

Articles

Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials

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Summary

Background Many trials have been done to compare primary percutaneous transluminal coronary angioplasty (PTCA) with thrombolytic therapy for acute ST-segment elevation myocardial infarction (AMI). Our aim was to look at the combined results of these trials and to ascertain which reperfusion therapy is most effective.

Methods We did a search of published work and identified 23 trials, which together randomly assigned 7739 thrombolytic-eligible patients with ST-segment elevation AMI to primary PTCA (n=3872) or thrombolytic therapy (n=3867). Streptokinase was used in eight trials (n=1837), and fibrin-specific agents in 15 (n=5902). Most patients who received thrombolytic therapy (76%, n=2939) received a fibrin-specific agent. Stents were used in 12 trials, and platelet glycoprotein IIb/IIIa inhibitors were used in eight. We identified short-term and long-term clinical outcomes of death, non-fatal reinfarction, and stroke, and did subgroup analyses to assess the effect of type of thrombolytic agent used and the strategy of emergent hospital transfer for primary PTCA. All analyses were done with and without inclusion of the SHOCK trial data.

Findings Primary PTCA was better than thrombolytic therapy at reducing overall short-term death (7% [n=270] vs 9% [360]; p=0.0002), death excluding the SHOCK trial data (5% [199] vs 7% [276]; p=0.0003), non-fatal reinfarction (3% [80] vs 7% [222]; p<0.0001), stroke (1% [30] vs 2% [64]; p=0.0004), and the combined endpoint of death, non-fatal reinfarction, and stroke (8% [253] vs 14% [442]; p<0.0001). The results seen with primary PTCA remained better than those seen with thrombolytic therapy during long-term follow-up, and were independent of both the type of thrombolytic agent used, and whether or not the patient was transferred for primary PTCA.

Interpretation Primary PTCA is more effective than thrombolytic therapy for the treatment of ST-segment elevation AMI.

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Introduction

In the mid-1970s, acute myocardial infarction (AMI) was identified, in nearly all cases, as being the result of a ruptured atherosclerotic plaque, causing thrombosis and occlusion of the coronary artery.¹ Subsequently, the reperfusion era was ushered in with the realisation that an occlusive thrombus in a coronary artery could be managed by use of a combination of a guidewire to mechanically initiate coronary blood flow and the intracoronary infusion of streptokinase.² The recognition that the prompt restoration of flow salvages myocardium, reduces infarct size, and prolongs life has been the driving force behind a large number of clinical trials, assessing thrombolytic therapy for AMI. The results of these trials, done in the early 1980s and involving tens of thousands of patients, unequivocally showed that thrombolytic therapy resulted in preserved left-ventricular function and decreased mortality in patients with AMI.³

Primary percutaneous transluminal coronary angioplasty (PTCA), defined as balloon angioplasty undertaken as the primary reperfusion strategy for AMI without previous or concomitant thrombolytic therapy, was initially compared with intracoronary thrombolytic therapy.⁴ Over the next decade, ten trials, comparing primary PTCA with intravenous thrombolytic therapy for ST-segment elevation AMI were undertaken. In 1995⁵ and in 1997,⁶ systematic reviews of this topic were published, with the later analysis of 2606 patients, showing improved short-term clinical outcomes, including death, with primary PTCA compared with thrombolytic therapy. Since this quantitative review, however, 13 new trials, comparing these two reperfusion modalities, have been done, more than doubling the number of randomised trials, and tripling the number of patients studied. Moreover, long-term clinical outcomes are now available for many of these trials. Our aim was, therefore, to provide an updated quantitative analysis of the results of the randomised trials of primary PTCA versus thrombolytic therapy.

Methods

Protocol

We identified all randomised trials done to date, published and unpublished, comparing primary PTCA with thrombolytic therapy for the treatment of acute ST-segment AMI, by searching the Medline database. We also searched scientific sessions abstracts in the *New England Journal of Medicine*, *Journal of the American College of Cardiology*, *Circulation*, *European Heart Journal*, *Heart*, and *Clinical Cardiology*, and questioned the principal investigators of most trials to ensure validity of the data, obtain additional unpublished data, and to verify that the study was randomised in design.

Our primary aim was to ascertain which reperfusion therapy, intravenous thrombolytic therapy or primary PTCA, is most effective for treatment of patients with

	Patients' characteristics	Symptom duration (h)	Number randomised to PTCA (n=3872)	Number randomised to thrombolysis (n=3867)	Stents used	Glycoprotein IIb/IIIa antagonists used	Thrombolytic agent used, administration time	Time to treatment (min)	
								PTCA	Thrombolytic therapy
Streptokinase trials (n=1837)									
Zijlstra ⁸	Age ≤75 years, ST↑	<6	152	149	No	No	1.5 million U SK, 1h	62*	30*
Riberio ⁹	Age <75 years, ST↑	<6	50	50	No	No	1.2 million U SK, 1h	238	179
Grinfeld ¹⁰	ST↑	<12	54	58	No	No	1.5 million U SK, 1h	63†	18†
Zijlstra ¹¹	ST↑, low risk	<6	47	53	No	No	1.5 million U SK, 1h	68*	30*
Akhras ¹²	ST↑	<12	42	45	No	No	1.5 million U SK, 1h	NA	NA
Widimsky ^{13**}	ST↑, LBBB	<6	101	99	Yes	No	1.5 million U SK, 1h	80†	70†
de Boer ¹⁴	Age ≥76 years; ST↑	<6	46	41	Yes	No	1.5 million U SK, 1h	59*	31*
Widimsky ¹⁵	ST↑	<12	429	421	Yes	Yes	1.5 million U SK, 1h	277‡§	245‡§
Fibrin-specific trials (n=5902)									
DeWood ¹⁶	Age ≤76 years; ST↑	<12	46	44	No	No	Duteplase, 4h	126*	84*
Grines ¹⁷	ST↑	<12	195	200	No	No	t-PA, 3h	60†	32†
Gibbons ¹⁸	Age <80 years; ST↑	<12	47	56	No	No	Duteplase, 4h	45†	20†
Ribichini ^{19,20}	Age <80 years; inferior MI, anterior ST↓	<6	55	55	No	No	Accelerated t-PA	40†	33†
Garcia ^{21,22}	anterior MI	5	95	94	No	No	Accelerated t-PA	84*	69*
GUSTO IIb ²³	ST↑, LBBB	<12	565	573	No	No	Accelerated t-PA	114†	72†
Le May ²⁴	ST↑, LBBB	<12	62	61	Yes	Yes	Accelerated t-PA	77†¶	15†
Bonnefoy ²⁵	ST↑	<6	421	419	Yes	Yes	Accelerated t-PA	190†	130†
Schomig ²⁶	ST↑	<12	71	69	Yes	Yes	Accelerated t-PA	65*¶	30*¶
Vermeer ^{27**}	Age <80 years; ST↑	<6	75	75	Yes	No	Accelerated t-PA	100†	85†
Andersen ²⁸	ST↑	<12	790	782	Yes	NA	Accelerated t-PA	NA	NA
Kastrati ²⁹	ST↑, LBBB	<12	81	81	Yes	Yes	Accelerated t-PA	75*¶	35*¶
Aversano ³⁰	ST↑	<12	225	226	Yes	Yes	Accelerated t-PA	102*¶	46*¶
Grines ³¹	ST↑	<12	71	66	Yes	Yes	Accelerated t-PA	155*	51*
Hochman ⁷	Cardiogenic shock	<36	152	150	Yes	Yes	Accelerated t-PA	75†¶	6168†¶

LBBB=left bundle branch block; MI=myocardial infarction; NA=data not available; SK=streptokinase; ST↑=elevation; ST↓=depression; t-PA=tissue-type plasminogen activator; accelerated t-PA²²=15 mg intravenous bolus, followed by an infusion of 0.75 mg/kg bodyweight over 30 min (maximum 50 mg) and then 0.50 mg/kg bodyweight over 60 min (maximum 35 mg) for a maximum dose of 100 mg. 68% of patients in the Grines Study³¹ and 70% of patients in the Hochman study⁷ received accelerated t-PA. *From admission. †From randomisation. ‡Average time. §From symptom onset to reperfusion. ¶Median time. ||Time to the permitted delayed revascularisation procedure (percutaneous or surgical) in the initial medical stabilisation group. **Both the PRAGUE¹³ and the LIM¹⁷ trials included a third group of individuals, who had thrombolytic therapy followed by transfer for subsequent PTCA (n=100 and n=74 patients, respectively); these 174 patients were excluded from our analyses.

Table 1: Summary of the 23 randomised trials of primary angioplasty versus thrombolytic therapy

AMI. The definition of eligible patients differed between studies, but typically required ischaemic symptoms and ST segment elevation of at least 1 mm in two contiguous leads or a left bundle branch block, and no contra-indications for the use of thrombolytic therapy. We analysed the data of all trials together, and in the absence of data from the SHOCK trial.⁷ We assessed the effect on clinical outcomes of the thrombolytic regimen used (streptokinase or fibrin-specific), and the strategy of emergent hospital transfer for primary PTCA compared with on-site thrombolysis.

We compared the following outcomes: total mortality, reinfarction (defined as recurrent ischaemic chest pain associated with new ST-segment changes and a re-elevation of cardiac enzymes), recurrent ischaemia, total stroke, haemorrhagic stroke, major bleeding (defined as intracranial haemorrhage or bleeding that caused haemodynamic compromise or blood transfusion, or both), and the combined endpoint of death, reinfarction, and disabling stroke. Outcomes as defined by each individual trial were used. Because case-specific event rates were not available for every study at the same time points, we defined short-term as 4–6 weeks and long-term as 6–18 months, when available, as the primary timepoints of interest.

Statistical analysis

We combined study results by use of the actual counts for each outcome within each trial, and obtained a combined outcome for all studies together. All comparisons were based on an intention-to-treat analysis, according to randomised groups. The odds ratios, 95% CI, and p values were calculated with exact tests for categorical data. We did χ^2 tests or, when appropriate, Fisher's exact

tests to compare PTCA with thrombolytic therapy for all outcomes to assess differences between proportions with calculations of odds ratios and exact 95% CI. A p value of

	Crossover data available	Crossover from PTCA to thrombolysis Number (%)	Crossover from thrombolysis to PTCA Number (%)
Streptokinase trials			
Zijlstra ⁸	Yes	0/152	14/149 (9%)
Riberio ⁹	Yes	0/50	5/50 (10%)
Grinfeld ¹⁰	No	NA	NA
Zijlstra ¹¹	No	NA	NA
Akhras ¹²	No	NA	NA
Widimsky ¹³	No	NA	NA
de Boer ¹⁴	No	NA	NA
Widimsky ¹⁵	Yes	4/429 (1%)	0/421
Fibrin-specific trials			
DeWood ¹⁶	No	NA	NA
Grines ¹⁷	Yes	0/195	14/200 (7%)
Gibbons ¹⁸	Yes	0/47	5/56 (9%)
Ribichini ^{19,20}	Yes	0/55	2/55 (4%)
Garcia ^{21,22}	No	NA	NA
GUSTO IIb ²³	Yes	0/565	8/573 (1%)
Le May ²⁴	Yes	1/62 (2%)	0/61
Bonnefoy ²⁵	Yes	2/421 (0.5%)	5/419 (1%)
Schomig ²⁶	No	NA	NA
Vermeer ²⁷	Yes	2/75 (3%)	0/75
Andersen ²⁸	No	NA	NA
Kastrati ²⁹	Yes	0/81	5/81 (6%)
Aversano ³⁰	Yes	7/225 (3%)	2/226 (1%)
Grines ³¹	No	NA	NA
Hochman ⁷	Yes	0/152	4/150 (3%)
Total	..	16/2509 (0.6%)	64/2516 (3%)

NA=not available.

Table 2: Available crossover data

	Death Number (%)		Non-fatal reinfarction Number (%)		Total stroke Number (%)		Haemorrhagic stroke Number (%)		Death, reinfarction, stroke Number (%)	
	PTCA	Thrombolytic therapy	PTCA	Thrombolytic therapy	PTCA	Thrombolytic therapy	PTCA	Thrombolytic therapy	PTCA	Thrombolytic therapy
Streptokinase trials (n=1837)										
Zijlstra ⁸	2/152 (1%)	11/149 (7%)	1/152 (1%)	18/149 (12%)	1/152 (0.7%)	3/149 (2%)	1/152 (1%)	2/149 (1%)
Riberio ⁹	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/50 (2%)	0/50	0/50	0/50	0/50
Grinfeld ¹⁰	5/54 (9%)	8/58 (14%)	1/54 (2%)	2/58 (3%)
Zijlstra ¹¹	1/47 (2%)	1/53 (2%)	0/47	7/53 (13%)	1/47 (2%)	2/53 (4%)	0/47	0/53	2/47 (4%)	10/53 (19%)
Akhras ¹²	0/42	4/45 (9%)	0/42	5/45 (11%)
Widimsky ¹³	7/101 (7%)	14/99 (14%)	1/101 (0.01%)	10/99 (10%)	0/101	1/99 (1%)	8/101 (8%)	23/99 (23%)
de Boer ¹⁴	3/46 (7%)	9/41 (22%)	1/46 (2%)	6/41 (15%)	1/46 (2%)	3/41 (7%)	4/46 (9%)	12/41 (29%)
Widimsky ¹⁵	29/429 (7%)	42/421 (10%)	36/429 (8%)	64/421 (15%)
All	50/921 (5%)	90/916 (10%)	6/492 (1%)	49/495 (10%)	3/396 (1%)	9/392 (2%)	1/249 (0.4%)	2/252 (0.8%)	50/623 (8%)	109/614 (18%)
OR (95% CI)	0.53 (0.37–0.75)		0.11 (0.05–0.26)		0.32 (0.09–1.21)		0.50 (0.05–5.59)		0.40 (0.28–0.58)	
Fibrin-specific trials (n=5902)										
DeWood ¹⁶	3/46 (7%)	2/44 (5%)
Grines ¹⁷	5/195 (3%)	13/200 (7%)	5/195 (3%)	14/200 (7%)	0/195	7/200 (4%)	0/195	4/200 (1%)	10/195 (5%)	32/200 (16%)
Gibbons ¹⁸	2/47 (4%)	2/56 (4%)	1/47 (2%)	3/56 (5%)	0/47	0/56	0/47	0/56
Ribichini ^{19,20}	1/55 (2%)	3/55 (6%)	1/55 (2%)	6/55 (11%)	0/55	0/55	0/55	0/55
Garcia ^{21,22}	3/95 (3%)	10/94 (11%)	4/95 (4%)	5/94 (5%)
GUSTO IIb ²³	32/565 (6%)	40/573 (7%)	25/565 (4%)	37/573 (7%)	6/565 (1%)	11/573 (2%)	0/565	8/573 (1%)	54/565 (10%)	78/573 (14%)
Le May ²⁴	3/62 (5%)	2/61 (3%)	3/62 (5%)	8/61 (13%)	1/62 (2%)	2/61 (3%)	7/62 (11%)	10/61 (16%)
Bonnefoy ²⁵	20/421 (5%)	16/419 (4%)	7/421 (2%)	15/419 (4%)	0/421	4/419 (1%)	0/421	2/419 (1%)	26/421 (6%)	34/419 (8%)
Schomig ²⁶	3/71 (4%)	5/69 (7%)	2/71 (3%)	4/69 (6%)	5/71 (7%)	9/69 (13%)
Vermeer ²⁷	5/75 (7%)	5/75 (7%)	1/75 (1%)	7/75 (9%)	2/75 (3%)	2/75 (3%)	0/75	1/75 (1%)	8/75 (11%)	14/75 (19%)
Andersen ²⁸	52/790 (7%)	59/782 (8%)	13/790 (2%)	49/782 (6%)	9/790 (1%)	16/782 (2%)	63/790 (8%)	107/782 (14%)
Kastrati ²⁹	2/81 (3%)	5/81 (6%)	0/81	4/81 (5%)	1/81 (1%)	1/81 (1%)
Aversano ³⁰	12/225 (5%)	16/226 (7%)	11/225 (5%)	20/226 (9%)	3/225 (1%)	8/226 (4%)	24/225 (11%)	40/226 (18%)
Grines ³¹	6/71 (8%)	8/66 (12%)	1/71 (1%)	0/66	0/71	3/66 (5%)	0/71	2/66 (3%)	6/71 (9%)	9/66 (14%)
Hochman ⁷	71/152 (47%)	84/150 (56%)	5/152 (3%)	1/150 (1%)	0/152 (0%)	2/150 (1%)
All	220/2951 (8%)	270/2951 (9%)	74/2753 (3%)	172/2757 (6%)	27/2739 (1%)	55/2744 (2%)	0/1581	19/1594 (1%)	203/2475 (8%)	333/2471 (14%)
OR (95% CI)	0.80 (0.66–0.96) 0.79 (0.63–0.99)*		0.42 (0.31–0.55)		0.49 (0.31–0.77)		..		0.57 (0.48–0.69)	
Combined results for all trials										
	270/3872 (7%)	360/3867 (9%)	80/3245 (3%)	222/3252 (7%)	30/3135 (1%)	64/3136 (2%)	1/1830 (0.05%)	21/1846 (1%)	253/3098 (8%)	442/3085 (14%)
	199/3720 (5%)*	276/3717 (7%)*
OR (95% CI)	0.73 (0.62–0.86) 0.70 (0.58–0.85)*		0.35 (0.27–0.45)		0.46 (0.30–0.72)		0.05 (0.006–0.35)		0.53 (0.45–0.63)	

OR=odds ratio. *Without SHOCK trial data.

Table 3: **Short-term clinical outcomes**

less than 0.05 was judged significant. Short-term and long-term outcomes for all trials were analysed, if available.

The SHOCK trial enrolled a high-risk group of patients in cardiogenic shock and compared a direct invasive strategy with an initial medical stabilisation strategy (thrombolysis and intra-aortic balloon pump). Of those

randomised to a direct invasive strategy, 87% underwent an invasive procedure and, in the initial medical stabilisation group, 63% received thrombolytic therapy. Due to the distinctive characteristics of this trial compared with the other trials, the endpoint of mortality was analysed both with and without these patients.

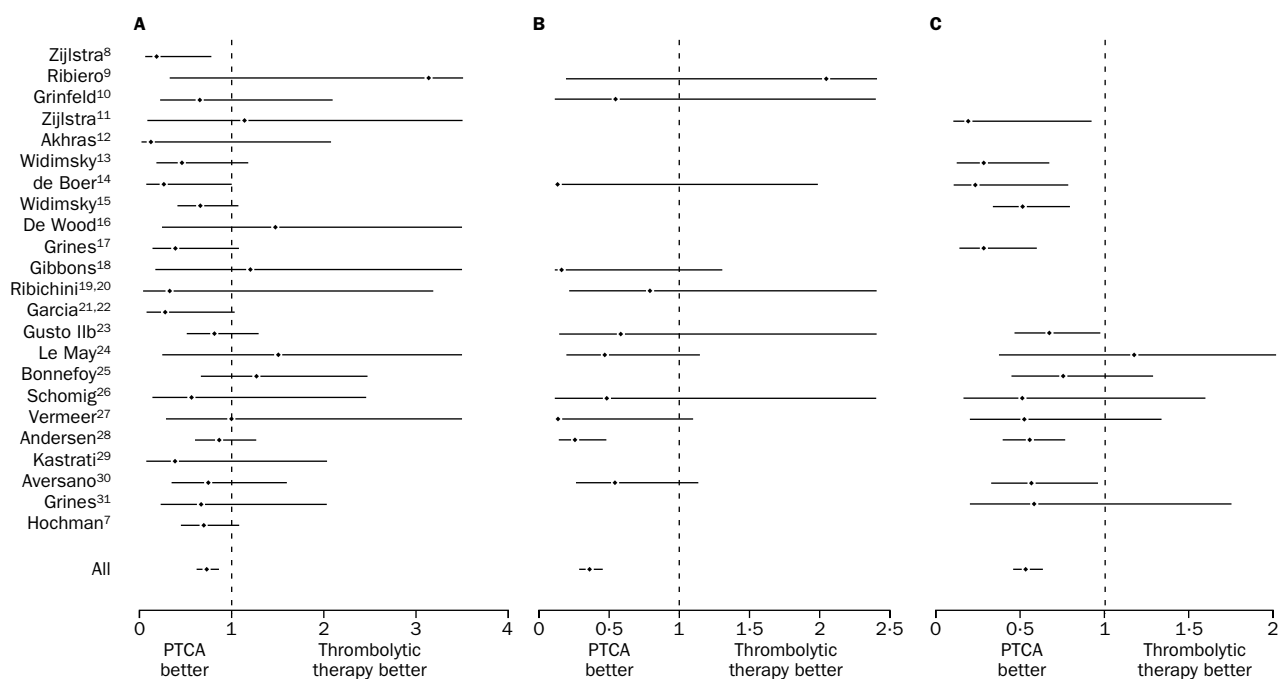


Figure 1: Odds ratios (95% CI) of short-term death (A), non-fatal reinfarction (B), and combined endpoint of death, non-fatal reinfarction, and stroke (C) for individuals treated with primary PTCA or thrombolytic therapy
Not all endpoints were reported in all trials.

We examined the odds ratios for each outcome for each study for heterogeneity with the Mantel-Haenszel odds ratio (Biostat, version 1). A Mantel-Haenszel p value of 0.05 was judged significant. The p values were as follows: death 0.56, reinfarction 0.19, total stroke 0.85, haemorrhagic stroke 0.75, the combined endpoint of death, stroke, and reinfarction 0.35, and the combined endpoint of death and reinfarction 0.03. Because the p value for the combined endpoint of death and reinfarction was 0.03, showing significant heterogeneity, this endpoint was not included in the analysis.

Results

Table 1 shows a summary of the features of the 23 trials we assessed.⁷⁻³¹ In total, 7739 patients were randomly assigned either PTCA or thrombolytic therapy. There were eight trials of primary PTCA versus streptokinase ($n=1837$), and 15 of primary PTCA versus fibrin-specific agents ($n=5902$). Of the 3867 patients randomly assigned thrombolytic therapy, most (76%, $n=2939$) received a fibrin-specific agent (tissue-type plasminogen activator, t-PA). Stents were used in 12 trials, and platelet glycoprotein IIb/IIIa inhibitors in eight. The criterion for time to treatment was 6 h or less in nine of the trials, 12 h in 13 trials, and up to 36 h in the SHOCK trial.⁷ Crossover data was available in 13 of the trials (table 2). Of the patients randomised to primary PTCA, 0.6% crossed over to thrombolytic therapy, and 3% to primary PTCA (table 2).

Table 3 and figures 1 and 2 show the short-term and long-term clinical outcomes for the 23 trials. Overall, patients assigned to primary PTCA were less likely to die (figure 1A), have a non-fatal reinfarction (figure 1B), or fall within the group who had a combined endpoint of death, non-fatal reinfarction, and stroke (figure 1C), than those assigned thrombolytic therapy. These outcomes were significantly decreased not only in the short-term, but also over long-term follow-up (figure 2). Major bleed was the only endpoint for which individuals were at

greater risk when treated with primary PTCA rather than thrombolysis (7% [$n=161$] vs 5% [$n=127$], $p=0.032$; odds ratio 1.30, 95% CI 1.02–1.65).

We calculated the odds ratios and corresponding CIs for the primary endpoints, according to the type of thrombolytic regimen received (table 3, figure 3). Compared with streptokinase treatment, primary PTCA resulted in significant decreases in short-term death ($p=0.0004$), non-fatal reinfarction ($p<0.0001$), and the combined endpoint ($p<0.0001$). There was no significant difference between primary PTCA and streptokinase therapy for total stroke ($p=0.078$) and haemorrhagic stroke ($p=1.0$; table 3). Since there were fairly few cases of stroke in the streptokinase trials, there might not have been sufficient power to detect a significant difference in this subgroup. Compared with treatment with fibrin-specific thrombolytic agents, primary PTCA resulted in a significant reduction in short-term overall death ($p=0.018$), death excluding the SHOCK trial ($p=0.038$), non-fatal reinfarction ($p<0.0001$), total stroke ($p=0.0019$), haemorrhagic stroke ($p<0.0001$), and the combined endpoint ($p<0.0001$; table 3, figure 3).

We also calculated the odds ratios and corresponding CI for the five trials^{13,15,27,28,31} that compared emergent hospital transfer for primary PTCA to on-site thrombolysis (figure 4). Combined data from these five trials indicate that, despite the delay inherent in transfer (average 39 min), primary PTCA was associated with significant reductions in non-fatal reinfarction, total stroke, and the combined endpoint when compared with on-site thrombolysis. Primary PTCA was non-significantly associated with decreased death compared with thrombolytic therapy. There was no significant difference between the two groups for haemorrhagic stroke. Overall, events arising during transfer occurred infrequently: 0.5% risk of death (reported in one study only¹⁵), 0.7% to 1.4% risk of ventricular arrhythmias,^{13,15,27,28} and a 2% risk of second-degree or third-degree heart block (reported in one study only²⁸).

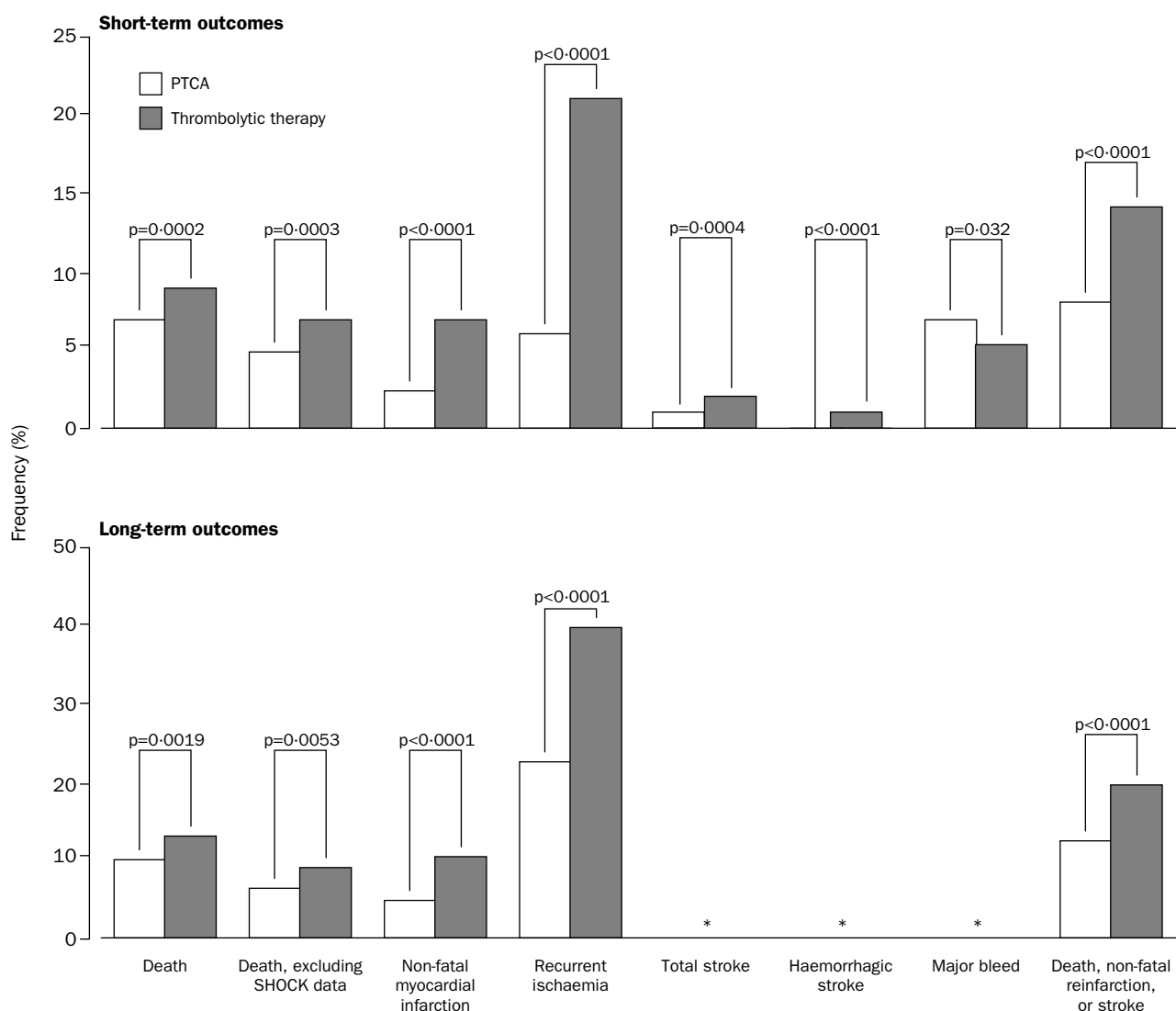


Figure 2: **Short-term**⁷⁻³¹ and **long-term**^{7-9,11,12,14,17,18,20,22-24,26,27,29,30,33-38} clinical outcomes in individuals treated with primary PTCA or thrombolytic therapy

*Data not available.

Finally, we compared results from the first ten trials done^{8-11,16-23} with those of the last 13 (figure 5),^{7,12-15,24-31} The results were nearly identical, showing better outcomes with primary PTCA for the endpoints of death, total stroke, and haemorrhagic stroke. The combined endpoint of death and non-fatal reinfarction was not analysed because of significant heterogeneity among studies.

Discussion

Our findings indicate that primary PTCA is better than thrombolytic therapy at reducing short-term major adverse cardiac events, including death in individuals with ST-segment elevation AMI. Furthermore, these favourable results are sustained during long-term follow-up. Primary PTCA was associated with better clinical outcomes than thrombolytic therapy irrespective of the type of thrombolytic regimen used, and even when reperfusion was delayed because of transfer for primary PTCA.

Since the previous systematic review of this topic was published in 1997,⁶ several new trials comparing primary PTCA with thrombolytic therapy have been undertaken, significantly increasing the total number of patients studied. These new trials reflect the rapid evolution of

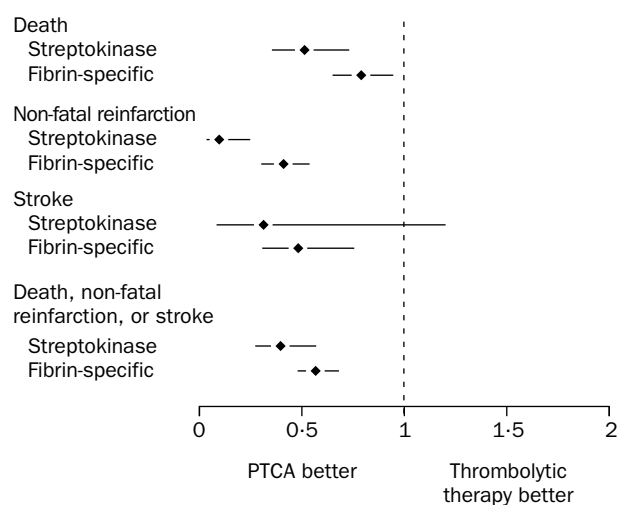


Figure 3: **Short-term clinical outcomes**⁷⁻³¹ in individuals treated with primary PTCA or thrombolytic therapy, according to type of thrombolytic agent used

Odds ratios and 95% CI are shown.

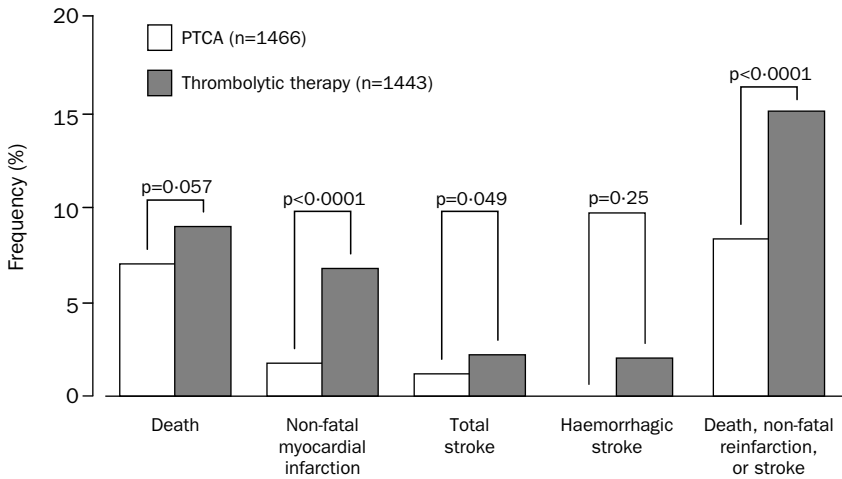


Figure 4: Short-term clinical outcomes in individuals treated with on-site thrombolysis or after emergent transfer for primary PTCA^{13,15,27,28,31}

percutaneous technology and medical therapy and its effect on care of patients. For example, of the 13 new trials, nine used fibrin-specific thrombolytic agents,^{7,24-31} 12 used stents,^{7,13-15,24-31} and eight allowed use of platelet glycoprotein IIb/IIIa inhibitors.^{7,15,24-26,29-31} Additionally, the more recent trials included in this review address important questions with respect to the safety and efficacy of emergent hospital transfer for primary PTCA,^{13,15,27,28,31} primary PTCA done in high risk subgroups (such as elderly individuals¹⁴ and patients with cardiogenic shock⁷), primary PTCA undertaken in hospitals without surgical capabilities,³⁰ and prehospital thrombolysis.²⁵

Our results are strengthened by the fact that they concur with those of a previous review;⁶ primary PTCA remains the best treatment option, despite changes in patients' care over time between the earlier ten trials and the subsequent 13 trials. Consistent with the previous analysis, we noted that the beneficial effect of primary PTCA was similar irrespective of the thrombolytic regimen used (streptokinase or fibrin-specific). This finding is particularly important in our review, since t-PA was associated with a 1% decrease in mortality compared with streptokinase in one study.²³ As a result, a large proportion of the new trials (69%, n=1929) used fibrin-specific-based regimens rather than streptokinase-based regimens (31%, 606), clearly indicating present standard of care for patients presenting with an ST-segment elevation AMI.

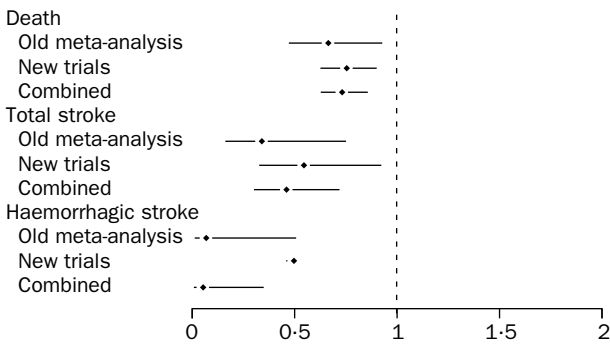


Figure 5: Occurrence of short-term clinical outcomes based on data from the first ten trials^{9-11,16-23} and from the subsequent 13 trials^{7,12-15,24-31} of primary PTCA versus thrombolytic therapy. Odds ratios and 95% CI are shown.

There are several other aspects unique to our systematic review that strengthen our findings. Variation in individual operator experience and hospital volume of primary PTCA implies that this procedure is applicable in a wide range of hospitals undertaking these procedures. Inclusion of several large trials with similar or greater numbers of patients than the GUSTO IIb trial statistically strengthens our analysis. Long-term follow-up (primarily 6 months) was available for many of the patients, affording us an opportunity to assess the durability of primary PTCA over time. High-risk patients, including elderly individuals and those in cardiogenic shock, were included in our analysis, making the results applicable to a diverse group of patients with AMI.

Finally, not only has primary PTCA been shown to be better than thrombolytic therapy in hospitals that do primary PTCA without on-site surgical back-up, but emergent hospital transfer has been shown to be feasible, safe, and associated with improved clinical outcomes when compared with on-site thrombolytic therapy.

Primary PTCA has several limitations. Major bleeding was significantly more frequent in the group who had primary PTCA than in those receiving thrombolytic therapy. However, overall major bleeding complications were fewer in our study than in a previous review.⁶ Since most of these bleeds were localised to the access site, lower doses of intravenous heparin, smaller sheath sizes, and improved operator technique used during primary PTCA in the 13 most recent trials probably contributed to the overall improved bleeding risk. Additional reported side-effects of PTCA included the need for vascular repair (0.4-2% of patients)^{17,30} and development of acute renal failure (0.5-13%).^{7,17} It is noteworthy that acute renal failure developed in 13% of patients randomised to a direct invasive strategy in the SHOCK trial, whereas the complication arose in 24% of those randomised to initial medical stabilisation.

Another potential limitation with primary PTCA is the inherent delay in transferring patients to the cardiac catheterisation laboratory. In a prospective survey³⁹ of 10 484 patients, the median time from arrival in the emergency room to administration of thrombolytic therapy was 40 min, whereas that to first balloon inflation was 93 min. The issue of time delay and its effect on clinical outcomes has been addressed previously;³⁶ Zijlstra and colleagues noted that patients randomised to primary PTCA had fewer adverse events than did those who received thrombolytic therapy, irrespective of whether they presented within 2 h, between 2 h and 4 h, or more than 4 h after initiation of symptoms. Results of another trial²⁸ indicated that patients who presented within 3 h of onset of symptoms had better outcomes with primary PTCA than with thrombolytic therapy, whereas in the PRAGUE-2 trial¹⁵ better outcomes with primary PTCA than with thrombolytic therapy were seen only in patients treated later than 3 h after onset of symptoms. Furthermore, Bonnefoy and colleagues²⁵ reported that primary PTCA was no better than prehospital thrombolytic therapy in patients who presented within 6 h of an ST-segment elevation AMI (although rescue PTCA was done in 26% of the patients randomised to

thrombolysis). Studies of combination therapy (thrombolytic therapy with low molecular weight heparin, and platelet glycoprotein IIb/IIIa inhibitors) and facilitated percutaneous transluminal coronary intervention (low-dose thrombolytics, platelet glycoprotein IIb/IIIa inhibitors, or a combination of both before primary PTCA) are continuing. The favourable results with primary PTCA are only applicable to hospitals with well-established primary PTCA programmes, and dedicated and experienced teams of operators.^{40,41}

Our study has several limitations. Although we contacted the principal investigators of most studies to clarify inconsistencies in data, issues of time delay, and stent and platelet glycoprotein IIb/IIIa inhibitor use, we did not contact all the principal investigators directly for verification of the published data, which could have affected our results. Furthermore, there are differences among the trials; some are single-centred studies whereas others are multicentre and multinational trials, and some trials concentrate on specific subgroups—eg, elderly individuals and those in cardiogenic shock—and their findings might not be applicable to a wider range of patients. Although tests for heterogeneity of treatment effect for each outcome analysed were negative, these tests might not be powered sufficiently to detect such differences. Finally, earlier hospital discharge in PTCA patients can underestimate the adverse events associated with primary PTCA. However, the long-term follow-up data now available for many of the studies enabled us to show consistency of these findings in favour of primary PTCA.

Contributors

E C Keeley and C L Grines both participated in study design, data gathering, verification, and management, planning of statistical analyses, and interpretation of the results. C L Grines was responsible for the original study idea and design. E C Keeley wrote the first draft of the manuscript. J A Boura was responsible for data management, statistical analyses, and interpretation of results. All three authors participated in multiple revisions of the manuscript.

Conflict of interest statement

C L Grines has unrestricted research grants from Boston Scientific, Guidant, and Scimed companies, and has served as a consultant for Aventis and Guidant.

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Clinical picture

Medial longitudinal fascicles

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A 30-year-old man was admitted with diplopia of 15 days duration. Neurological examination showed bilateral internuclear ophthalmoplegia, with paresis of the medial recti and nystagmus of the abducted eye on both lateral gaze directions. Vertical eye movements, convergence, accommodation, and light reflexes were normal. Cerebrospinal fluid analysis showed 18 lymphocytes/mL (NR: 0–5/mL) and a protein content of 0.54 g/L (0.1–0.45 g/L). There were no oligoclonal bands. Visual evoked potentials, somatosensory evoked potentials and motor evoked potentials in the four limbs were normal. Cerebral magnetic resonance imaging showed an isolated lesion involving the medial longitudinal fascicles, the classical seat of internuclear ophthalmoplegia. The lesion is displayed in a T-2 weighted median sagittal section (arrow, figure). No other lesions were visible in the brain or spinal cord. A 5-day course of intravenous methylprednisolone at 1 g a day was started with lansoprazole for gastric protection. Diplopia and gaze abnormalities subsided within 10 days, and repeat magnetic resonance imaging obtained after gadolinium administration showed no enhancement. We suspected an early manifestation of multiple sclerosis. However, we then had two reasons to rejoice: the patient promptly recovered and the medial longitudinal fascicles are really in the right place.



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