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(Accepted 15 April 1996)

Prospective evaluation of eligibility for thrombolytic therapy in acute myocardial infarction

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BMJ 1996;312:1637–41

Abstract

***Objective*—To determine the proportion of patients presenting with acute myocardial infarction who are eligible for thrombolytic therapy.**

***Design*—Cohort follow up study.**

***Setting*—The four coronary care units in Auckland, New Zealand.**

***Subjects*—All 3014 patients presenting to the units with suspected myocardial infarction in 1993.**

***Main outcome measures*—Eligibility for reperfusion with thrombolytic therapy (presentation within 12 hours of the onset of ischaemic chest pain with ST elevation ≥2 mm in leads V1-V3, ST elevation ≥1 mm in any other two contiguous leads, or new left bundle branch block); proportions of (a) patients eligible for reperfusion and (b) patients with contraindications to thrombolysis; death (including causes); definite myocardial infarction.**

***Results*—948 patients had definite myocardial infarction, 124 probable myocardial infarction, and nine ST elevation but no infarction; 1274 patients had unstable angina and 659 chest pain of other causes. Of patients with definite or probable myocardial infarction, 576 (53.3%) were eligible for reperfusion, 39 had definite contraindications to thrombolysis (risk of bleeding). Hence 49.7% of patients (537/1081) were eligible for thrombolysis and 43.5% (470) received this treatment. Hospital mortality among patients eligible for reperfusion was 11.7% (55/470 cases) among those who received thrombolysis and 17.0% (18/106) among those who did not.**

***Conclusions*—On current criteria about half of patients admitted to coronary care units with definite or probable myocardial infarction are eligible for thrombolytic therapy. Few eligible patients have definite contraindications to thrombolytic therapy. Mortality for all community admissions for myocardial infarction remains high.**

Introduction

Because of the mortality benefit conferred by thrombolytic therapy in acute myocardial infarction[1-6] strategies must be aimed at delivering treatment to the maximum number of eligible patients presenting to hospital from the general community. The proportion of patients eligible for thrombolytic therapy reportedly varies from 15-16%[7 8] to 79%.[9] These figures are affected by whether eligibility is based on admission electrocardiographic and time window criteria or a discharge diagnosis of myocardial infarction. Patients entering thrombolytic trials such as the fourth international study of infarct survival,[9] which reported 79% utilisation of thrombolytic therapy, may represent only a subset of those who present to general hospitals with suspected myocardial infarction. This is within the range (70-80%) suggested by Ketley and Woods[10 11] as the likely optimum rate of eligibility for thrombolytic therapy and less than the National Health Service recommended rate (90%).[12] By contrast, some studies reporting low rates of thrombolytic use may have excluded potentially eligible patients—for example, elderly patients, diabetic patients, or patients treated by primary angioplasty.[7 8]

To determine the eligibility of consecutive, unselected patients with suspected acute myocardial infarction presenting to community hospitals for reperfusion with thrombolytic therapy we prospectively evaluated patients presenting to the four coronary care units in Auckland, New Zealand, in 1993.

Table 1—*Baseline characteristics*

	Definite infarction (n = 948)	Probable infarction (n = 124)	Total* (n = 1081)
Mean (SD) age (years)	64 (12)	65 (11)	64 (12)
No (%) male	672 (71)	88 (71)	766 (71)
No (%) with previous infarction	208 (22)	36 (29)	247 (23)
No (%) with angina	301 (32)	58 (47)	363 (34)
No (%) with hypertension	332 (35)	48 (39)	384 (36)
No (%) with diabetes	106 (11)	18 (15)	124 (11)
No (%) smokers	332 (35)	41 (33)	375 (35)
No (%) with family history of premature coronary heart disease	252 (27)	34 (27)	288 (27)
No (%) with previous percutaneous transluminal coronary angioplasty	18 (2)	1 (1)	19 (2)
No (%) with previous coronary artery bypass grafting	44 (5)	10 (8)	55 (5)

*Includes nine patients with ST elevation and no increase in creatine kinase activity who received thrombolytic therapy (aborted infarction).

Methods

The coronary care units accepted patients of any age with suspected myocardial infarction unless cardiopulmonary resuscitation was precluded by comorbidity. Patients considered to have unstable angina at presentation were also usually admitted to the units. The recommended time window and electrocardiographic criteria for thrombolytic therapy were presentation within 12 hours of symptom onset with either ST elevation ≥1 mm in at least two leads (≥2 mm in leads V1-V3)[5 13] or new onset left bundle branch block.[6] Specific contraindications included uncontrolled hypertension (blood pressure ≥180/110 mm Hg which could not be lowered); surgery, trauma, or invasive procedures within two weeks; prolonged (15 minutes or more) or traumatic cardiopulmonary resuscitation; known haemostatic disorder; haemorrhagic diabetic retinopathy; recent gastrointestinal or genitourinary bleeding; or stroke within six months.

Definite myocardial infarction was defined as two of the following: 20 minutes or more of ischaemic chest pain; peak creatine kinase activity ≥ twice normal; development of Q waves or persistent T wave changes in the electrocardiogram. When creatine kinase activity was increased to less than twice normal for our laboratory and there were no evolutionary Q waves or persistent T wave changes probable myocardial infarction was diagnosed. Patients who presented with ST elevation and received thrombolytic therapy but did not have peak creatine kinase activity >300 U/l were recorded as having aborted infarction.

Data were collected prospectively. A family history of premature coronary heart disease was defined as sudden death, myocardial infarction, or angina in mother or sisters aged under 60 or in father or brothers aged under 55. Hypertension was recorded as currently receiving treatment. Smoking was defined as current or having quit for less than one month. A history of dyslipidaemia was not recorded. The time to hospital admission and time to thrombolytic therapy from the onset of pain were also recorded. Cardiogenic shock was defined as hypotension with systolic blood pressure ≤90 mm Hg for ≥30 minutes with evidence of hypoperfusion despite correction of reversible factors. Heart failure was defined as radiological evidence of pulmonary interstitial or alveolar oedema.

The significance of categorical variables was determined by χ^2 test and of continuous variables by Student's t test. 95% Confidence intervals were calculated when appropriate.

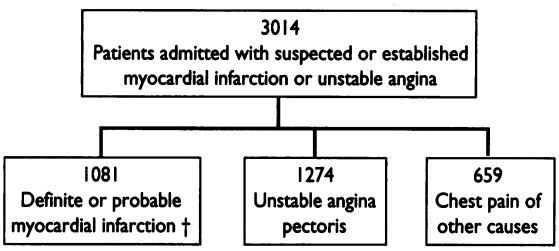

Fig 1—*Flow chart of 3014 patients admitted with suspected or established myocardial infarction or unstable angina*

Results

Admissions to the coronary care units in 1993 included 1072 patients with probable or definite myocardial infarction, 1274 patients with unstable angina pectoris, and 659 patients considered to have other causes for their chest pain (fig 1). Additionally, nine patients who presented with ST elevation had no increase in creatine kinase activity or persistent electrocardiographic changes after thrombolytic therapy. Patients with unstable angina pectoris and chest pain of other causes are excluded from this study. Mean hospital stay was 7.4 (SD 5.3) days. Table 1 gives the baseline characteristics of the patients with myocardial infarction.

ELIGIBILITY FOR THROMBOLYTIC THERAPY

Five hundred and seventy six patients (53.3%; 95% confidence interval 50.3% to 56.2%) fulfilled the time and electrocardiographic criteria for eligibility for reperfusion, including 12 patients (2.1%; 1.2% to 3.6%) with new onset left bundle branch block. Of reperfusion eligible patients, 39 (6.8%; 5.0% to 9.1%) had definite contraindications to thrombolytic therapy (table 2). Additionally, at the physicians' discretion eight patients who were eligible for reperfusion but had a history of peptic ulceration (six), non-haemorrhagic diabetic retinopathy (one), and advanced oropharyn-

Table 2—*Reasons for non-use of thrombolysis in patients eligible by time and electrocardiographic criteria (n = 106)*

	No of patients
Contraindications to therapy	
Hypertension (blood pressure >180/110 mm Hg)	3
Recent surgery or trauma*	17
Recent gastrointestinal or genitourinary bleeding	7
Stroke	11
Bleeding diathesis	1
Total	39
Relative contraindications	
Previous peptic ulcer disease	6
Diabetic retinopathy	1
Cancer	1
Total	8
Diagnostic uncertainty	
? Dissection	4
? Pericarditis	1
Transient or borderline ST elevation	15
? New left or right bundle branch block	12
Total	32
Other	
Severe comorbid disease	3
Age†	5
Physician discretion†	12
Shock†	1
Unknown	6
Total	27

*Includes five traumatic cardiac arrests.
†See discussion.

Table 3—*Characteristics and outcome of patients presenting within 12 hours and with ST elevation or new onset left bundle branch block in electrocardiogram*

	Thrombolytic therapy (n = 470)	No thrombolytic therapy (n = 106)
Mean (SD) age (years)	64 (11)	66 (12)
No (%) male	337 (72)	66 (62)
No (%) with previous infarction	88 (19)	36 (34)
No (%) with angina	125 (27)	39 (37)
No (%) with hypertension	157 (33)	43 (41)
No (%) with diabetes	40 (9)	18 (17)
No (%) smoking	170 (36)	33 (31)
Mean (SD) peak creatine kinase (U/l)	2250 (1704)	1637 (1325)
No (%) with previous percutaneous transluminal coronary angioplasty	5 (1)	2 (2)
No (%) with previous coronary artery bypass grafting	18 (4)	8 (8)
Mortality	55 (12)	18 (17)

geal carcinoma (one) were not given thrombolytic therapy. Of all patients who fulfilled the electrocardiographic and time window criteria for thrombolytic therapy, 470 (81.6%; 78.2% to 84.6%) received thrombolytic therapy; 455 (79.0%) received streptokinase and 15 (2.6%) recombinant tissue plasminogen activator. One patient who had surgery 10 days previously was treated by primary angioplasty. Table 3 lists the characteristics of patients eligible for reperfusion who did and did not receive thrombolytic therapy.

Of the 948 patients with a discharge diagnosis of definite myocardial infarction, 534 (56.3%; 53.2% to 59.5%) fulfilled electrocardiographic and time window criteria for thrombolytic therapy and 428 of these patients (80.2%; 76.6% to 83.3%) received thrombolytic therapy.

THROMBOLYTIC THERAPY IN PATIENT SUBGROUPS

Of patients who were eligible for reperfusion on electrocardiographic and time window criteria, 50 (23.0%; 17.9% to 29.1%) of 217 aged 70 or more did not receive thrombolytic therapy as compared with 56 (15.6%; 12.2% to 19.7%) of 359 aged under 70 ($\chi^2 = 4.51$; P = 0.03). This difference could not be attributed to decreased utilisation of thrombolytic therapy among eligible elderly women compared with elderly men (71/94 (75.5%; 65.9% to 83.2%) *v* 96/123 (78.0%; 69.9% to 84.5%)). There was a trend towards decreased utilisation of thrombolytic therapy among eligible women (women 133/173 (76.9%; 70.0% to 82.6%); men 337/403 (83.6%; 79.7% to 86.9%)) ($\chi^2 = 3.5$; P = 0.06). Thrombolytic therapy was also used less commonly in patients with diabetes than in non-diabetic patients (40/58 (69.0%; 56.0% to 79.5%) *v* 430/518 (83.0%; 79.5% to 86.0%)) ($\chi^2 = 6.8$; P = 0.02).

PATIENTS PRESENTING LATE OR WITHOUT ST ELEVATION

One hundred and fifty six patients (14.4%; 12.5% to 16.7%) (including 26 with presumed new onset left bundle branch block) were eligible for reperfusion on electrocardiographic criteria but presented more than 12 hours after symptom onset. Of these patients, 36 (23.1%) received thrombolytic therapy and 120 (76.9%) did not. Twenty three of 349 patients (6.6%) presenting with ST depression, T wave inversion, or a normal electrocardiogram received thrombolytic therapy (table 4).

MORTALITY

Patients presenting with ST elevation or new onset left bundle branch block within 12 hours had an overall hospital mortality of 12.7% (73/576 cases; 95% confidence interval 10.2% to 15.6%). Of these deaths, 55 (11.7%; 9.1% to 14.9%) occurred among the 470 patients given thrombolytic therapy and 18 (17.0%; 11.0% to 25.3%) among the 106 not given thrombolytic therapy (table 4). Mortality among patients presenting more than 12 hours after symptom onset with ST elevation or new onset left bundle branch block was 21.2% (33/156 cases; 15.4% to 28.3%). Of the entire cohort of 1081 patients, 138 died (overall mortality 12.8%; 10.9% to 14.9%). Among the 948 patients with definite myocardial infarction (age range 24-94 years) and 124 patients with probable myocardial infarction were 130 (13.7%; 95% confidence interval 11.5% to 15.9%) and eight (6.5%; 2.2% to 10.8%) respectively. The most common cause of death was cardiogenic shock (55 cases; 39.9%) or heart failure (30;

Table 5—*Causes of death*

	No of patients
Cardiogenic shock	55
Congestive heart failure	30
Confirmed rupture	5
Presumed rupture*	12
Ventricular arrhythmia	17
Unwitnessed death	2
Other cardiovascular	13
No data	4
Total	138

*Electromechanical dissociation.

Table 4—*Mortality according to presenting electrocardiogram, age, and thrombolytic therapy. Figures are percentages (whole numbers in parentheses)*

	Thrombolytic therapy				No thrombolytic therapy				Total			
	Age (years)				Age (years)				Age (years)			
	<55	55-69	≥70	All ages	<55	55-69	≥70	All ages	<55	55-69	≥70	All ages
ST elevation or bundle branch block ≤12 hours	1.9 (2/108)	8.7 (17/195)	21.6 (36/167)	11.7 (55/470)	5.9 (1/17)	7.7 (3/39)	28.0 (14/50)	17.0 (18/106)	2.4 (3/125)	8.5 (20/234)	23.0 (50/217)	12.7 (73/576)
ST elevation or bundle branch block >12 hours*	0 (0/9)	12.5 (2/16)	27.3 (3/11)	13.9 (5/36)	18.2 (4/22)	18.4 (7/38)	28.3 (17/60)	23.3 (28/120)	12.9 (4/31)	16.7 (9/54)	28.2 (20/71)	21.2 (33/156)
ST depression	50.0 (1/2)	0 (0/2)	60.0 (3/5)	44.4 (4/9)	0 (0/17)	7.4 (4/54)	20.7 (17/82)	13.7 (21/153)	5.3 (1/19)	7.1 (4/56)	23.0 (20/87)	15.4 (25/162)
T wave inversion or normal electrocardiogram†	0 (0/3)	0 (0/6)	20.0 (1/5)	7.1 (1/14)	0 (0/53)	2.6 (2/76)	9.1 (4/44)	3.5 (6/173)	0 (0/56)	2.4 (2/82)	10.2 (5/49)	3.7 (7/187)

*Or time not specified.
†Includes paced rhythm.

21.7%) (table 5). Confirmed or presumed cardiac rupture occurred in 17 cases (12.3%) and one patient died of a haemorrhagic stroke after thrombolytic therapy.

Discussion

For reperfusion therapy with thrombolytic agents to significantly reduce overall hospital mortality from myocardial infarction we need to rapidly identify and treat patients who may benefit. The electrocardiographic criteria that we used for eligibility for thrombolytic therapy have been accepted internationally.[5 13] Nevertheless, they differed slightly from those used in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) and other studies of thrombolytic therapy (table 6). Most studies included patients with ST elevation, though there were two minor differences in the electrocardiographic criteria: ≥1 mm versus ≥2 mm ST elevation in leads V4-V6 and one or more versus two or more leads showing ST elevation. Some studies, however, including the second international study of infarct survival (ISIS-2), did not use electrocardiographic criteria, whereas others such as the GISSI-I study included patients with ST depression.

We evaluated prospectively eligibility for reperfusion therapy with thrombolytic agents and utilisation of this treatment in patients admitted from the community with suspected acute myocardial infarction. Patients were admitted irrespective of age provided that they had no serious comorbidity that might have made admission to a coronary care unit inappropriate. We did not collect data on patients with chest pain admitted direct to medical wards. Nor did we collect data on patients admitted direct to medical wards with other symptoms, such as confusion or breathlessness, who later turned out to have myocardial infarction.

Of patients admitted to coronary care units, 53.3% (576/1081) presented within 12 hours of symptom onset and had ST elevation or new left bundle branch block in the electrocardiogram, thus fulfilling our usual criteria for eligibility for reperfusion therapy.[5 13] A total of 6.8% (39) of these eligible patients had definite contraindications to thrombolytic therapy. Of patients with a discharge diagnosis of definite myocardial infarction, 56.3% (534/948) were eligible for thrombolytic therapy on time and electrocardiographic criteria. This figure is lower than that reported (79%).[9] These ISIS study differences may relate either to patient selection or to whether eligibility is based on time and electrocardiographic criteria at admission or on a discharge diagnosis of myocardial infarction. Patients with a discharge diagnosis of myocardial infarction include many without ST elevation or new left bundle branch block in the electrocardiogram at presentation, resulting in a smaller proportion of reperfusion eligible patients.

In this study 32.3% of patients (349/1081) with definite or probable myocardial infarction presented with ST depression, T wave inversion, or a normal electrocardiogram. There is no evidence for the efficacy of thrombolytic therapy in reducing mortality in patients with these electrocardiographic criteria.[6]

In the GISSI-I study roughly one fifth of patients had no ST elevation in the electrocardiogram and 13.8% had contraindications to streptokinase[1] whereas GISSI-2 required ST elevation in only one lead and 10.3% of patients had contraindications to thrombolysis.[14]

CAUTIONS WITH THROMBOLYTIC THERAPY

In the early years of clinical treatment with thrombolytic agents there was caution about its use in older patients, in patients presenting after six hours, and in those with relative contraindications.[15] The fibrinolytic therapy trialists' overview found a significant reduction in mortality with thrombolytic therapy in patients irrespective of age—namely, 15 (SD 4) lives saved per 1000 aged under 55; 21 (5) lives saved per 1000 aged 55-64; 37 (6) lives saved per 1000 aged 65-74; 13 (14) lives saved per 1000 aged 75 and over.[6] Our findings show that thrombolytic therapy remains underutilised in elderly patients who may otherwise be eligible on time and electrocardiographic criteria. Also some patients presenting after 12 hours benefit from reperfusion therapy with thrombolytic agents,[16] though predicting which patients may benefit at admission may be difficult.

Concern about the risk of retinal haemorrhage in diabetic patients with retinopathy[17] probably explains the decreased use of thrombolysis in these patients. Recent evidence suggests that the risk of this complication may be low[18] and if it occurs it can usually be treated without long term loss of vision.[19] Because diabetic patients are at high absolute risk[6] they should be considered for thrombolytic therapy irrespective of retinopathy.

Other potential bleeding risks, including traumatic cardiopulmonary resuscitation (four (0.4%) cases excluded in this study) and menstruation (none excluded), have been considered contraindications to thrombolytic therapy. Several reports suggest that these are only relative contraindications and that the risks of major bleeding are small.[20-23] The role of reperfusion strategies in cardiogenic shock requires definition. Finally, patients who are eligible for thrombolytic therapy on electrocardiographic and time window crite-

Table 6—*Eligibility criteria for thrombolytic therapy from clinical trials*

Trial	Time from symptom onset (hours)	ST elevation			Amount of ST depression (No of leads)	Other	Drug (intravenous unless otherwise stated)
		Limb leads (No)	Leads V1-V3 (No)	Leads V4-V6 (No)			
GISSI[1]	≤12	≥1 mm (1)	≥2 mm (1)	≥2 mm (1)	As for ST elevation	—	Streptokinase
USIM[28]	≤4	≥1 mm (1)	≥2 mm (1)	≥2 mm (1)	As for ST elevation	—	Urokinase
Interuniversity[29]	≤4	≥1 mm (1)	≥2 mm (1)	≥2 mm (1)	Not eligible	—	Intracoronary + intravenous streptokinase
AIMS[30]	≤6	≥1 mm (2)	≥2 mm (2)	≥2 mm (2)	Not eligible	—	Anisoylated plasminogen streptokinase activator complex
ISIS-2[2]	≤24	—	—	—	—	Acute infarction clinically suspected	Streptokinase
ASSET[31]	≤5	—	—	—	—	Acute infarction clinically suspected	Tissue plasminogen activator
EMERAS[32]	6-24	—	—	—	—	Acute infarction clinically suspected	Streptokinase
LATE[16]	6-24	≥1 mm (2)	≥2 mm (2)	≥2 mm (2)	≥2 mm (2)	Abnormal Q or T waves (≥2 leads)	Tissue plasminogen activator
Western Washington[4]	≤12	≥1 mm (2)	≥1.5 mm (2)	≥1 mm (2)	Not eligible	One lead with ST elevation if no Q waves or hyperacute T waves	Intracoronary streptokinase
White *et al*[5 13]	≤6	≥1 mm (2)	≥2 mm (2)	≥1 mm (2)	Not eligible	—	Streptokinase
ISAM[3]	≤6	≥1 mm (1)	≥2 mm (1)	≥2 mm (1)	Not eligible	—	Streptokinase

Key messages

- About half of patients with myocardial infarction present within 12 hours and have ST elevation ≥1 mm in two leads (≥2 mm in leads V1-V3) or new onset left bundle branch block
- Less than 10% of patients eligible for reperfusion have contraindications to thrombolysis
- The hospital mortality for all patients with acute myocardial infarction remains high (14%)
- Better treatments are required to reduce mortality in both reperfusion eligible and reperfusion ineligible patients

ria but who have definite contraindications to thrombolytic therapy should not be denied reperfusion therapy and should have primary angioplasty. Only one patient in this series was referred for primary angioplasty in these circumstances and potentially others could have been considered.

In addition to absolute contraindications to thrombolytic therapy, there are numerous relative contraindications, including pancreatitis, the presence of left atrial thrombus, infective endocarditis, pregnancy, oral anticoagulant therapy, and advanced liver disease. Overall these relative contraindications are uncommon. The possible risks and likely benefits of treatment need to be assessed and considered individually in each patient. Having considered absolute and relative contraindications, there remained 59 patients (10.2%) who were eligible for thrombolytic therapy on time and electrocardiographic criteria but who did not receive this treatment. Most commonly either these patients had equivocal or transient ST elevation or there were other, unstated physicians' reasons for withholding treatment. Also, some patients had differential diagnoses which may have precluded thrombolysis. The overall rate of non-administration of reperfusion therapy (roughly 10%) among otherwise eligible patients is low compared with recent registry data in the same era.[24]

The hospital mortality in this series among patients considered eligible for reperfusion was 13.7% (95% confidence interval 11.5% to 15.9%); 11.7% among patients who received thrombolysis, 17.0% among those who did not. These results are similar to recent reports of European registries.[25 26] The respective 30 and 35 day death rates were about 7% in the global utilisation of streptokinase and tissue plasminogen activator for occluded coronary arteries study[27] and the fourth international study of infarct survival.[9] This suggests that patients randomised in trials represent a subgroup of patients presenting to community hospitals with suspected acute myocardial infarction.

In conclusion, the community hospital mortality from myocardial infarction remains high. Definite contraindications to thrombolysis are uncommon but only half of patients with suspected acute myocardial infarction and slightly more with definite myocardial infarction fulfil current eligibility criteria. Thrombolytic therapy should be used as widely and expeditiously as possible in these patients. Other strategies should be directed at facilitating hospital admission, and in order to lower overall community death rates additional treatments are required for patients not considered eligible for thrombolytic therapy.

We thank Loretta Bush and Judy Grant for help with data collection and the nurses and physicians who cared for patients.

Funding: This work was supported in part by a grant from the Health Research Council of New Zealand.

Conflict of interest: None.

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(Accepted 24 April 1996)