

# Transferring Patients With ST-Segment Elevation Myocardial Infarction for Mechanical Reperfusion: A Meta-Regression Analysis of Randomized Trials

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**Study objective:** Primary angioplasty is associated with benefits in survival as compared with thrombolysis among patients with ST-segment elevation myocardial infarction (STEMI). However, in daily practice only a minority of STEMI patients are admitted to 24-hour primary percutaneous coronary intervention hospitals. A previous meta-analysis failed to show significant benefits in terms of survival, potentially because of a limited statistical power. Thus, the aim of the current study is to perform an updated meta-analysis of randomized trials to evaluate whether transfer for primary angioplasty provides significant benefits in terms of survival compared with on-site thrombolysis among STEMI patients.

**Methods:** The literature was scanned by formal searches of electronic databases (MEDLINE, CENTRAL, EMBASE) and the Cochrane Central Register of Controlled trials ([http://www.mrw.interscience.wiley.com/cochrane/Cochrane\\_clcentral\\_articles\\_fs.html](http://www.mrw.interscience.wiley.com/cochrane/Cochrane_clcentral_articles_fs.html)) from January 1990 to April 2008. The following key words were used: “randomized trial;” “myocardial infarction;” “reperfusion;” “thrombolysis;” “primary angioplasty;” “angioplasty;” “mechanical reperfusion;” “facilitation;” “transfer;” “transportation;” “mortality;” and “survival.” Inclusion criteria were (1) randomized comparison between on-site thrombolysis and transferring for primary angioplasty; and (2) complete data on mortality. We did not exclude trials or trial arms that specifically addressed transfer for percutaneous coronary intervention after thrombolysis. Crude data were extracted by 2 investigators. No language restrictions were enforced. The relationship between benefits in mortality and reinfarction, baseline mortality of the thrombolytic group in each study (study level variable), and percutaneous coronary intervention-related time delay was evaluated by using a weighted least-square regression.

**Results:** A total of 11 randomized trials were identified, including 5,741 patients (51.8% transferred for primary angioplasty and 48.2% treated with thrombolysis). Transfer for primary angioplasty was associated with a significant reduction in mortality (5.6% versus 6.8%;  $P=.02$ ), reinfarction (2.1% versus 4.7%;  $P<.0001$ ) and stroke (0.7% versus 1.7%,  $P=.0005$ ) at 30-day follow-up. The benefits in mortality and reinfarction of transfer for primary percutaneous coronary intervention over thrombolysis were not significantly related to baseline mortality of the lytic group or to percutaneous coronary intervention-related time delay.

**Conclusion:** This meta-analysis demonstrates that, among STEMI patients, transfer for mechanical reperfusion is associated, in addition to benefits in reinfarction and stroke, with a significant reduction in mortality at 30-day follow-up. [Ann Emerg Med. 2008;52:665-676.]

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## INTRODUCTION

Several randomized trials and a meta-analysis have shown that primary angioplasty is associated with benefits in survival as compared to thrombolysis.<sup>1,2</sup> However, in clinical practice only a minority of ST-segment elevation myocardial infarction (STEMI) patients are admitted to 24-hour primary percutaneous coronary intervention hospitals. In a recent

STEMI registry, only 39% of the 1,506 participating US hospitals<sup>3</sup> had the recommended primary percutaneous coronary intervention capabilities.<sup>4</sup> Transferring for primary percutaneous coronary intervention implies longer delay to treatment, with potential loss of benefits compared with on-site thrombolysis. A previous meta-analysis, including 6 trials with 3,750 patients, showed significant benefits in reinfarction and

stroke but only a trend in benefits in terms of survival because of a limited statistical power.<sup>5</sup> Thus, the aim of the current study was to perform an updated meta-analysis of randomized trials to evaluate whether transfer for mechanical reperfusion provides significant benefits in terms of 30-day survival compared with on-site thrombolysis.

## MATERIALS AND METHODS

### Search Strategy and Inclusion Criteria

The literature was scanned by formal searches of electronic databases (MEDLINE, CENTRAL, EMBASE) and the Cochrane Central Register of Controlled trials ([http://www.mrw.interscience.wiley.com/cochrane/Cochrane\\_ccentral\\_articles\\_fs.html](http://www.mrw.interscience.wiley.com/cochrane/Cochrane_ccentral_articles_fs.html)) from January 1990 to April 2008 and the scientific session abstracts in *Circulation*, *Journal of College of Cardiology*, *European Heart Journal*, and *American Journal of Cardiology* from January 1990 to April 2007. Various combinations of the following key words were used: “randomized trial;” “myocardial infarction;” “reperfusion;” “thrombolysis;” “primary angioplasty;” “angioplasty;” “mechanical reperfusion;” “facilitation;” “transfer;” “transportation;” “mortality;” “survival.” Inclusion criteria were (1) randomized comparison between on-site thrombolysis and transferring for mechanical reperfusion; and (2) complete data on survival. We did not exclude trials or trial arms that specifically addressed transfer for percutaneous coronary intervention within 6 hours after starting thrombolysis. No language restrictions were enforced.

### Data Extraction and Validity Assessment

Data were independently abstracted by 2 experienced cardiologists (G.D.L., G.B.-Z.), blinded to each other’s findings. Agreement between investigators was evaluated by  $\kappa$  statistics. In case of disagreements, a third investigator was additionally involved to obtain a consensus. In case of incomplete or unclear data, authors, where possible, were contacted. The study quality was evaluated by the same 2 investigators according to a score modified from Jadad et al<sup>6</sup> and Biondi-Zoccai et al,<sup>7</sup> expressed on an ordinal scale, allocating 1 point for the presence of each of the following: (1) statement of objectives, (2) explicit inclusion and exclusion criteria, (3) description of interventions, (4) objective means of follow-up, (5) description of adverse events, (6) power analysis, (7) description of statistical methods, (8) multicenter design, (9) discussion of withdrawals, and (10) details on medical therapy (eg, antithrombotic regimens) during and after coronary procedures. Data were managed according to the intention-to-treat principle.

### Outcome Measures

The primary clinical endpoint was mortality assessed at 30-day follow-up. Secondary clinical endpoints were reinfarction and stroke assessed at 30-day follow-up.

### Data Analysis

Statistical analysis was performed using the Review Manager 4.27 freeware package (Cochrane Collaboration, Oxford, UK) and SPSS 15.0 statistical package (SPSS, Inc., Chicago, IL). Odds ratio (OR) and 95% confidence intervals (CIs) were used as summary statistics, as previously described.<sup>4</sup> The pooled OR was calculated by using both a fixed-effect model (the Mantel-Haenszel method) and random-effect model. Between-study heterogeneity was analyzed by means of  $I^2 = [(Q - df)/Q] \times 100\%$ , where Q is the  $\chi^2$  statistic, and df is its degrees of freedom. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered substantial heterogeneity. Prespecified subanalyses were performed for all endpoints after the exclusion of trials with randomization occurring in the out-of-hospital setting. Sensitivity analysis was performed according to quality score (lower than or median versus higher than median quality score). Potential publication bias was examined by constructing a “funnel plot,” in which the standard error of the ln OR was plotted against OR (for 30-day mortality).<sup>8</sup> In addition, a linear regression approach to measure funnel plot asymmetry was used.<sup>9</sup>

The relationship between benefits in mortality and reinfarction, baseline mortality (odds) of the thrombolytic group in each study (study level variable—due to unavailability of individual patient’s data), and percutaneous coronary intervention-related time delay (in this analysis we excluded trials on percutaneous coronary intervention post-thrombolysis) was evaluated by using a weighted least-square regression in which results from each trial (OR) were weighted by the square root of the number of patients in that trial. Results are reported as regression coefficients with 95% CIs and 2-sided *P* values.<sup>10</sup>

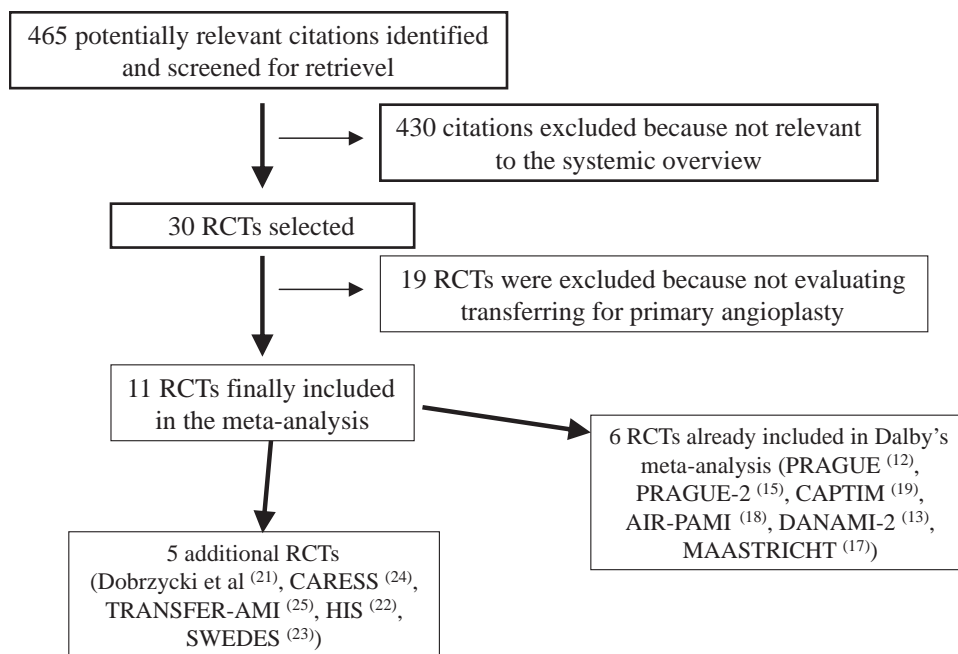
The study was performed in compliance with the Quality of Reporting of Meta-Analyses (QUORUM) guidelines.<sup>11</sup>

## RESULTS

### Eligible Studies

Among 465 potentially relevant publications, a total of 11 randomized trials comparing immediate on-site thrombolysis (at randomization) versus transfer for mechanical reperfusion were finally identified.<sup>12-25</sup> A total of 5,741 patients were included (2,974 patients [51.8%] transferred for mechanical reperfusion and 2,767 [48.2%] patients treated with thrombolysis) (Figure 1).  $\kappa$  Statistics showed a good agreement between investigators in data extraction ( $\kappa = 0.73$ ).

Characteristics of included trials are shown in Table 1. All trials were conducted in experienced high-volume centers. In the Comparison of Angioplasty and Pre-hospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial,<sup>19</sup> patients were randomized and started the pharmacologic treatment in the out-of-hospital setting. In the Swedish Early Decision (SWEDES) trial<sup>23</sup> 42% and 43% of patients in the lytic and invasive group, respectively, were randomized and received pharmacologic therapies in an out-of-hospital setting, whereas



**Figure 1.** Flow diagram of the systematic overview process. *RCT*, Randomized controlled trials.

the majority of remaining patients were randomized at a primary percutaneous coronary intervention center. The Holland Infarction Study (HIS) trial aimed at including 900 patients. However, it was prematurely stopped after the inclusion of 48 patients because of slow recruitment and withdrawal of financial funding.<sup>22</sup> In the Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) trial, a total of 443 of 1,572 (28.2%) patients were randomized at invasive centers and thus excluded from the current analysis.<sup>13</sup>

The Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS in AMI [CARESS])<sup>24</sup> and Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI)<sup>25</sup> evaluated a pharmacoinvasive strategy. In these studies, patients presenting at community hospitals were randomized to on-site pharmacologic reperfusion (combined reteplase and abciximab in the CARESS and full-dose TNK in the TRANSFER-AMI) or pharmacoinvasive strategy with transfer to percutaneous coronary intervention centers for mechanical reperfusion within 6 hours from pharmacologic reperfusion therapy.

Follow-up data were available at 30 days in all trials. Longer follow-up data were available in the HIS<sup>23</sup> and MAASTRICHT trials<sup>12</sup> and in the Dobrzycki et al<sup>21</sup> (1 year) study, whereas they were available in the DANAMI-2<sup>14</sup> and Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis (PRAGUE-2)<sup>16</sup> trials at 3 and 5 years, respectively.

## Mortality

As shown in [Figure 2](#), transfer for primary angioplasty was associated with a significant reduction in mortality (5.6% versus 6.8%; OR=0.77 [95% CI 0.62 to 0.96],  $P=.02$  [fixed-effect model]; OR=0.77 [95% CI 0.62 to 0.96],  $P=.02$  [random-effect model];  $p_{\text{het}}=0.92$ ; NNT=83.3). The benefits in favor of primary percutaneous coronary intervention were confirmed even after the exclusion of CAPTIM<sup>19</sup> and SWEDES<sup>23</sup> trials (5.8% versus 7.5%; OR=0.73 [95% CI 0.58 to 0.92],  $P=.008$  [fixed-effect model], OR=0.73 [95% CI 0.58 to 0.92],  $P=.008$  [random-effect model];  $p_{\text{het}}=0.97$ ; number needed to treat=58.8) ([Figure 2](#)). The results were not affected by study quality ([Table 2](#)).

By the use of a meta-regression analysis, benefits in mortality with transfer for angioplasty were not related to percutaneous coronary intervention-related time delay ( $r=-0.002$ ;  $\beta=0.00001$  [95% CI  $-0.008$  to  $0.008$ ];  $P=.99$ ).

Benefits in mortality with transfer for angioplasty were related to baseline mortality of the lytic group ( $r=-0.63$ ;  $\beta=-3.84$  [95% CI  $-7.39$  to  $0.29$ ];  $P=.037$ ). However, this relationship did not reach the statistical significance when the CAPTIM<sup>19</sup> and SWEDES<sup>23</sup> trials were excluded from the analysis ( $r=-0.57$ ;  $\beta=-2.78$  [95% CI  $-6.33$  to  $0.77$ ];  $P=.11$ ) or when percutaneous coronary intervention-related time delay was included in the regression model as an additional covariate ( $r=-0.53$ ;  $\beta=-3.13$  [95% CI  $-10.26$  to  $3.99$ ];  $P=.29$ ).

## Reinfarction

As shown in [Figure 3](#), transfer for primary angioplasty was associated with a significant reduction in 30-day reinfarction (2.1% versus 4.7%; OR=0.42 [95% CI 0.31 to 0.57];

**Table 1.** Characteristics of trials comparing immediate thrombolysis to transfer for primary angioplasty.

Study	Year	Multicenter	Inclusion Criteria	Exclusion Criteria	Study Design	Pts PCI	Time to PCI (From Random- ization)	Pts Lytic	Time to Lytic (From Random- ization)	Lytic Agent	Primary End Point
MAASTRICHT <sup>17</sup>	1995–1997	Yes	Pain >30 min and <6 h ST elevation	Contraindication to lysis, cardiogenic shock, severe concomitant disease with life expectancy <12 months, known logistic problems for transport or angiography (transport within 60 min), and anticipated incomplete follow-up.	On-site TL (n=75) vs transfer for PCI post-TL (n=74), transfer for PCI (n=75)	149	93	75	10	tPA	Safety and feasibility of acute transfer for PCI
PRAGUE-1 <sup>12</sup>	1997–1999	Yes	Pain <6 h ST elevation or new LBBB	Contraindication to lysis and absence of bilateral femoral artery pulsations, transportation time >60 minutes, inability to start transportation within 30 min after randomization	On-site TL (n=99) vs transfer for PCI post-TL (n=100) vs transfer for PCI (n=101)	101	80	99	10	SK	Combined death, re-MI, or stroke at 30 days
AIR-PAMI <sup>18</sup>	n.r.	Yes	Pain <12 h with ST elevation/new LBBB, plus 1 or more high-risk criteria <sup>8</sup>	Contraindication to lysis, or life expectancy <12 mo	On-site TL (n=66) vs transfer for PCI (n=71)	71	122	66	19	By center. If tPA, bolus plus 72 h heparin infusion	Combined death, re-MI, or stroke at 30 days
CAPTIM <sup>19</sup>	1997–2000	Yes	Pain >30 min and <6 h ST elevation/new LBBB	Contraindication to lysis, severe renal and hepatic insufficiency, aortofemoral bypass or any condition that could hamper femoral artery access, cardiogenic shock, previous CABG, or current oral anticoagulation, and transportation time longer 1 h	Out-of-hospital TL (n=419) vs transfer for PCI (n=421)	421	82	419	23	tPA	Combined death, re-MI, or stroke at 30 days

**Table 1.** (Continued) Characteristics of trials comparing immediate thrombolysis to transfer for primary angioplasty.

Study	Year	Multicenter	Inclusion Criteria	Exclusion Criteria	Study Design	Pts PCI	Time to PCI (From Random- ization)	Pts Lytic	Time to Lytic (From Random- ization)	Lytic Agent	Primary End Point
DANAMI-2 <sup>13</sup>	1997–2001	Yes	Pain <12 h with ST elevation	Contraindication to lysis, LBBB, AMI, and fibrinolysis within 30 days, pulseless femoral arteries, previous CABG, renal failure, diabetes treated with metformin, nonischemic heart disease, noncardiac disease with life expectancy of less than 12 mo, patients at high risk during transportation, such as cardiogenic shock, severe heart failure, persistent life-threatening arrhythmias, or a need for mechanical ventilation.	On-site TL (n=562) vs transfer for PCI (n=567)	567	90	562	20	tPA	Combined death, re-MI, or stroke at 30 days
PRAGUE-2 <sup>15</sup>	1999–2002	Yes	ST elevation MI <12 h	Contraindication to lysis, absence of bilateral femoral artery pulsation, distance to PCI center >120 km, inability to start transportation within 30 min after randomization	On-site TL (n=421) vs transfer for PCI (n=429)	429	97	421	17	SK	Death at 30 days
HIS <sup>22</sup>	2003–2004	Yes	Pain >20 min but <4.5 h and ST elevation with total deviation >12 mm	Contraindication to lysis, Killip class >1, previous CABG, pulseless femoral artery, known allergy or hypersensitivity to aspirin, clopidogrel enoxaparin, or abciximab, coma or severe concomitant disease with life expectancy <12 mo	On-site TL (n=23) vs transfer for abciximab-facilitated PCI (n=25)	25	NA	23	NA	Fibrin-specific lytics	Death or reinfarction at 30 days
Dobrzycki <sup>21</sup>	2002–2003	No	Pain >30 min and <12 h ST elevation	Contraindication to lysis, LBBB, previous CABG, severe renal or hepatic dysfunction	On-site TL (n=200) vs transfer for PCI (n=201)	201	145	200	35	SK	Combined death, re-MI, or stroke at 30 days

**Table 1.** (Continued) Characteristics of trials comparing immediate thrombolysis to transfer for primary angioplasty.

Study	Year	Multicenter	Inclusion Criteria	Exclusion Criteria	Study Design	Pts PCI	Time to PCI (From Random- ization)	Pts Lytic	Time to Lytic (From Random- ization)	Lytic Agent	Primary End Point
SWEDES <sup>23</sup>	2001–2003	Yes	Pain >30 min with ST elevation	Contraindication to lysis, age >75 years, cardiogenic shock, cardiopulmonary resuscitation >10 min within 2 weeks before, ongoing treatment with oral anticoagulation of LMWHs, allergy to study drugs, body weight >120 kg, and renal insufficiency	On-site TL (n=104) vs transfer for PCI (n=101)	101	NA	104	NA	Reteplase	ST-segment resolution >50% and TIMI 3 flow
CARESS <sup>24</sup>	2002–2007	Yes	STEMI <12 h with: cumulative ST-segment elevation >15 mm, new onset LBBB, previous MI, Killip class >1, LVEF <35%	Contraindication to lysis, abciximab, aspirin, or clopidogrel, previous CABG or coronary stenting; cardiogenic shock, need for concomitant major surgery, severe chronic renal and hepatic dysfunction, previous (within 2 weeks) myocardial infarction	On-site combotherapy (half-dose reteplase+abciximab) with (n= . .) or without (n=) routine transfer for PCI	298	135	300	12	Reteplase	Mortality, reinfarction and recurrent ischemia at 30 days
TRANSFER-AMI <sup>25</sup>	2004–2007	Yes	Pain >30 min with ST elevation within 12 h with at least: (1) SBP <100 mm Hg, or (2) HR >100 beats/min or (3) Killip 2–3, or (4) >2 mm ST segment depression in anterior leads; or (5) >1 mm ST elevation in V4R	Cardiogenic shock; primary PCI available within 60 min; consent not obtained within 30 min of TNK; PCI within 1 mo; previous CABG; Use of enoxaparin in last 12 h in patients >75 years old	On-site TL with (n=512) or without (n=498) routine transfer for PCI	512	NA	498	NA	TNK	Combined death, reMI, recurrent ischemia, CHF, shock at 30 days

Study	Primary Outcome Estimates, OR (95% CI)	% Gp IIb-IIIa Inhibitors in PCI Arm	Randomization Location	Routine Postlysis Angiography (%)	Rescue PCI, %	Age		Sex		Diabetes		Killip >1		Quality Score
						PCI	Lysis	PCI	Lysis	PCI	Lysis	PCI	Lysis	
MAASTRICHT <sup>17</sup>	Not estimable	0	Community hospital	No	n.a.	58	59	54	56	NA	NA	NA	NA	7
PRAGUE-1 <sup>12</sup>	0.43 (0.23–0.81)	0	Community hospital	No	7	62	61	73	68	NA	NA	23	21	6
AIR-PAMI <sup>18</sup>	0.57 (0.19–1.71)	0	Community hospital	No	n.a.	62	64	76	65	23	20	35	23	9
CAPTIM <sup>19</sup>	0.75 (0.44–1.27)	23%	Out-of-hospital	No	26	58	58	81.5	82.5	13.5	11.1	NA	NA	10
DANAMI-2 <sup>13</sup>	0.56 (0.38–0.81)	40%	Community hospital	No	1.9	62	64	73.5	73.4	7.4	7	n.r.	n.r.	9

**Table 1.** (Continued) Characteristics of trials comparing immediate thrombolysis to transfer for primary angioplasty.

Study	Primary Outcome Estimates, OR (95% CI)	% Gp IIb/IIIa Inhibitors in PCI Arm	Randomization Location	Routine Postlysis Angiography (%)	Rescue PCI, %	Age		Sex		Diabetes		Killip >1		Quality Score
						PCI	Lysis	PCI	Lysis	PCI	Lysis	PCI	Lysis	
PRAGUE-2 <sup>15</sup>	0.65 (0.40–1.07)	n.a.	Community hospital	No	6.4	65	64	70	71	25	23	18	17	7
HIS <sup>22</sup>	0.28 (0.03–2.88)	100	Community hospital	No	26	61	66	72	57	8	4	0	0	8
Dobrzycki <sup>21</sup>	0.47 (0.27–0.82)	0	Community hospital	No	3	63	64	76	72	15	17	NA	NA	7
SWEDES <sup>23</sup>	1.07 (0.85–1.35); 1.31 (1.00–1.72)	100	Out-of-hospital (42%), primary PCI centers (54%), referral hospitals (4%)	Yes	23	65	64	73	75	14	11	NA	NA	8
CARESS <sup>24</sup>	0.4 (0.21–0.76)	100	Community hospital	No	30.3	30	60	78	79	15	15	45	43	9
TRANSFER-AMI <sup>25</sup>	0.59 (0.41–0.85)	n.a.	Community hospital	Yes	38	57	56	79	80	15	15	8	8	6

TL, Thrombolysis; LBBB, left bundle-branch block; MI, myocardial infarction; CABG, coronary artery bypass graft; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; n.a., Not available.

$P < .0001$  [fixed-effect model]; OR=0.42 [95% CI 0.31 to 0.57];  $P < .0001$  [random-effect model];  $p_{het} = 0.95$ ; NNT=38.5). The benefits in favor of primary percutaneous coronary intervention were confirmed even after the exclusion of CAPTIM<sup>19</sup> and SWEDES<sup>23</sup> trials (2.2% versus 5.0%; OR=0.42 [95% CI 0.30 to 0.58];  $P < .0001$  [fixed-effect model], OR=0.42 [95% CI 0.30 to 0.58];  $P < .0001$  [random-effect model];  $p_{het} = 0.88$ ; NNT=35.7) (Figure 3). The results were not affected by study quality (Table 2).

By the use of a meta-regression analysis, no significant relationship was observed between baseline mortality of the lytic group ( $r = -0.075$ ;  $\beta = -0.37$  [95% CI -4.06 to 3.32];  $P = .83$ ), percutaneous coronary intervention-related time delay ( $r = 0.004$ ;  $\beta = -0.00002$  [95% CI -0.0005 to 0.0005];  $P = .99$ ), and benefits in reinfarction with transfer for primary angioplasty.

Similar data were observed after the exclusion of CAPTIM<sup>19</sup> and SWEDES<sup>23</sup> trials for both baseline mortality of the lytic group ( $r = -0.21$ ;  $\beta = -0.97$  [95% CI -4.73 to 2.79];  $P = .57$ ), percutaneous coronary intervention-related time delay ( $r = 0.004$ ;  $\beta = -0.00002$  [95% CI -0.0005 to 0.0005];  $P = .99$ ).

**Stroke**

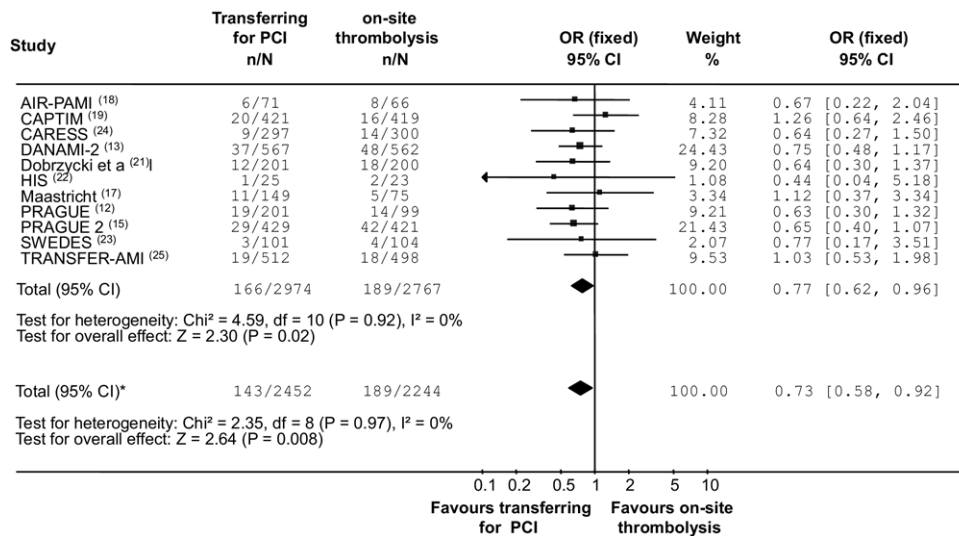
As shown in Figure 4, transfer for primary angioplasty was associated with a significant reduction in 30-day stroke (0.7% versus 1.7%; OR=0.40 [95% CI 0.24 to 0.67];  $P = .0005$  [fixed-effect model]; OR=0.41 [95% CI 0.20 to 0.84];  $P = .02$  [random-effect model];  $p_{het} = 0.27$ ; NNT=100). Similar data were observed after the exclusion of CAPTIM<sup>19</sup> and SWEDES<sup>23</sup> trials (0.9% versus 1.7%; OR=0.45 [95% CI 0.26 to 0.78];  $P = .004$  [fixed-effect model]; OR=0.46 [95% CI 0.21 to 1.01];  $P = .05$  [random-effect model];  $p_{het} = 0.23$ ; NNT=125). The results were not affected by study quality (Table 2).

**Potential Publication Bias**

The potential publication bias (for the primary endpoint) was based on visual analysis of the funnel plot (Figure 5) and on the mathematical estimate of the asymmetry of this plot provided by a linear regression approach. The intercept of the regression line did not deviate significantly from zero ( $\alpha = -0.13$ ; 95% CI -0.43 to 0.17;  $P = .67$ ).

**LIMITATIONS**

We did not observe any publication bias. However, it cannot be completely excluded by both visual and mathematical analysis. To overcome this limitation, we preferred to apply both fixed- and random-effect models that showed similar results. The availability of individual patients' data would have certainly strengthened our analysis. In fact, baseline mortality of the lytic group was not based on individual patients' data, but rather was based on the baseline mortality of the thrombolytic group in each trial (study level variable). Furthermore, the



**Figure 2.** Transfer for primary angioplasty versus immediate thrombolysis and mortality benefits at 30-day follow-up, with ORs and 95% CIs. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. \*Pooled data after the exclusion of the SWEDES and CAPTIM trials.

**Table 2.** Sensitivity analyses for death, reMI, and stroke according to study quality.

Outcome	Trials	Meta-analytic Pooled OR (95% CI)	P Value
Death	High study quality	0.83 (0.60–1.13)	.24
	All studies	0.77 (0.62–0.96)	.02
ReMI	High study quality	0.39 (0.24–0.63)	<.0001
	All studies	0.42 (0.31, 0.57)	<.0001
Stroke	High study quality	0.40 (0.2–0.81)	.01
	All studies	0.40 (0.24–0.67)	<.0005

results of this analysis may have been affected by the difference in care provided at smaller local hospitals compared with bigger hospitals with percutaneous coronary intervention facilities. In fact, in the DANAMI-2 trial,<sup>13</sup> even though no difference was observed among patients randomized to primary percutaneous coronary intervention, a larger mortality was observed among patients randomized to on-site thrombolysis in the referral hospital compared with invasive treatment centers (8.5% versus 5.9%). Streptokinase was used in many randomized controlled trials, and thus, the conclusions cannot be extended to new lytics, such as tenecteplase, reteplase, or alteplase.

We did not observe a significant effect of percutaneous coronary intervention-related time delay on the benefits from primary percutaneous coronary intervention compared with thrombolysis, and these results could be potentially explained by a low statistical power of our meta-analysis because of the inclusion of few trials. Thus, extreme caution should be exercised in the interpretation of these results that cannot be extended to our daily practice, in which the time of presentation (especially within the first 3 hours), percutaneous coronary intervention-related time delay (longer than 60 minutes), and baseline mortality of the lytic group should be strictly taken into

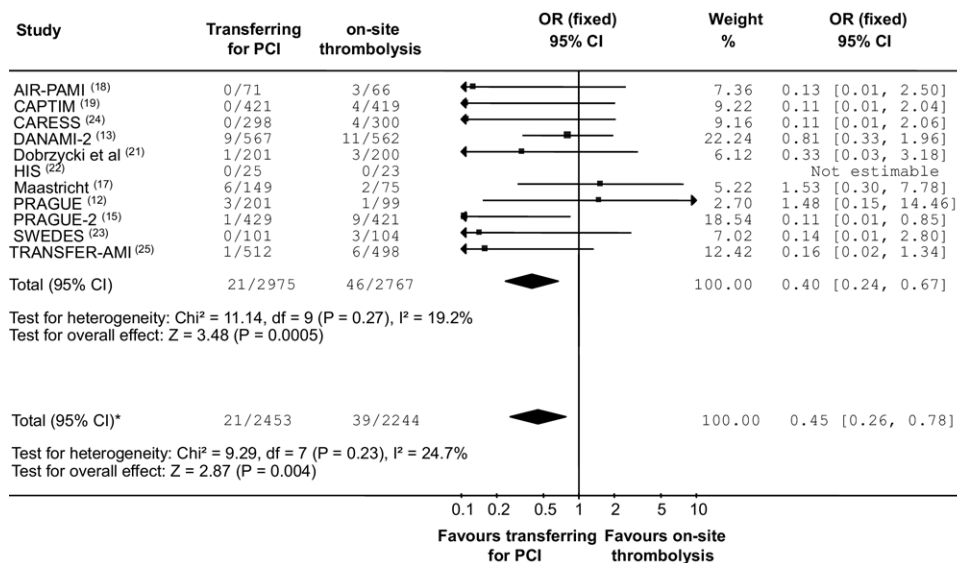
account in the choice of the reperfusion strategy (primary angioplasty or thrombolysis plus transferring to primary percutaneous coronary intervention centers).

We did not find statistical heterogeneity. However, a clinical heterogeneity between trials, caused by different inclusion and exclusion criteria, different lytic agents, and use of glycoprotein IIb-IIIa inhibitors,<sup>26</sup> cannot be excluded. Despite the difference in trial design in the CAPTIM<sup>19</sup> (patients randomized in an out-of-hospital setting, and a relatively large proportion—26%—of rescue percutaneous coronary intervention), the total exclusion of this study would have left the analysis without a trial of optimal early thrombolysis and would have led to a potential bias in favor of primary angioplasty. Furthermore, the SWEDES study<sup>23</sup> did not report outcome data according to the site of randomization (out-of-hospital setting, percutaneous coronary intervention or non-percutaneous coronary intervention centers). To overcome these potential limitations, prespecified subanalyses were performed for all endpoints after the exclusion of these 2 trials, thus including only trials with randomization occurring at referral hospitals.

In our meta-analysis, only a minority of patients (in the HIS<sup>22</sup> and SWEDES<sup>23</sup> trials) underwent abciximab-facilitated angioplasty. In fact, a recent meta-analysis has shown that facilitation with glycoprotein IIb-IIIa inhibitors, mainly abciximab, is associated with improved preprocedural and postprocedural epicardial and myocardial reperfusion, with a significant improvement in survival.<sup>27</sup>

We did not observe any relationship between baseline mortality of the lytic group, percutaneous coronary intervention-related time delay, and benefits in reinfarction. A larger use of early angiography in high-risk patients might have reduced the benefits in terms of reinfarction.

**Figure 3.** Transfer for primary angioplasty versus immediate thrombolysis and reinfarction at 30-day follow-up, with ORs and 95% CIs. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. \*Pooled data after the exclusion of the SWEDES and CAPTIM trials

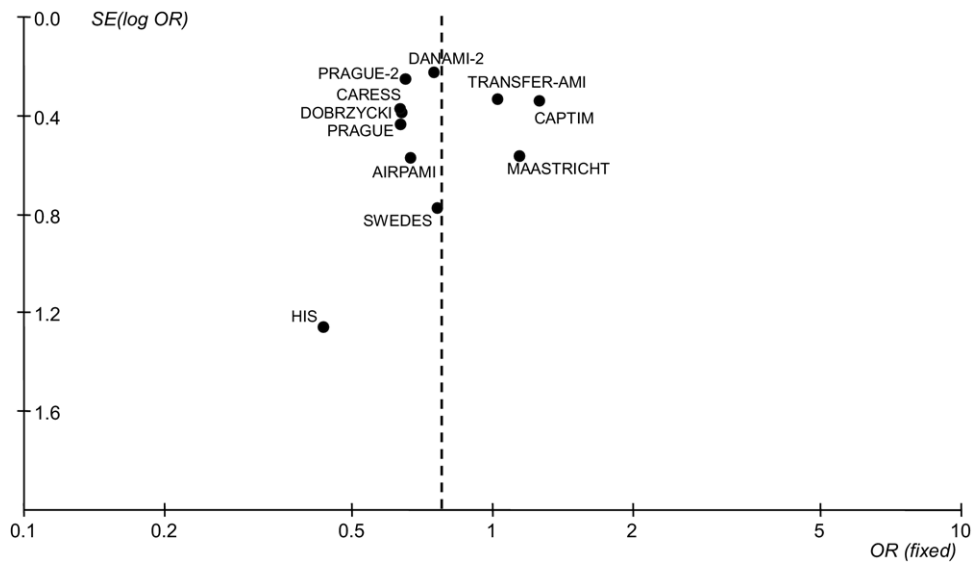


**Figure 4.** Transfer for primary angioplasty versus immediate thrombolysis and stroke at 30-day follow-up, with ORs and 95% CIs. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. \*Pooled data after the exclusion of the SWEDES and CAPTIM trials.

**DISCUSSION**

Primary angioplasty has been demonstrated to be superior to thrombolysis in terms of death, reinfarction or stroke.<sup>1,2</sup> However, these advantages may be lost when transportation to a primary percutaneous coronary intervention center is needed because of longer delay to treatment. In fact, time to treatment is a determinant of survival not only for thrombolysis but also for primary angioplasty.<sup>28,29</sup> Bednar et al,<sup>30</sup> in a retrospective analysis of the PRAGUE trial, showed that the benefits in terms of 30-day mortality compared with thrombolysis were less pronounced when longer transportation was needed.

A previous meta-analysis of randomized trials, despite the benefits in terms of stroke and reinfarction, showed only a trend in benefits in terms of mortality (6.3% versus 7.7%; *P* = .08).<sup>3</sup> However, several additional trials have been published in the meantime, and their inclusion would provide large power in the analysis of survival benefits. Dalby et al<sup>5</sup> did not exclude from their analysis patients randomized in primary percutaneous coronary intervention centers in the DANAMI trial,<sup>13</sup> except those in a subanalysis of the combined endpoint, but not for single endpoints such as death, reinfarction and stroke.



**Figure 5.** Funnel plot of all studies included in the meta-analysis. Each study's standard error (a function of sample size) is plotted against its effect size. The distribution is roughly symmetrical; thus, there is not strong evidence of publication bias.

All trials so far conducted have shown the safety of transfer for mechanical reperfusion among STEMI patients, even in trials including high-risk patients, such as the Air Primary Angioplasty in Myocardial Infarction (AIR-PAMI)<sup>18</sup> CARESS,<sup>24</sup> and TRANSFER-AMI.<sup>25</sup> Despite differences in trial designs and type of lytic therapy, all trials showed benefits in mortality with transfer that in no study reached statistical significance because of obvious limited statistical power. In fact, in no study mortality was the primary endpoint. Only the CAPTIM trial<sup>19</sup> showed a trend in benefits in mortality with on-site thrombolysis that was administered in an out-of-hospital setting. In fact, out-of-hospital thrombolysis has been shown to provide benefits in mortality compared with in-hospital administration.

In the current study, we performed a comprehensive, updated meta-analysis of all randomized trials comparing among STEMI patients immediate thrombolysis versus transfer for mechanical reperfusion, including those patients soon after thrombolysis. Five trials (SWEDES, Dobrzycki et al,<sup>21</sup> HIS, CARESS, TRANSFER-AMI), with a total of 2,435 patients, were additionally included compared with the previous meta-analysis. The main finding of this study is that transfer for mechanical reperfusion is associated with a significant reduction in mortality, in addition to a reduction in reinfarction and stroke at 30-day follow-up. The inclusion or exclusion of SWEDES and CAPTIM (the only 2 trials with randomization occurring in the out-of-hospital setting) did not modify our results. By meta-regression analysis, we found that the benefits in mortality were related to baseline mortality of the lytic group but not percutaneous coronary intervention-related time delay. The relationship between benefits in mortality and baseline mortality of the lytic group was not statistically significant when

both covariates were included in the regression model.

However, these results may depend on low statistical power and the study level analysis. In fact, a previous trial has shown no benefits with primary angioplasty compared with thrombolysis in low-risk patients.<sup>31</sup> Similar findings have been confirmed in a recent risk-benefit analysis of randomized trials.<sup>32</sup>

Even though a meta-analysis of randomized trials on pharmacologic facilitation concluded that this strategy should not be recommended in daily clinical practice,<sup>33</sup> a facilitated angioplasty might be considered in high-risk patients, for whom the prognostic implications of ischemia time and preprocedural recanalization are more pronounced.<sup>34,35</sup> In fact, Keeley et al<sup>33</sup> did not take into account the baseline mortality of the lytic group. Furthermore, they did not analyze the effect of the time from symptom onset to drug administration. The amount of myocardial salvage that could be obtained by early reperfusion may vary according to the length of ischemia and may certainly be larger within 2 or 3 hours from symptom onset.<sup>36,37</sup> These factors contribute to explain the benefits in mortality with out-of-hospital thrombolysis observed in the CAPTIM trial only among patients randomized within the first 2 hours.<sup>38</sup> Pinto et al<sup>39</sup> analyzed the importance of percutaneous coronary intervention-related delays in a population of 200,000 patients from the National Registry of Myocardial Infarction 2, 3, and 4. They observed that the percutaneous coronary intervention-related delay at which mortality with percutaneous coronary intervention or thrombolysis was equal was shorter in patients with early presentation (within 120 minutes) than those presenting later (94 minutes versus 190 minutes, respectively). Data from the CARESS trial<sup>24</sup> and TRANSFER-AMI<sup>25</sup> have clearly shown that a combined strategy of thrombolysis followed by early invasive strategy is feasible, and this can help to

minimize any deleterious effects of prolonged ischemia time while patients wait for mechanical reperfusion, especially within the first hours from symptom onset.

### Conclusions

This meta-analysis demonstrates that, among STEMI patients, transfer for mechanical reperfusion is associated, in addition to benefits in reinfarction and stroke, with a significant reduction in mortality at 30-day follow-up.

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