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Clinical research

Percutaneous coronary intervention and 1 year survival in patients treated with fibrinolytic therapy for acute ST-elevation myocardial infarction

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KEYWORDS

ST-elevation myocardial infarction;
Primary percutaneous coronary intervention;
Fibrinolytic therapy

Aims To assess the predictors of 1 year mortality in patients treated with fibrinolytic therapy for ST-segment elevation myocardial infarction (STEMI) and to determine whether a strategy of early percutaneous coronary intervention (PCI) improves outcome.

Methods and results Consecutive patients ($n = 474$) admitted to our unit (1998–2001) with STEMI were treated with fibrinolytic therapy. For each patient, age, gender, admission via mobile coronary care unit (MCCU), infarct location, initial systolic blood pressure and Killip class, prior history of ischaemic heart disease, hypertension, diabetes mellitus, smoking status, family history, hyperlipidaemia, and in-hospital PCI ($n = 154$) were recorded. Mortality at 1 year was obtained from medical records ($n = 473$). Binary logistic regression analysis was performed to determine independent predictors of 1 year mortality. Mortality in the non-PCI group was 21 vs. 7% in the PCI group. Independent predictors of 1 year mortality were age (risk ratio 1.12, 95% CI 1.08–1.15, $P < 0.0001$), initial SBP ≤ 80 mmHg (risk ratio 4.34, 95% CI 1.68–11.2, $P = 0.002$), initial Killip class ≥ 3 (risk ratio 2.97, 95% CI 1.42–6.2, $P = 0.004$), and lack of in-hospital PCI (risk ratio 0.39, 95% CI 0.19–0.81, $P = 0.012$). Although the PCI group were younger ($P = 0.007$), more likely to be admitted via the MCCU ($P = 0.008$), with a shorter pain to needle time ($P = 0.04$), multivariable analysis adjusted for these differences.

Conclusion In-hospital PCI in patients treated with fibrinolytic therapy for STEMI is associated with a substantial reduction in 1 year mortality.

Introduction

The primary goal of treatment of acute coronary occlusion is the achievement of early, complete, and sustained epicardial and myocardial reperfusion. Until, recently,

fibrinolytic therapy constituted the dominant approach for reperfusion in ST-segment elevation myocardial infarction (STEMI). Primary percutaneous coronary intervention (PCI) is now used as an alternative to fibrinolysis with increasing frequency. This approach is supported by a recent comprehensive meta-analysis of 23 trials demonstrating that with primary PCI, compared with fibrinolytic therapy, there were reductions in death, recurrent myocardial infarction, and stroke of 2, 4, and 1 per 100

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patients, respectively, through 4–6 weeks.¹ However, the benefits of primary PCI are limited by the delays in treatment incumbent in this approach. In the meta-analysis by Keeley *et al.*,¹ there was no significant mortality benefit of emergency hospital transfer for primary PCI compared with on-site fibrinolysis. Furthermore, the PRAGUE-2 study randomized 850 patients with STEMI presenting within <12 h to the nearest community hospital without a catheter laboratory to either fibrinolytic therapy (streptokinase) in that hospital ($n = 421$) or immediate transport for primary PCI ($n = 429$).² Patients randomized within 3 h of symptom onset ($n = 551$) had no difference in 30 day mortality whether treated by fibrinolytic therapy (7.4%) or transferred for PCI (7.3%).² The Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction (CAPTIM) trial compared early, pre-hospital fibrinolytic therapy (with transfer to an interventional facility for possible rescue angioplasty) with primary PCI in 840 patients presenting within 6 h of onset of symptoms.³ Overall there was no benefit of primary PCI at preventing the composite endpoint of death, non-fatal re-infarction, or non-fatal stroke at 30 days.³ In a further analysis of the data, it emerged that in patients treated with pre-hospital fibrinolytic therapy within 2 h of symptom onset, there was a strong trend toward lower 30 day mortality (2.2 vs. 5.7%, $P = 0.058$) and a reduction of cardiogenic shock (1.3 vs. 5.3%, $P = 0.032$) compared with primary PCI.⁴ In the pre-hospital fibrinolytic arm of the CAPTIM trial, 26% of patients underwent rescue PCI for persistent ischaemia and 70% of patients had PCI by day 30. Therefore, this study really compares a strategy of pre-hospital fibrinolytic therapy, transfer to an interventional centre, and subsequent PCI with primary PCI.⁴ In addition, the lower mortality in the lytic group was sustained at 1 year. Although early studies on the use of PCI post-fibrinolytic therapy showed no benefit over a conservative approach,⁵ they were carried out before the era of stenting and modern antiplatelet therapy. It has thus recently been suggested that a therapeutic strategy that incorporates both fibrinolytic therapy and PCI will best serve most patients with STEMI.^{4,6}

At present, there are very limited data available on this combined approach. From our registry of patients, we therefore aimed to assess the predictors of 1 year mortality in patients first treated with fibrinolytic therapy for STEMI either out of or in-hospital and to determine whether a strategy of early PCI (during in-hospital stay) would improve outcome.

Methods

Patients

Consecutive patients admitted with chest pain to the coronary care unit and cardiology wards of the Royal Victoria Hospital between February 1998 and March 2001 and who received fibrinolytic therapy for STEMI were reviewed. Patients transferred from other hospitals after acute myocardial infarction (AMI) for further investigations were excluded.

Data were collected prospectively and entered into a database (constructed using Microsoft Access) by a research nurse. The diagnosis of AMI was based on a suggestive history with ST-elevation ≥ 2 mm in two or more precordial leads, or ST-elevation ≥ 1 mm in two or more limb leads, or new left bundle branch block on the 12-lead electrocardiograph with a concomitant rise in creatine kinase MB to ≥ 2 times the upper limit of normal.

Patients were deemed eligible for fibrinolytic therapy up to 12 h from onset of symptoms. Contraindications to fibrinolytic therapy included hypertension ($>180/110$ mmHg), prior stroke, recent major surgery/trauma, prolonged cardiopulmonary resuscitation, active bleeding, oral anticoagulation with warfarin, or haemorrhagic diathesis. Age was not a contraindication to fibrinolytic therapy. Invasive investigations and interventional treatment were at the discretion of the consultant cardiologist. As the unit participates in many international multi-centre fibrinolytic trials, varying fibrinolytic regimens were used during the study period.

The following data were noted on each patient: age, gender, history of hypertension, diabetes mellitus, hyperlipidaemia (cholesterol > 5.0 mmol/L), smoking, family history (first degree relative with previous ischaemic heart disease), and whether the patient had a previous history of ischaemic heart disease/myocardial infarction. The following characteristics were also noted: initial systolic blood pressure and Killip class, infarct location (based on the 12-lead electrocardiograph), symptom onset to needle time (time delay between onset of symptoms and administration of fibrinolytic therapy), admission via the mobile coronary care unit (MCCU) (with administration of pre-hospital fibrinolytic therapy) or not, and whether the patient underwent in-hospital PCI.

Data for death, further PCI, or coronary artery bypass grafting (CABG) at 1 year were obtained from hospital records (patient administration system) or by contacting the patient's general practitioner.

Statistical analysis

Categorical variables were compared with the Pearson's χ^2 test and continuous variables with the independent samples *t*-test. Multivariable analysis was performed using forward, stepwise binary logistic regression to determine independent predictors of 1 year mortality. All variables (age, gender, admission via MCCU, infarct location, initial systolic blood pressure and Killip class, prior history of ischaemic heart disease, hypertension, diabetes mellitus, smoking status, family history, hyperlipidaemia, and in-hospital PCI) were included in the multivariable analysis. The test also included a quadratic term for age, as linearity was not assumed. The test was repeated using only the univariate predictors of death. All tests were two-sided. $P < 0.05$ was taken as significant. All means are shown with standard deviation and medians with interquartile range (25th–75th percentiles). All calculations were carried out with the SPSS version 10.0 software package.

The study complies with the Declaration of Helsinki and was approved by the Queen's University Of Belfast Research Ethics Committee. All patients gave informed consent.

Results

In the study period, 474 patients were treated with fibrinolytic therapy for STEMI. Mortality data were available for 473 patients with one lost to follow-up due to taking up residence in another country. Baseline demographics and clinical characteristics are shown in *Table 1*.

Admission via the MCCU occurred in 256 (54%) patients (*Tables 1 and 2*). Infarct locations were classified as anterior in 182 (38%), inferior in 265 (56%), and lateral in 26 (6%) patients. The pain to needle time (median) was 3 h (1.9–5.1) with 378 (80%) patients receiving fibrinolytic therapy within 6 h. An initial systolic blood pressure ≤ 80 mmHg occurred in 30 (6%) patients, and 47 (10%) had a Killip class ≥ 3 .

Table 1 Baseline demographics and clinical characteristics

Mean age ($\pm$ SD)	64 (12)
Male	325 (69)
Infarct location	
Anterior	182 (38)
Inferior	265 (56)
Lateral	26 (6)
Initial SBP ≤ 80 mmHg	30 (6)
Initial Killip class ≥ 3	47 (10)
Admission via MCCU	256 (54)
Pain to needle time (median, h)	3 (1.9–5.1)
Previous AMI	120 (25)
Diabetes mellitus	64 (14)
Hyperlipidaemia	318 (67)
Hypertension	139 (29)
Current smoker	199 (42)
Family history of IHD	290 (61)
Thrombolytic agent	
Alteplase/reteplase/tenecteplase	317 (67)
Streptokinase	156 (33)

Data are number (%) or median (interquartile range: 25th and 75th percentiles) or mean (SD). SBP, systolic blood pressure; IHD, ischaemic heart disease.

In-hospital PCI was carried out in 154 (33%) patients (*Table 2*). The PCI group compared with the non-PCI group were younger [62 (± 11) vs. 65 (± 13) years, $P=0.007$], were more likely to be admitted via the MCCU [97 (63%) vs. 159 (50%), $P=0.008$], and had a shorter median pain to needle time [2.5 (1.7–4.0) h vs. 3.9 (2.2–5.5) h, $P=0.04$]. In the PCI group, 86% of patients had fibrinolytic therapy within 6 h vs. 77% in the non-PCI group ($P=0.2$). The PCI and non-PCI groups were also comparable with regard to gender, anterior/inferior infarction, initial systolic blood pressure/Killip class, and history of previous AMI, diabetes mellitus, hyperlipidaemia, hypertension, current smokers, or family history of ischaemic heart disease. There was no difference in discharge medication between the groups except for the use of clopidogrel in the PCI group.

Angiographic data for the PCI group are summarized in *Table 3*. In the PCI group, 63 (41%) patients underwent their procedure within 24 h of admission, with 27 (18%) of these as 'rescue PCI' because of persistent ischaemia.

One year outcomes (death/PCI/CABG) are summarized in *Table 4*. Death at 1 year occurred in 77 (16%) of the 473 patients. Of the 378 who received lytic therapy within 6 h of the onset of symptoms, 133 had in-hospital PCI and 245 had no in-hospital PCI with a 1 year mortality of 7.5% (10/133) and 18.8% (46/245) ($P=0.004$), respectively. Of the 95 patients who received lytic therapy >6 h after onset of symptoms, 21 had in-hospital PCI and 74 had no in-hospital PCI with a 1 year mortality of 4.8% (1/21) and 27% (20/74) ($P=0.036$), respectively. Univariate predictors of 1 year mortality are shown in *Tables 5 and 6*. Age, initial Killip class ≥ 3 , initial systolic blood pressure ≤ 80 mmHg, no PCI in-hospital, female gender, non-smoking, and

Table 2 Demographics and clinical characteristics according to occurrence of in-hospital PCI

	In-hospital PCI ($n=154$)	No in-hospital PCI ($n=319$)	P -value
Mean age ($\pm$ SD)	62 (11)	65 (13)	0.007
Admission via MCCU	97 (63)	159 (50)	0.008
Pain to needle time (median, h)	2.5 (1.7–4.0)	3.9 (2.2–5.5)	0.04
Fibrinolytic therapy ≤ 6 h	133 (86)	245 (77)	0.2
Male	113 (73)	212 (67)	0.2
Anterior AMI	57 (37)	125 (39)	0.5
Inferior AMI	93 (60)	172 (54)	0.5
Initial SBP ≤ 80 mmHg	10 (6)	20 (6)	0.2
Initial Killip class ≥ 3	10 (6)	37 (12)	0.3
Previous AMI	40 (26)	80 (25)	0.9
Diabetes mellitus	21 (14)	43 (14)	1
Hyperlipidaemia	99 (64)	219 (69)	0.4
Hypertension	47 (31)	92 (29)	0.7
Current smoker	65 (42)	134 (42)	0.5
Family history of IHD	98 (64)	192 (60)	0.5
Discharge medication			
Aspirin	137 (89)	290 (91)	0.8
β -Blocker	109 (71)	233 (73)	0.7
ACE-inhibitor	83 (54)	163 (51)	0.4
Statin	112 (73)	220 (69)	0.7
Clopidogrel	99 (64)	6 (2)	<0.0001

Data are numbers (%) or median (interquartile range: 25th and 75th percentiles). SBP, systolic blood pressure; IHD, ischaemic heart disease.

Table 3 Angiographic data for in-hospital PCI group (n = 154)

Indications for PCI	
Rescue PCI	27 (18)
Unstable angina	37 (24)
Post-AMI	90 (58)
Time from admission to PCI	
0–24 h	63 (41)
>24 h	91 (59)
Clinically significant coronary artery disease	
Single-vessel disease	77 (50)
Two-vessel disease	43 (28)
Three-vessel disease	34 (22)
Infarct related artery	
Left anterior descending artery	59 (38)
Circumflex artery	17 (11)
Right coronary artery	78 (51)
Left main stem	0
Intervention performed (stents)	
Single vessel	145 (94)
Two vessels	9 (6)
Angioplasty without stenting	0

Data are numbers (%).

Table 4 1-Year outcomes (death/PCI/CABG) according to occurrence of in-hospital PCI

Outcome	PCI (n = 154)	No PCI (n = 319)	P-value
Death	11 (7)	66 (21)	<0.001
PCI	8 (5)	57 (18)	0.001
CABG	5 (3)	13 (4)	0.7

Data are numbers (%).

Table 5 Univariate predictors of 1 year mortality (categorical variables)

Variable		<i>n</i>	Mortality	<i>P</i> -value
Initial Killip Class	<3	426	58 (14)	<0.001
	≥3	47	19 (40)	
Initial SBP	>80 mmHg	443	64 (14)	<0.001
	≤80 mmHg	30	13 (43)	
In-hospital PCI	Yes	154	11 (7)	<0.001
	No	319	66 (21)	
Gender	Male	325	44 (14)	0.02
	Female	148	33 (22)	
Current Smoker	Yes	199	19 (10)	0.001
	No	274	58 (21)	
Admitted via MCCU	Yes	256	34 (13)	0.06
	No	217	43 (20)	

Data are numbers (%). SBP, systolic blood pressure.

a longer pain to needle time were associated with increased 1 year mortality. There was also a trend towards higher mortality in patients not admitted via the MCCU ($P = 0.06$). Previous history of hypertension,

Table 6 Univariate predictors of 1 year mortality (continuous variables)

	Survived	Died	P-value
Age (mean ± SD)	62 (11)	75 (11)	<0.001
Pain to needle time (median and IQR)	2.9 (1.9–4.8)	3.6 (1.9–6.3)	0.03

IQR, interquartile range (25th–75th percentiles).

Table 7 Independent predictors of 1 year mortality (multi-variable analysis using binary logistic regression)

	Risk ratio	95% CI	P-value
Age	1.12	1.08–1.15	<0.0001
Initial SBP ≤ 80 mmHg	4.34	1.68–11.2	0.002
Initial Killip class ≥ 3	2.97	1.42–6.2	0.004
In-hospital PCI	0.39	0.19–0.81	0.012

CI, confidence interval; SBP, systolic blood pressure.

diabetes mellitus, hyperlipidaemia, and AMI, family history, anterior/inferior infarction and treatment with lytic therapy within 6 h were not predictors of 1 year mortality.

All significant univariate predictors were included in the multiple logistic regression model to examine their independent predictive value for 1 year mortality (Table 7). Age, initial systolic blood pressure ≤80 mmHg, initial Killip class ≥3, and no in-hospital PCI were significant independent predictors of 1 year mortality. Furthermore, the test also included a quadratic term for age (age^2) as linearity was not assumed with all variables remaining significant.

Discussion

The present study shows that patients treated with fibrinolytic therapy for STEMI who undergo in-hospital PCI have improved outcome (risk ratio 0.39, 95% CI 0.19–0.81, $P = 0.012$) at 1 year compared with patients who do not undergo PCI (Table 7).

Although primary PCI is now used as an alternative to fibrinolytic therapy with increasing frequency, <20% of patients presenting with STEMI are treated with primary PCI.⁷ There remain some doubts about the overall superiority of primary PCI over fibrinolytic therapy. Melandri^{8,9} points out that although Keeley *et al.*¹ report a significant 2.0% absolute reduction in total mortality in favour of primary PCI ($P = 0.0002$). In the absence of the SHOCK trial,¹⁰ this difference falls to a non-significant 1.2% when comparing primary PCI with accelerated tissue plasminogen activator. There is also concern about the incumbent delays in transferring patients for primary PCI. The median time delay (door to balloon time) in 661 centres was 1 h 56 min, with

nearly half of patients waiting >2 h before balloon inflation, which was associated with an increase in in-hospital mortality of 41–62%.¹¹ A meta-analysis of published randomized trials of primary PCI vs. fibrinolytic therapy shows that when the time delay related to angiography (that is the door to balloon minus the door to needle time) is >60 min, the mortality benefits of primary PCI over thrombolytic therapy are lost.¹² For every 10 min delay, there is a 1% reduction in impact of primary PCI on the composite endpoint of death, re-infarction, or stroke, so that by 90 min there is no measurable difference between primary PCI and immediate thrombolytic therapy.¹²

Some studies have suggested that combining early fibrinolytic therapy with subsequent PCI in the setting of STEMI may be a very effective strategy,^{13–16} particularly because it would reduce the time to optimal myocardial reperfusion compared with primary PCI and may reduce the risk of recurrent infarction compared with fibrinolytic therapy. This was particularly evident in the CAPTIM trial where pre-hospital fibrinolytic therapy within 2 h of symptom onset resulted in a strong trend toward lower mortality and a reduction of cardiogenic shock compared with primary PCI at 30 days.⁴ Also, the recently published GRACIA-1 trial randomized 500 patients with thrombolysed STEMI to angiography and intervention (if indicated) within 24 h of thrombolysis, or to an ischaemia-guided conservative approach. By comparison with patients receiving conservative treatment, by 1 year, patients in the invasive group had a 12% absolute reduction in the combined rate of death, re-infarction, or revascularization ($P = 0.0008$).¹⁷

Although our results are based on a multivariable analysis adjusting for many confounding variables, an observational study cannot adjust for all confounders. Nevertheless, our study lends support to the need for randomized controlled trials to determine whether primary PCI or a strategy incorporating fibrinolysis and PCI (facilitated PCI, rescue PCI, or delayed PCI) best serves patients with STEMI.

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