urokinase from Germany showed no difference in global ejection fraction or regional wall movement at discharge [21].

Roth and colleagues showed no difference in global ejection fraction on admission or on discharge as measured by radionuclide ventriculography. However, the pre-hospital group was relatively late after the onset of symptoms. The 74 patients in whom treatment was started at home had a time delay of 94 minutes compared with in-hospital treatment at a mean of 137 minutes [27].

A double-blind placebo-controlled study from Belfast using rt-PA (150 mg) failed to show significant differences in global ejection fraction a mean of 10.7 days after admission, when measured by contrast ventriculography or radionuclide ventriculography. The study involved 24 patients treated at home compared with 26 patients in hospital. However, pre-hospital treatment was also relatively late in this study (mean 119 minutes from the onset of symptoms with a time gain of 68 minutes over in-hospital treatment) [19]. Nevertheless, this study demonstrated a significant

improvement in infarct-related regional wall movement 10–14 days after infarction in those patients who received pre-hospital thrombolysis.

In a study from France, 1.5 MU streptokinase was infused by anaesthetists in emergency ambulances, and global and regional ejection fraction were improved, but only in those patients where reperfusion was evident within two hours from the onset of symptoms [31]. Thus, measurements of global ejection fraction have not revealed consistent differences as a result of pre-hospital treatment, despite the time gain of 40–60 minutes in these studies. However, a trend is apparent consistent with the earlier hypothesis. Very early treatment (median 1 hour after the onset of symptoms) [19,26,31] does appear to show benefit as a result of the time gain of 40–60 minutes. It must be emphasised that these are relatively small studies and similar sized studies in the early development of thrombolytic therapy did not even show consistent benefit of thrombolytic treatment over placebo.

In the interpretation of left ventricular function studies, additional potentially confounding factors must be considered. These include the compensatory enhancement of contractility in non-infarct-related regions resulting from maintenance of global left ventricular function [33]. Furthermore, patients with severe left ventricular dysfunction may survive as a result of pre-hospital treatment whereas they may have died if treatment had been delayed until hospital admission. Such patients would tend to obscure the benefits of pre-hospital treatment.

Infarct size (Table 3)

In the study from Weiss and colleagues in Jerusalem, hourly creatine phosphokinase (CK) levels were measured and significantly lower peak CK levels were seen in patients allocated to pre-hospital treatment. Upon subgroup analysis, significant differences were restricted to patients with inferior myocardial infarction [26]. There were no significant differences in peak CK with pre-hospital treatment in the urokinase study from Germany [21], or the study by Roth and colleagues [27]. However, Bosker and colleagues did show a significantly lower level of 72-hour hydroxybutyrate dehydrogenase (by 32%) in patients with anterior myocardial infarction and pre-hospital treatment [23,28]. Similarly, both Weiss [26] and McNeill [19] showed significant reductions in infarct size when assessed by a QRS scoring system, either at six days or at 10–14 days.

In summary, based upon cardiac enzyme release, some but not all of the relatively small studies have revealed that early pre-hospital treatment results in reduced infarct size.

Feasibility of pre-hospital thrombolysis

The studies performed thus far have provided ample evidence that pre-hospital thrombolysis is feasible in urban and probably also in rural communities [34]. Either bolus injection or infusion of the thrombolytic drug has been administered by cardiologists [20], physicians [26], anaesthetists [27], general practitioners [35] or paramedical ambulance personnel [36, 37].

Thus, the pilot studies have demonstrated that pre-hospital treatment is feasible and consistently achieved approximately 40–60 minutes of time gain compared with waiting to start treatment in hospital. By reducing the delay to treatment, more patients may become eligible for thrombolytic therapy [38].

It should be remembered, however, that most of the published studies have compared pre-hospital treatment with coronary care unit treatment. There are frequently long delays between admission to hospital and the start of thrombolytic therapy [39]. It is important to recognise that previous in-hospital regimens cannot be regarded as optimal in-hospital treatment. A new standard of in-hospital treatment is required with rapid identification and thrombolytic administration by a single team (the 'Fast Track' system) [40].

Potential adverse effects of pre-hospital thrombolytic therapy

Serious adverse effects, within the first hour, are uncommon. As with in-hospital thrombolytic administration, the principal adverse effects are transient hypotension and symptomatic bradycardia. Ventricular arrhythmias including ventricular fibrillation are seen more commonly during the first hour of myocardial infarction, and the major mortality studies demonstrated that thrombolytic treatment reduced the frequency of major cardiovascular complications including cardiogenic shock [10].

Arrhythmias and cardio-respiratory arrest

Roth and colleagues reported no significant difference in the incidence of complications during transportation, with or without pre-hospital treatment. Ventricular fibrillation occurred in 2.7% with pre-hospital treatment compared with 4.5% without; ventricular tachycardia in 2.7% compared with 2.3%; and bradycardia in 4% compared with 4.5% [27].

Castaigne reported one out-of-hospital death among 57 patients given intravenous anistreplase before transfer, and one death in the placebo-control group. There were five hypotensive episodes during transportation of the treatment group and two such episodes among controls [18].

McNeill reported three episodes of ventricular fibrillation during infusion of rt-PA prior to admission to the coronary care unit and one episode during placebo infusion. Ventricular fibrillation was no more common during rt-PA treatment than seen in an earlier study of acute myocardial infarction without thrombolysis [19].

Table 3. Assessment of size of myocardial infarction

Study	Agent used	DOT	Saving	No. treated	Assessment of infarct size	
McNeill [19]	rt-PA, 150 mg	119	68	27 (v30)	QRS score ≤ 3 in 15 of 25 pre-hospital group QRS score ≤ 3 in 8 of 27 in-hospital group	} $p < 0.05$
Schofer [21]	Uro, 2 mU	85	40	40 (v38)	Peak CK 726 IU in pre-hospital group Peak CK 748 IU in in-hospital group	} n.s.
Weiss [26]	SK, 0.75 MU	63	55	29 (v84)	Peak CK 900 IU/QRS score 4.1 in pre-hospital group Peak CK 1298 IU/QRS score 6.4 in in-hospital group	} $p < 0.05$
Roth [27]	rt-PA, 120 mg	94	43	74 (v44)	Peak CK 1346/AUC CK 7109 in pre-hospital group Peak CK 1228/AUC CK 6864 in in-hospital group	} n.s.
Bosker [28]	SK, 0.5 MU	75	50	59 (v37)	HBD reduced by 32% in patients with anterior myocardial infarction	

SK = streptokinase; Uro = urokinase; CK = creatine phosphokinase.
HBD = hydroxybutyrate dehydrogenase; AUC = area under CK curve.
DOT = delay from onset of symptoms to treatment (all times are means).
No. treated = those receiving pre-hospital thrombolytic agents.
Figures in parentheses refer to patients receiving thrombolysis in hospital used as a comparative group.
Those studies in italics are double-blind placebo-controlled trials.

Hypotension and bleeding

Hypotension appears to be reported more frequently among patients treated with streptokinase or anistreplase but this has not been associated with excess mortality. Bleeding during transfer to hospital has not been reported as a complication, and stroke following thrombolysis has not been evident prior to hospital admission in any of the studies [41]. Although uncommon, the impact of stroke (0.5–1.0% incidence) may be devastating, and fear of stroke may restrict pre-hospital thrombolysis in the USA [42].

Incorrect diagnosis

False positive diagnosis during pre-hospital evaluation occurs, but with a very low frequency. Castaigne and colleagues reported six false positives out of 155 diagnoses of acute myocardial infarction in a pilot study involving junior anaesthetists and mobile intensive care units. In the trial that followed, three patients out of 100 were randomised to receive anistreplase or placebo but were later excluded because the diagnosis of acute myocardial infarction was incorrect. The correct diagnoses were old myocardial infarction, angina and coronary artery spasm [18]. Two cases of pericarditis and one of aortic dissection were correctly diagnosed outside hospital [43]. In the study from Israel, physicians or interns in the mobile intensive care unit misdiagnosed two of 118 patients with suspected acute myocardial infarction. Alteplase (t-PA) infusions were given to a patient with pericarditis and to a patient whose ECG did not meet the study criteria [27].

There were, however, no reported false positive diagnoses among 110 patients treated by emergency care physicians in Berlin [29], in 41 patients treated by Dutch ambulance personnel in conjunction with ECG transmission to a cardiologist [30], or among 111 patients treated by ambulance nurses utilising computer analysis of the ECG [37]. It must be stressed that these findings concerning the accuracy of diagnosis cannot be extrapolated to non-ECG-confirmed diagnoses, or to diagnoses made by non-specialist care teams.

Studies in progress

The Grampian Regional Early Anistreplase Trial (GREAT) involves 30 general practices, with a combined patient population of 140,000 located more than an hour from the nearest admitting cardiac centre. Entry into the trial requires a clinical diagnosis of acute myocardial infarction without necessitating ECG confirmation [44]. This study is likely to confirm a large time saving consequent upon pre-hospital treatment and will potentially be widely applicable to rural general practice in Britain. However, the benefit/risk ratio must be defined in terms of morbidity and mortality.

A Dutch study (REPAIR) involved highly trained paramedic ambulance personnel equipped with computerised ECG recorders and a standardised questionnaire to identify contraindications to thrombolysis [36, 37]. Based upon the ECG and the completed questionnaire, the computer advises commencement of treatment or immediate transfer to hospital based upon pre-defined criteria. This approach, with no direct

medical involvement, could be readily adapted for use in a wide variety of settings.

Two large-scale trials of pre-hospital therapy are in progress (EMIP and MITI) and will be highly influential in the future planning of the emergency medical treatment of myocardial infarction.

The European Myocardial Infarction Project (EMIP)

This is a large scale (projected 5,000 patients) multi-centred placebo-controlled double-blind trial involving intravenous anistreplase (30 U by i.v. injection over five minutes). It is supported, in part, by the European Community. Entry criteria require typical cardiac chest pain of less than six hours duration, and ECG criteria are not defined. The majority of the participating centres will employ medically manned mobile coronary care units. The principal endpoints are one month and long-term mortality and secondary endpoints include non-fatal in-hospital major events, eg recurrent myocardial infarction. Individual centres will be encouraged to analyse left ventricular function and/or infarct size. A preliminary report based upon the data of recruitment to EMIP (patient numbers $n = 2,500$) demonstrated a time saving of approximately 60 minutes in the major centres contributing to the study (France and Northern Ireland) (presentation at European Society of Cardiology 1990) [45].

Myocardial Infarction Triage and Intervention Project (MITI)

This project involves 19 hospitals and five paramedic systems operating in the city of Seattle and the surrounding suburban area of King County in Washington state. Following an initial 'phase 1' feasibility study, patients were entered into the full study which began in November 1988 [46]. This is a randomised, non-blinded controlled trial of oral aspirin and alteplase infusion commenced outside hospital and administered by ambulance paramedics. The diagnosis is based upon strict ECG criteria and validated by a physician at the base station following telephone transmission [47]. The major endpoints are ejection fraction and infarct size, measured with radionuclide techniques at three weeks.

The results of the 'phase 1' study indicate that only 107 of 2,472 patients assessed by the paramedics met the criteria for administration of thrombolytic therapy; 23.9% of all patients admitted and discharged with evidence of acute myocardial infarction met both the clinical and ECG criteria for treatment by paramedics. There was a potential time saving of just over one hour [48].

Conclusions (Table 4)

The feasibility and significant time savings of pre-hospital thrombolysis have been demonstrated in prelimi-

Table 4. The current status of pre-hospital thrombolysis

- Feasibility established: time savings of 40–60 minutes.
- Mortality and functional impact: not yet proven.
- Pre-hospital therapy should be compared with optimal 'Fast Track' in-hospital treatment.
- Measures to reduce in-hospital delay should be implemented (these may result in similar time savings).
- Patient education campaigns to reduce patient delay: overall, effects are transient and disappointing.
- Co-ordinated policies required: family practitioners; ambulance/paramedic systems; acute admission units and A/E departments.
- Hypothesis: shortening of ischaemic time is critical within the first 60–90 minutes: a 40 minutes time gain may only have a marginal benefit after 3 hours.

nary studies. Provided that criteria for selection and treatment of patients are carefully defined, and the administering personnel trained and equipped at resuscitation, then safety of pre-hospital treatment appears to be acceptable. The relatively small studies which have been completed do not reveal a clear benefit in terms of mortality. There is insufficient evidence to support the adequacy of surrogate endpoints such as patency, left ventricular function and infarct size. However, it must be remembered that the original studies of thrombolysis also failed to demonstrate objective measures of benefit in studies of similar size.

The results of the two large-scale studies (EMIP and MITI) are awaited with interest, and optimal design for pre-hospital thrombolysis systems will be influenced by their results. The design of the North American study is not directly applicable to European centres, and the European study (EMIP) is only currently applicable to centres with a physician-manned mobile coronary care unit. The GREAT study may provide an answer to the role of the general practitioner, particularly in rural communities.

Pre-hospital thrombolysis reopens the debate about the potential role of mobile coronary or intensive care units [49,50]. Thrombolytic therapy enforces a re-examination of current ambulance and paramedic practice. Should the patient be evaluated, stabilised and thrombolysis initiated before transfer to hospital, or transferred with minimal delay?

The current large-scale studies should not delay the implementation of all other means of reducing in-hospital delay. Virtually all hospitals in Britain have scope for substantial improvement. The role of patient education in minimising delay remains to be proven but this should not prevent future initiatives aimed at minimising this important component of overall delay [51]. In this review, our hypothesis suggests that the time savings of 40–60 minutes are potentially most relevant to those with very early presentation (within 60–90 minutes), a large volume of myocardium at risk, and the potential for very rapid treatment.

Hospital services need to develop policies for acute

management of myocardial infarction, including thrombolysis. A major emphasis is required, with the aim of minimising delay and the identification of clear-cut infarction by a 'Fast Track' system. These policies must consider open access chest pain clinics, and possibly direct admission to coronary care units [52], provided that sufficient staff and beds are available to cope with 'rule out' infarction. Accident and emergency specialists must form part of the co-ordinated team with responsibility for early diagnosis of myocardial infarction and initiation of thrombolytic treatment. Establishing mortality benefit in large-scale studies has only been the first step.

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