Int J Clin Exp Med 2016;9(11):20761-20776
www.ijcem.com /ISSN:1940-5901/IJCEM0035617

Original Article

Prehospital facilitated intervention as a potential "sally port" for the rescue of acute ST-segment elevation myocardial infarction: a meta-analysis

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Received July 12, 2016; Accepted September 1, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: Background: Early reperfusion in ST-segment elevation myocardial infarction (STEMI) is associated with improved clinical outcomes. The purpose of this study was to characterize the benefits and risks of prehospital fibrinolysis with timely percutaneous coronary intervention (PCI) as a promising strategy which could reduce the reperfusion delay especially for the patients in remote areas. Methods: We identified clinical trials comparing the facilitated PCI versus primary PCI and divided them into two subgroups (prehospital treatment and in-hospital treatment). Results: We identified eighteen clinical trials involving 11118 patients. The facilitated PCI had higher rates of initial TIMI grade 3 flow compared with the primary PCI (44.6% *vs* 18.8%, *P*<0.01). Facilitated PCI with prehospital fibrinolysis was associated with lower incidences of cardiogenic shock (3.8% *vs* 5.7%, *P*=0.02), potential lower incidences of short-term mortality (4.3% *vs* 4.3%, *P*=0.94), heart failure (6.9% *vs* 8.3%, *P*=0.20) and major bleeding (2.4% *vs* 3.6%; *P*=0.06), and higher rates of urgent target vessel revascularization (5.2% vs 2.5%, *P*=0.0002) and total stroke (1.3% *vs* 0.4%, *P*=0.009) compared with primary PCI. Facilitated PCI with in-hospital fibrinolysis led to increased incidences of non-fatal reinfarction (3.4% *vs* 1.8%, *P*=0.0004) and total stroke (1.2% *vs* 0.4%, *P*=0.002), and potential risks for short-term death (4.5% *vs* 3.5%, *P*=0.10), cardiogenic shock (5.3% *vs* 4.7%, *P*=0.61), urgent target vessel revascularization (4.4% *vs* 3.5%, *P*=0.18), and major bleeding (5.8% *vs* 4.3%, *P*=0.11) compared with primary PCI. Conclusions: Facilitated PCI with prehospital fibrinolysis offered potential benefits over primary PCI for the treatment of STEMI, in spite of a slight increased risk of total stroke.

Keywords: Prehospital fibrinolysis, st segment elevation myocardial infarction, facilitated percutaneous coronary intervention, primary percutaneous coronary intervention

Introduction

An ideal therapy strategy for acute ST-segment elevation myocardial infarction (STEMI) was recognized as an approach initiating reperfusion within the shortest time interval, providing clinical benefits and resulting in lowest incidence of treatment complications. To date, guidelines for the treatment of STEMI from the European Society of Cardiology (ESC) and American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) emphasized on minimizing the delays in the implementation of reperfusion therapy unanimously [1, 2] since the greatest benefit gained from reperfusion therapy occurred within the first 2-3 hours of symptom onset [2-4].

The concept of "facilitated percutaneous coronary intervention (PCI)" with fibrinolytic agents was established based on the premise that fibrinolysis before angiography would result in earlier pharmacologic reperfusion before mechanical dilation (balloon inflation), smaller infarcts, lower infarct artery thrombus burden, greater procedural success rates and higher survival rates. Several randomized trials and meta-analyses showed that the facilitated PCI with in-hospital fibrinolysis resulted in worse clinical outcomes compared with the primary PCI for the patients with STEMI [5-10]. These results were consistent with the guidelines from American College of Cardiology (ACC) [11] which stated that a planned reperfusion strategy using full-dose fibrinolytic therapy followed by immediate PCI might be harmful.

It is well known that the intravenous fibrinolysis established in the first two hours after symptom onset can lead to a dramatic increase of

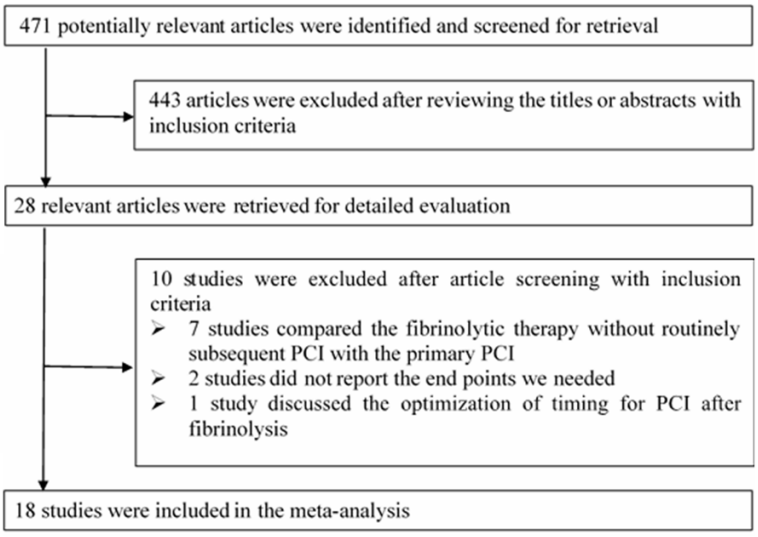

Figure 1. Study selection process. PCI = percutaneous coronary intervention.

survival due to its extreme time sensitiveness [12]. Prehospital fibrinolysis could effectively shorten the time interval between symptom onset and reperfusion treatment compared with in-hospital fibrinolysis in numerous trials [8, 9, 13, 14] and was considered as the strongest predictor of in-hospital survival for STEMI [15]. To date, there are no large-scale studies assessing clinical outcomes from facilitated PCI with pre-hospital fibrinolysis compared to primary PCI for STEMI. Therefore, we did a meta-analysis to elaborate the therapeutic effect of the two therapy strategies.

Materials and methods

Eligibility and search strategy

We did a computerized search of PubMed, the Cochrane Library, reviews and reference lists of relevant papers up to December 2015 to identify the eligible trials for our study. Two of the investigators, masked to the authors of the clinical trials and the journals in which the trials were published determined the eligibility of identified trials independently. Disagreements between the two investigators were resolved by joint review and consultations. Included trials should satisfy the three criteria. First, we included clinical randomized controlled trials of adult patients with STEMI assigned to either primary or facilitated intervention. The facilitated intervention was identified as a strategy of planned immediate PCI after initial fibrinolysis in the prehospital or in-hospital phase. Second, the data for angiographic and short-term clinical outcomes of the eligible trials could be obtained. Third, we enrolled the retrospective studies which compared the facilitated PCI with primary PCI for STEMI. The key words we used for literature search were: "ST segment elevation myocardial infarction", "acute myocardial infarction", "primary percutaneous coronary intervention", "facilitated percutaneous coronary intervention", "thrombolytic therapy", "fibrinolytic therapy", "prehospital thrombolytic therapy", "thrombolysis" and "fibrinolysis".

Data extraction

Two of the investigators independently abstracted data from published sources regarding study design, inclusion and exclusion criteria, number of patients enrolled, mean follow-up exposure, clinical short-term outcomes, angiographic data, ST-segment resolution data and time delay intervals. We retrieved the data according to the principle of "intention to treat". Disagreements were resolved by joint review and consultations.

The primary clinical endpoints were short-term death (up to 90 days), cardiogenic shock, heart failure, non-fatal reinfarcion, urgent target vessel revascularization, total stroke, intracranial hemorrhage, and major bleeding. The primary angiographic endpoints were TIMI grade 3 flow.

Statistical analyses

We analyzed the clinical and angiographic outcomes for the whole population of patients and for each subgroup: in-hospital fibrinolysis and prehospital fibrinolysis. All the comparisons were based on an intention-to-treat analyses. Meta-analyses of the trial results are presented as pooled ORs and associated 95% CIs calculated using the Mantel-Haenszel method for facilitated PCI compared with primary PCI [16]. A p value of 0.05 or less was considered statistically significant; all tests and CIs were two sided. We used a chi-square (χ^2 test), if appropriate, to compare the facilitated PCI with pri-

Table 1. Summary of 18 trials comparing facilitated PCI and primary PCI

Trials	Publication date	Population analyzed	Symptom duration (h)	Symptom-to-balloon time (min)	Door-to-balloon-time (min)	Symptom-to-thrombolysis time (min)	Fibrinolytic agent	Follow-up duration	Pre-hospital fibrinolysis
O'Neill WW, et al (n=122; FP=59, PP=63) [39]	1992	Age 18-76 y; STEMI	<4	199±60**	n/a	160±52**	Streptokinase	In-hospital	No
Ross AM, et al (PACT; n=606; FP=302, PP=304) [9]	1999	Age ≤75 y; STEMI	<6	n/a	FP: 49 PP: 49*	138 (96-198)*	rtPA	30-day	No
Widimsky P, et al (PRAGUE; n=201; FP=100, PP=101) [7]	2000	Age <80 y; STEMI	<6	FP: 220 PP: 215*	FP: 108 PP: 95*	152*	Streptokinase	30-day	No
Steg PG, et al (CAPTIM; n=840; FP=419, PP=421) [30]	2003	STEMI; LBBB	<6	FP: <360 PP: <360	FP: <360 PP: <360	<360	rtPA	30-day	Yes
Kastrati A, et al (BRAVE; n=253; FP=125, PP=128) [41]	2004	STEMI; new LBBB	<12	<180	n/a	n/a	Reteplase	30-day	No
Matthew TR, et al (ADVANCE MI; n=146; FP=69, PP=77) [40]	2005	Age >18 y; STEMI	<4	n/a	n/a	n/a	Tenecteplase	30-day	No
Armstrong PW, et al (WEST; n=204; FP=104, PP=100) [31]	2006	Age ≥18 y; STEMI; new LBBB	<6	FP: 425 (288-1331) PP: 176 (140-280)*	n/a	130 (75-185)*	Tenecteplase	30-day	Yes
Frans Van de Werf, et al (ASSENT-4PCI; n=1667; FP=829, PP=838) [8]	2006	Age ≥18 y; new LBBB; STEMI	<6	FP: 263 (213,-339) PP: 255 (200-335)*	FP: 115 (94-150) PP: 107 (85-140)*	153 (105-225)*	Tenecteplase	90-day	No
Agati L, et al (n=66; FP=30, PP=36) [37]	2007	Age <80 y; STEMI	<3	FP: n/a PP: 132 (78-177)*	n/a	118 (71-170)*	Tenecteplase	3-month	No
Fernandez-Aviles F, et al (GRACIA-2; n=212; FP=104, PP=108) [36]	2007	Age ≥18 y; STEMI; LBBB	<12	n/a	FP: 276 (204-486) PP: 60 (42-84)*	180 (120-240)*	Tenecteplase	30-day	No
Ellis SG, et al (FINESSE; n=1634; FP=828, PP=806) [6]	2008	Age ≥60 y; STEMI	<6	n/a	FP: 132 (108-168) PP: 132 (108-168)*	n/a	Reteplase	90-day	No
McKay RG, et al (n=1349, FP=582, PP=767) [35]	2009	STEMI	<6	n/a	FP: 162±57 PP: 113±61**	n/a	Reteplase; alteplase	In-hospital	No
Kanakakis J, et al (ATHENS PCI; n=284; FP=143, PP=141) [5]	2009	Age ≥18 y; STEMI	<6	FP: 232 (185-315) PP: 275 (190-380)*	FP: 122 (91-175) PP: 120 (89-175)*	135 (90-228)*	Tenecteplase	In-hospital	No
Gao RL, et al (n=311; FP=210, PP=101) [34]	2010	Age ≤70 y; STEMI	<12	FP: n/a PP: 367.8±252.1**	FP: n/a PP: 141.2±120.9**	303.3±183.9**	r-Sak rtPA	30-day	No
Itoh T, et al (IMPORTANT; n=66; FP=19, PP=47) [38]	2010	Age ≤70 y; STEMI	<6	FP: 258±102 PP: 216±84**	n/a	186±84**	rtPA	5-year	No
Czarnecki A, et al (GRACE & CANRACE; n=1103; FP=387, PP=716) [33]	2012	STEMI	<6	FP: n/a PP: 229 (161-370)*	n/a	143 (85-249)	n/a	In-hospital	No
Thiele H, et al (LIPSIA-STEMI; n=162; FP=81, PP=81) [42]	2011	STEMI	<3	FP: 158 (119-222) PP: 131 (106-175)*	FP: 23 (20-31) PP: 25 (18-34)*	75*	Tenecteplase	30-day	Yes
Armstrong PW, et al (STREAM, n=1892; FP=944, PP=948) [32]	2013	STEMI	<3	FP: 600 (245-1235) PP: 178 (135-230)*	n/a	100 (75-143)*	Tenecteplase	30-day	Yes

FP = facilitated PCI (percutaneous coronary intervention). PP = primary PCI. STEMI = ST-segment elevation myocardial infarction. LBBB = left-bundle branch block. n/a = data not available. *Median values with or without IQRs. **Mean ± SDs.

Table 2. ST-segment resolution after randomization in five trials

Trials	FP (n/N; %)	PP (n/N; %)	Time from randomization (min)	*P*
Ellis SG, et al; 2008 [6]*	364/828 (43.9%)	250/806 (31.0%)	60-90	<0.0001
Armstrong PW, et al; 2006 [31]*	59/85 (69.4%)	44/79 (55.7%)	180	0.0706
Matthew TR, et al; 2005 [40]*	16/40 (40.0%)	14/34 (41.2%)	60±15	0.9182
Fernandez-Aviles F, et al; 2007 [36]*	57/94 (60.6%)	41/95 (43.2%)	n/a	0.0167
Thiele H, et al; 2011 [42]	67/81 (83.1%)	57/81 (70.5%)	120	0.0668
Total	563/1128 (49.9%)	406/1095 (37.1%)	n/a	<0.0001

FP = facilitated PCI. PP = primary PCI. n/a = data not available. *ST-segment resolution of more than 70% from baseline.

Table 3. Initial and final TIMI grade 3 flows in fifteen trials

Trials	Initial TIMI 3 flow		*P*	Final TIMI 3 flow		*P*
	FP (n/N; %)	PP (n/N; %)		FP (n/N; %)	PP (n/N; %)	
O'Neill WW, et al; 1992* [39]	11/59 (18.6%)	15/63 (23.8%)	0.49	n/a	n/a	n/a
Ross AM, et al; 1999 [9]	100/302 (33.0%)	46/304 (15.1%)	<0.01	233/302 (77.2%)	229/304 (75.3%)	0.60
Widimsky P, et al; 2000 [7]	30/100 (30.0%)	12/101 (11.9%)	<0.01	91/100 (91.0%)	93/101 (92.1%)	0.78
Kastrati A, et al; 2004 [41]	50/125 (40.0%)	23/128 (18.0%)	<0.01	109/125 (87.2%)	111/128 (86.7%)	0.91
Matthew TR, et al; 2005 [40]	29/71 (40.8%)	15/72 (20.8%)	0.01	n/a	n/a	n/a
Armstrong PW, et al; 2006* [31]	n/a	30/100 (30.0%)	n/a	79/85 (93%)	87/90 (97%)	0.28
FransVan de Werf F, et al; 2006 [8]	361/829 (43.5%)	126/838 (15.0%)	<0.01	726/829 (87.6%)	743/838 (87.6%)	0.49
Agati L, et al; 2007 [37]	20/30 (66.7%)	6/36 (16.7%)	<0.01	26/30 (86.7%)	30/36 (83.3%)	0.71
Fernandez-Aviles F, et al; 2007 [36]	63/104 (60.6%)	13/108 (12.0%)	<0.01	82/104 (78.8%)	80/108 (74.1%)	0.41
Ellis SG, et al; 2008 [6]	272/828 (32.9%)	97/806 (12.0%)	<0.01	n/a	n/a	n/a
McKay RG; 2009 [35]	344/582 (59.1%)	195/767 (25.4%)	<0.01	565/582 (97.1%)	735/767 (95.8%)	0.23
Kanakakis J, et al; 2009 [5]	85/143 (59.4%)	52/141 (36.9%)	<0.01	122/143 (85.3%)	111/141 (78.7%)	0.15
Gao RL, et al; 2010 [34]	106/210 (50.5%)	n/a	n/a	n/a	85/101 (84.2%)	n/a
Thiele H, et al; 2011 [42]	36/81 (44.3%)	20/81 (24.4%)	0.0107	67/81 (83.2%)	72/81 (88.5%)	0.26
Armstrong PW, et al; 2013 [32]	517/884 (58.5%)	186/900 (20.7%)	<0.01	746/819 (91.1%)	816/884 (92.3%)	0.36
Total	2024/4348 (46.6%)	836/4445 (18.8%)	<0.01	2846/3200 (88.9%)	3302/3579 (92.3%)	0.85

FP = facilitated PCI. PP = primary PCI. n/a = data not available. *Reported as TIMI 2/3 flow.

mary PCI for the clinical outcomes. The heterogeneity for every outcomes was assessed using the I^2 value which described the percentage of total variation across studies due to heterogeneity rather than chance. The I^2>50% indicated significant heterogeneity between the trials [17]. We did the analyses using a fixed-effect model initially, and if the heterogeneity was observed, the analyses were repeated using a random-effect model [18]. We regarded an I^2>75% as high heterogeneity. We assessed the publication bias using a funnel plot of effect size against standard error [19]. The statistical software used for this study was Review Manager (RevMan [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Center, the Cochrane Collaboration, 2014).

Results

We identified 28 relevant articles after reviewing the titles or abstracts of 471 potentially relevant articles. Of these 28 studies, ten were subsequently excluded for the following reasons: seven of the omitted studies compared the fibrinolytic therapy without routinely subsequent PCI with the primary PCI [20-26]; two studies did not report the end points we concerned [27, 28]; and one trial discussed the optimization of timing for PCI after fibrinolysis [29]. A total of eighteen studies fulfilling our eligibility criteria were included in this meta-analysis ultimately [5-9, 30-42] (**Figure 1**).

All the studies enrolled for the analysis were published in English, the baseline characteristics of which were shown in **Table 1**. A total of 11118 patients were assigned to these trials (5335 to facilitated PCI, 5783 to primary PCI), with the trial sample sizes ranging from 66 to 1892. The fibrinolytic therapy was initiated during the prehospital phase in four trials [30-32, 42] (n=3098), and the other fourteen trials (n=8020) carried out the fibrinolysis after hospital admission. Fifteen of these trials were prospective, multicenter open-label randomized

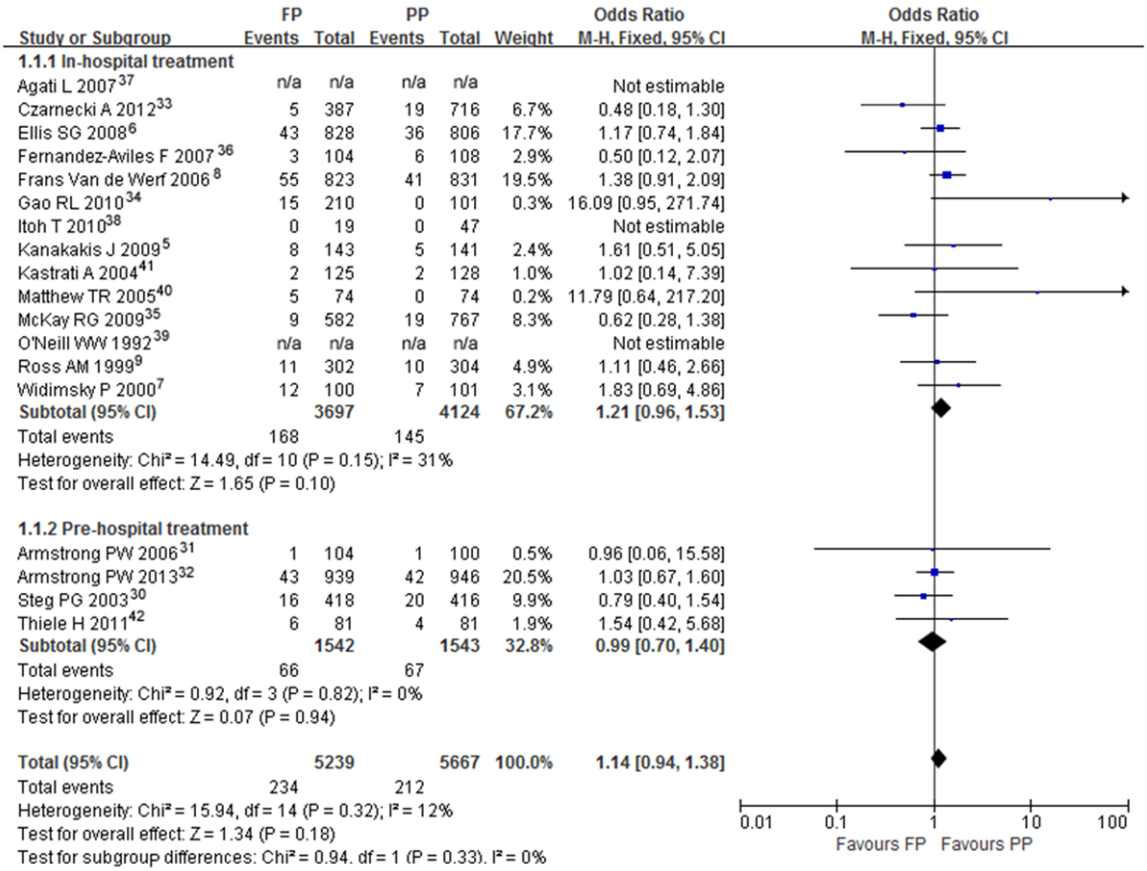

Figure 2. Short-term death in patients allocated to facilitated PCI group or primary percutaneous coronary intervention. Trials classified by the sites of fibrinolysis. Lines = 95% CIs. FP = facilitated PCI. PP = primary PCI. M-H = Mantel-Haenszel. n/a = data not available.

controlled trials, in which four were double-blinded [6, 9, 40, 41]. In addition, one randomized trial reported the data from a single center [37] and the last two trials were retrospective studies [33, 35]. Methodologic features were variable; trials with a larger sample size were associated with intact data of higher quality. Time interval from the symptom onset to balloon dilation was available for ten trials [5, 7, 8, 31-34, 37, 38, 42], door-to-balloon time for nine trials [5-9, 34-36, 42] and symptom-to-fibrinolysis time for thirteen trials [5, 7-9, 31-34, 36-39, 42]. The time intervals between symptom onset and fibrinolysis were shorter in trials with prehospital fibrinolysis (75-130 minutes) than in those with in-hospital fibrinolysis (118-303 minutes). Five trials reported the information of ST-segment resolution (**Table 2**) [6, 31, 36, 40, 42]. ST-segment resolution was improved significantly with facilitated PCI approach compared with primary PCI (49.9% *vs* 37.1%, OR 1.75; 95% CI 1.47-2.08, *P*<0.0001, I^2=0%).

The rate of initial TIMI (thrombolysis in myocardial infarction) grade 3 flow in patients allocated to facilitated PCI were nearly three and a half times of that in those allocated to primary PCI (46.6% *vs* 18.8%, 3.59; 2.86-4.52, *P*<0.01, I^2=74%). However, there was no significant difference in the final TIMI grade 3 flow rates between the two groups (88.9% *vs* 92.3%, 0.98; 0.83-1.17, *P*=0.85, I^2=0%) (**Table 3**).

Sixteen trials compared the short-term mortality between the facilitated PCI group and primary PCI group. There was a trend toward higher mortality with facilitated PCI than that with primary PCI (4.5% *vs* 3.7%, 1.14; 0.94-1.38, *P*=0.18, I^2=12%), especially with facilitated PCI coupled with in-hospital fibrinolysis (4.5% *vs* 3.5%, 1.21; 0.96-1.53, *P*=0.10, I^2=31%). However, a slight trend toward a lower mortality

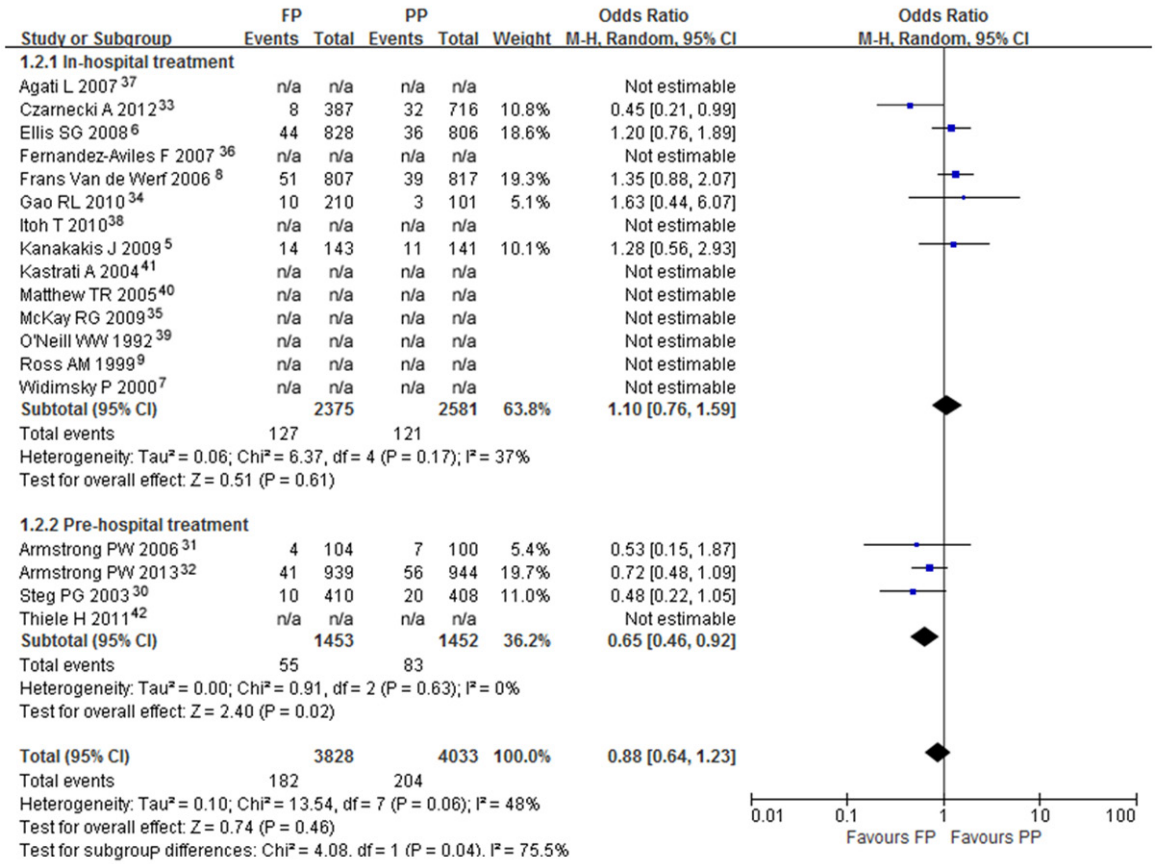

Figure 3. Short-term cardiogenic shock in patients allocated to facilitated PCI group or primary percutaneous coronary intervention. Trials classified by the sites of fibrinolysis. Lines = 95% CIs. See **Figure 2** legend for expansion of abbreviations.

occurred in patients receiving facilitated PCI with pre-hospital fibrinolysis than in those receiving primary PCI (4.3% *vs* 4.3%, 0.99; 0.70-1.40, *P*=0.94, I^2=0%) (**Figure 2**).

There was no difference in cardiogenic shock between facilitated PCI and primary PCI (4.8% *vs* 5.1%, 0.88; 0.64-1.23, *P*=0.46, I^2=48%), and the rate of cardiogenic shock from the facilitated PCI with in-hospital fibrinolysis seemed higher compared with the primary PCI (5.3% *vs* 4.7%, 1.10; 0.76-1.59, *P*=0.61, I^2=37%), indicating the facilitated PCI with in-hospital fibrinolysis was more harmful. On the contrary, cardiogenic shock rates were significantly lower in the trials with prehospital facilitated PCI than in those with primary PCI (3.8% *vs* 5.7%, 0.65; 0.46-0.92, *P*=0.02, I^2=0%) (**Figure 3**).

Overall, heart failure rates were similar in patients assigned to the facilitated PCI group and in those assigned to primary PCI (7.0% *vs* 7.4%, 0.96; 0.80-1.15, *P*=0.68, I^2=0%). However, for the analysis of subgroups, there were a trend toward a higher incidence of heart failure in patients receiving facilitated PCI with in-hospital fibrinolysis (7.0% *vs* 7.0%, 1.04; 0.83-1.30, *P*=0.69, I^2=0%) and a trend toward a lower incidence in patients receiving facilitated PCI with prehospital fibrinolysis (6.9% *vs* 8.3%, 0.81; 0.59-1.12, *P*=0.20, I^2=0%) than in those receiving primary PCI, respectively (**Figure 4**).

The meta-analysis showed that the incidence of non-fatal reinfarction from facilitated PCI was higher than that from primary PCI (3.3% *vs* 1.9%, 1.62; 1.26-2.08, *P*=0.0002, I^2=0%). This effect was mainly seen in facilitated PCI with in-hospital fibrinolysis (3.4% *vs* 1.8%, 1.73; 1.28-2.34, *P*=0.0004, I^2=14%). There was, however, no significant difference in non-fatal reinfarction between the facilitated PCI with prehospital fibrinolysis and primary PCI under

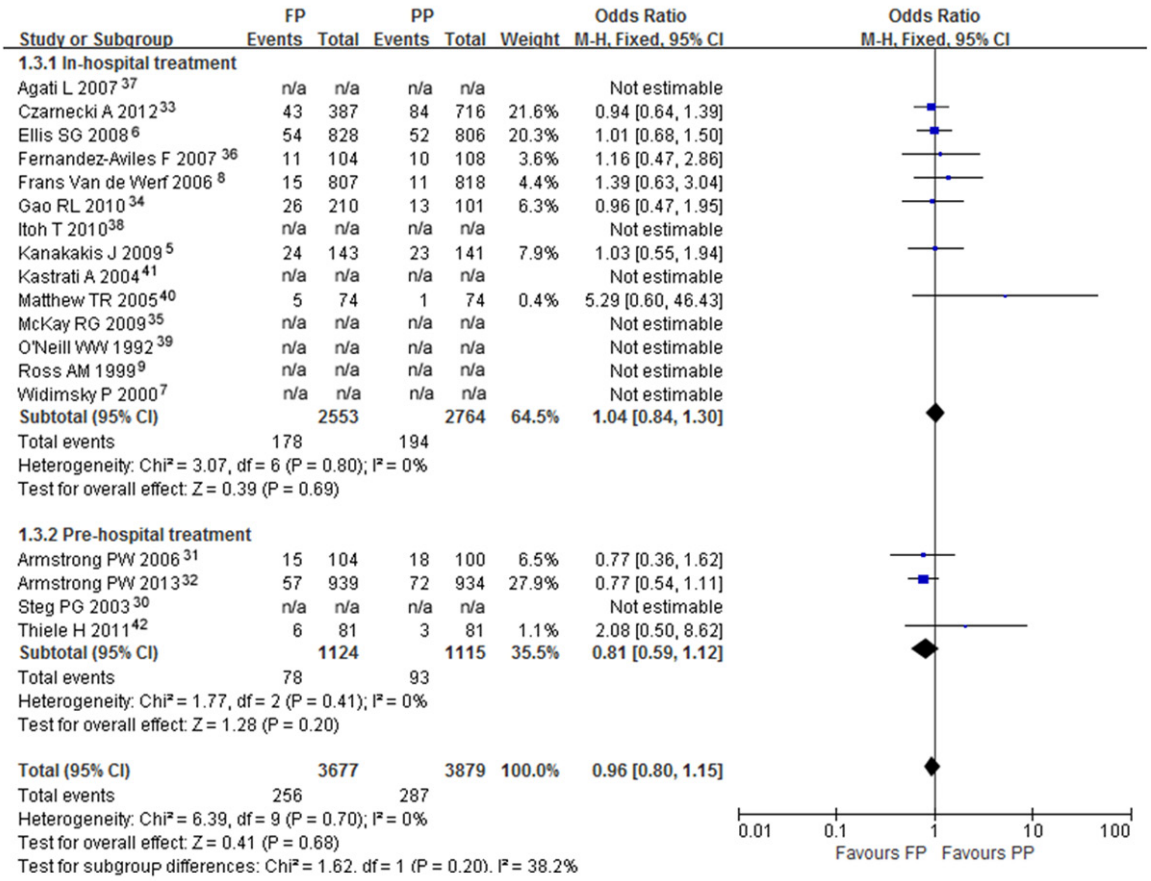

Figure 4. Short-term heart failure in patients allocated to facilitated PCI group or primary percutaneous coronary intervention. Trials classified by the sites of fibrinolysis. Lines = 95% CIs. See **Figure 2** legend for expansion of abbreviations.

the analysis of this subgroup (3.2% *vs* 2.3%, 1.41; 0.91-2.19, *P*=0.13, I^2=0%) (**Figure 5**).

Overall, facilitated PCI had a higher urgent target vessel revascularization rate than primary PCI had (4.7% *vs* 3.2%, 1.43; 1.15-1.78, *P*=0.001, I^2=37%). Similar result was seen with the prehospital facilitated PCI compared with the primary PCI (5.2% *vs* 2.5%, 2.14; 1.43-3.21, *P*=0.0002, I^2=0%). Meanwhile, the difference wasn't statistically significant with the facilitated PCI with in-hospital fibrinolysis (4.4% *vs* 3.5%, 1.19; 0.92-1.55, *P*=0.18, I^2=24%) (**Figure 6**).

The facilitated PCI, with either prehospital or in-hospital fibrinolysis, had a higher rate of total stroke than primary PCI. Facilitated PCI with prehospital fibrinolysis seemed associated with a lower rate of major bleeding compared with primary PCI (**Table 4**).

Publication bias

Publication bias was assessed with five funnel plots. The funnel plots for short-term death, cardiogenic shock, heart failure, non-fatal reinfarction and urgent target vessel revascularization appeared symmetric, suggesting the absence of publication bias (**Figures 7**-**11**).

Discussion

Our study confirmed that the facilitated strategy indeed increased the rates of TIMI grade 3 flow before angioplasty compared with primary PCI, but these improvements did not result in better clinical outcomes. Moreover, compared with primary PCI, the facilitated PCI with in-hospital fibrinolysis leaded to the increased incidences of non-fatal reinfection and total stroke and the trends toward higher rates of short-

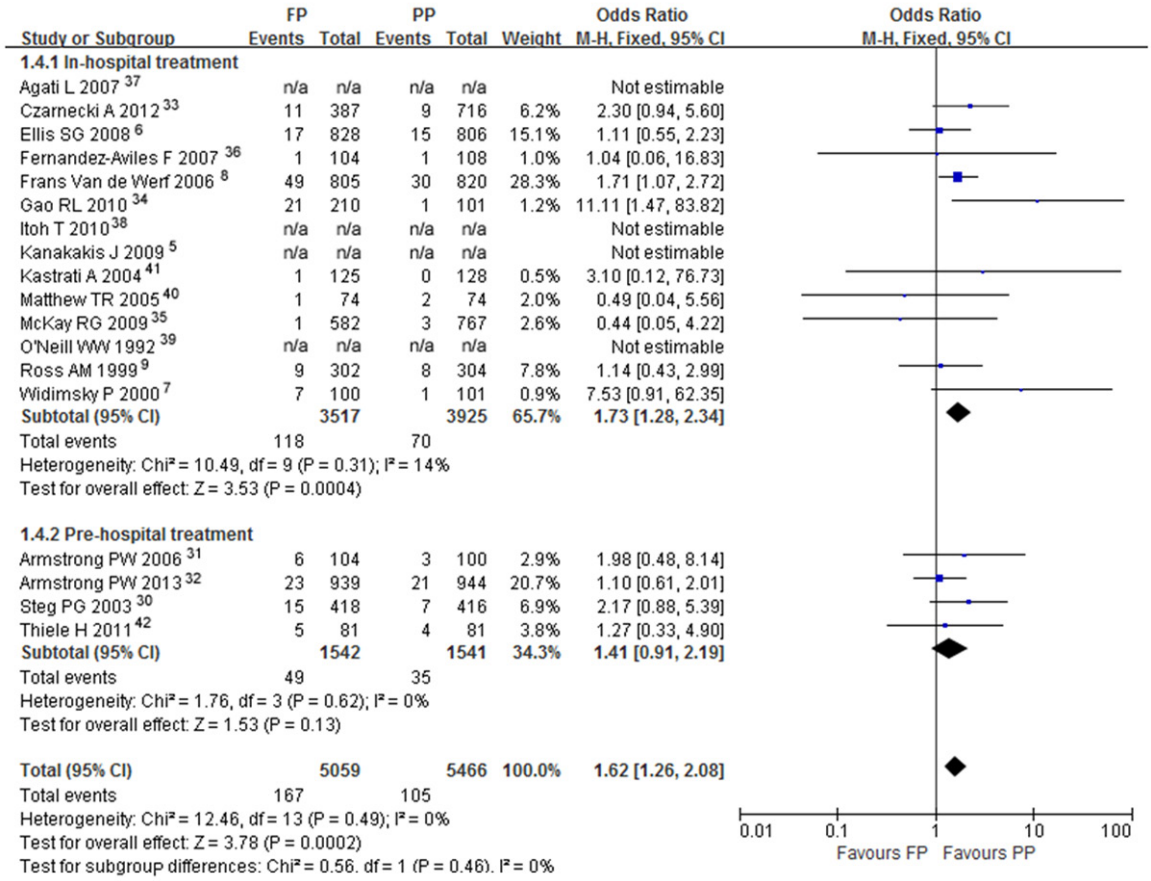

Figure 5. Short-term non-fatal reinfarction in patients allocated to facilitated PCI group or primary percutaneous coronary intervention. Trials classified by the sites of fibrinolysis. Lines = 95% CIs. See **Figure 2** legend for expansion of abbreviations.

term mortality, urgent revascularization, intracranial hemorrhage, cardiogenic shock, heart failure and major bleeding. However, facilitated PCI with prehospital fibrinolysis in our quantitative review brought about potential advantages in reducing the rates of short-term mortality, cardiogenic shock, heart failure and major bleeding without aggravating the non-fatal reinfaction and intracranial bleeding compared with primary PCI. It seemed that facilitated PCI with prehospital fibrinolysis possessed the non-inferiority and even potential superiority compared with primary PCI, while facilitated PCI with in-hospital fibrinolysis was inferior to the primary PCI.

The question remains that how the sites of fibrinolysis (in-hospital or prehospital) affected the clinical outcomes of facilitated PCI. We conjectured that the most possible reason was the time delay before fibrinolysis. It is well-known that the fibrinolytic therapy is extremely time-dependent. Our findings revealed that the time intervals from symptom onset to fibrinolysis were a median of 100 minutes to 130 minutes in the pre-hospital fibrinolysis trials [31, 32], while the time intervals were longer in the in-hospital fibrinolysis trials. If the fibrinolytic therapy could be initiated before the patients arriving at the hospital, the time delay from symptom onset to fibrinolysis would be reduced greatly along with better clinical outcomes. The investigators participating in five landmark clinical trials [43-47] for fibrinolysis consistently revealed that fibrinolytic therapy resulted in the most reduction of mortality in the first 3-4 hours after the symptom onset. Results from the famous GRACE (Global Registry of Acute Coronary Events) trial also revealed that 6-month mortality increased by 0.30% per 10-min delay in door-to-needle time between 30-60 minutes [48]. Another possible reason

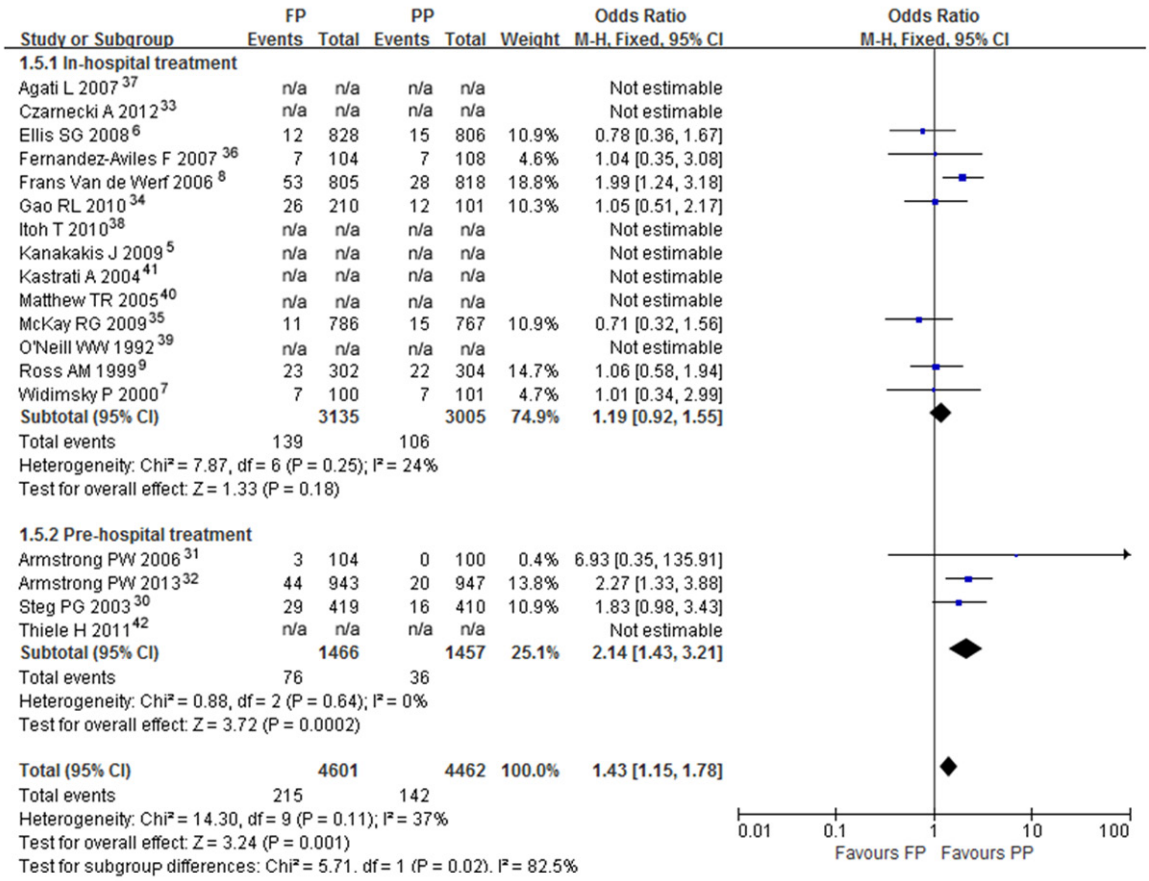

Figure 6. Short-term urgent target vessel revascularization in patients allocated to facilitated PCI group or primary percutaneous coronary intervention. Trials classified by the sites of fibrinolysis. Lines = 95% CIs. See **Figure 2** legend for expansion of abbreviations.

Table 4. Clinical complications in different facilitated PCI strategies

	Facilitated PCI (n/N; %)	Primary PCI (n/N; %)	*P*
Total stroke			
Prehospital treatment	20/1429 (1.3%)	6/1448 (0.4%)	0.009
In-hospital treatment	35/2876 (1.2%)	13/3093 (0.4%)	0.002
Total	55/4305 (1.3%)	19/4541 (0.4%)	<0.0001
Intracranial hemorrhage			
Prehospital treatment	4/932 (0.4%)	2/939 (0.2%)	0.41
In-hospital treatment	10/2938 (0.3%)	10/3163 (0.3%)	0.86
Total	14/3870 (0.4%)	12/4102 (0.3%)	0.59
Major bleeding			
Prehospital treatment	37/1543 (2.4%)	56/1546 (3.6%)	0.06
In-hospital treatment	206/3577 (5.8%)	172/3961 (4.3%)	0.11
Total	243/5120 (4.7%)	228/5507 (4.1%)	0.38

was the dosage adjustment of the fibrinolytic agent for patients of high risk. In the analyses for the subgroup of prehospital treatment, the STREAM (Strategic Reperfusion Early after Myocardial Infarction; n= 1982) trial, which had the largest weight of the four trials, reduced dosage for the patients ≥75 years and found no more cases of intracranial hemorrhage in this age group (0 of 97 patients) compared with 3 of 37 patients in this age group without the amendment [32]. In the other subgroup of in-hospital treatment, only two of the fourteen trials made the same adjustment [6, 40]. The two of the three clinical trials including dosage adjustment (STREAM [32] and FINESSE [Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events; n=2452] [6]) showed the non-inferiority of facilitated approach compared with primary PCI in clinical endpoints, excepting an

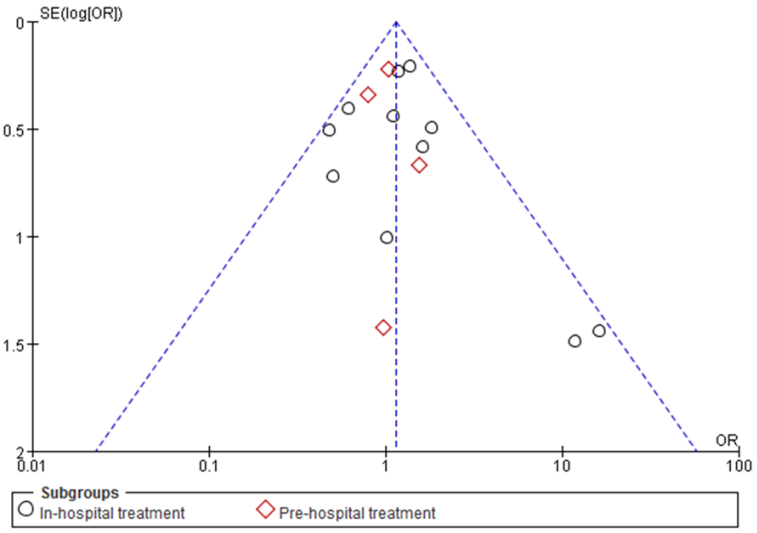

Figure 7. Funnel plot of all individual studies in the meta-analysis of short-term death in patients receiving facilitated PCI and primary PCI.

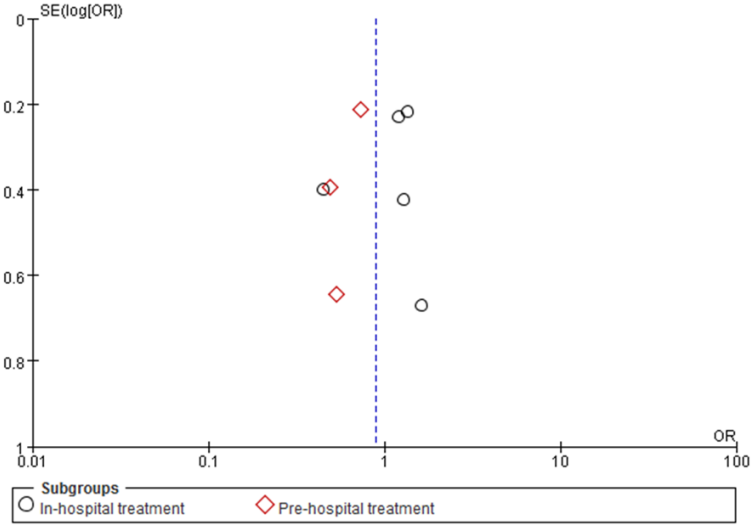

Figure 8. Funnel plot of all individual studies in the meta-analysis of short-term cardiogenic shock in patients receiving facilitated PCI and primary PCI.

increasing risk of bleeding inevitably for fibrinolytic therapy itself. We suggested the dosage adjustment made the non-inferiority of prehospital fibrinolysis compared with primary PCI visible in the way of reducing the bleeding complications of itself.

Prehospital fibrinolysis has more effectiveness and is as safety as in-hospital fibrinolysis. Several small-scale clinical trials performed by Koren G, et al [49], Castaigne AD, et al [50] and McAleer B, et al [14] indicated prehospital administration of fibrinolytic agent as a feasible, well-tolerated and good way to shorten the delay of fibrinolytic treatment in myocardial infarction. The European Myocardial Infarction Project Group organized a multicenter, double-blind study involving 5469 patients showed a significant reduction of the cardiac death in the prehospital fibrinolysis group compared with the in-hospital group [51]. Gale CP, et al analyzed the Myocardial Infarction National Audit Project (MINAP) database (n= 34722) to find out that in the "real word", the strongest predictors for in-hospital survival of patients with STEMI were prehospital fibrinolysis and aspirin therapy given acutely which were associated with a mortality risk reduction of over half [15].

Other clinical trials also supported the non-inferiority and even potential superiority of facilitated PCI with prehospital fibrinolysis. The data form SWEDES (The Swedish Early Decision reperfusion trial, n= 205) trial [52] and the randomized trial from Bonnefoy E, et al (n=840) [53] showed no significant difference in the incidence of the 30-day composite endpoint between prehospital fibrinolysis with rescue PCI when necessary and primary PCI.

Based on all of the clinical evidences above, we propose that the decision of reperfusion approach for patients with STEMI should be made as soon as the EMS (emergence medical service) staff meet the patients in order to shorten the time delay from symptom onset to reperfusion therapy. We made a slight change for the current organization of STEMI patient disposal [54]. When the EMS staff get to a STEMI patient who is a candidate for reperfusion, the time of transfer for primary PCI should be considered. If the patient could be transferred to primary PCI capable center within the

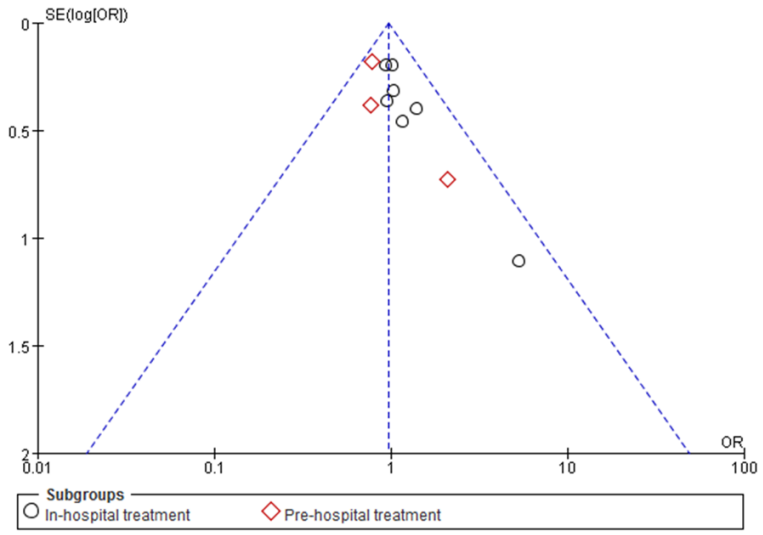

Figure 9. Funnel plot of all individual studies in the meta-analysis of short-term heart failure in patients receiving facilitated PCI and primary PCI.

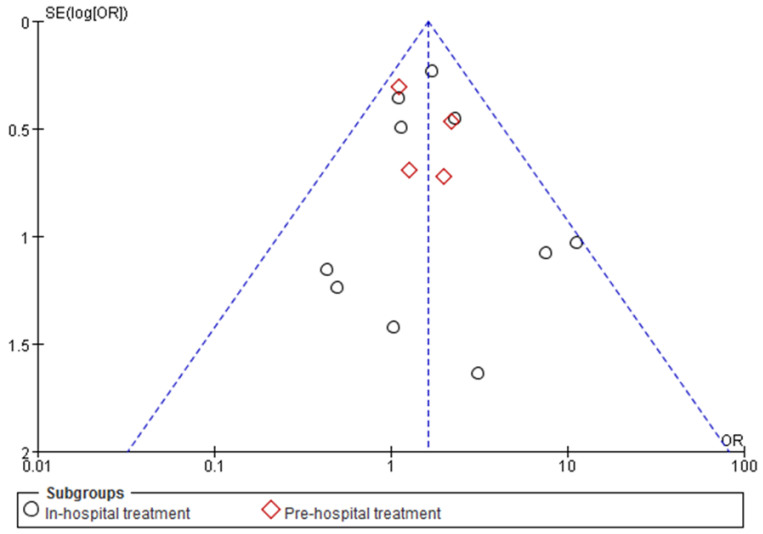

Figure 10. Funnel plot of all individual studies in the meta-analysis of short-term non-fatal reinfarction in patients receiving facilitated PCI and primary PCI.

FMCTB (first medical contact to balloon) time of 120 minutes, the patient should be transferred for primary PCI as soon as possible. If the time of transfer for primary PCI is more than 120 minutes, the prehospital fibrinolysis, with a dosage adjustment of fibrinolytic agents for high risk patients of bleeding, should be initiated immediately in a mobile-care unit or in an ambulance during transfer to a PCI capable center for angiogram no matter the fibrinolysis is successful or not (**Figure 12**).

Limitations

First, our study was a meta-analysis of relevant clinical trials based on extensive collection of medical publications. Two of the eighteen trials enrolling for our analysis were non-randomized retrospective study design [33, 35] but the meta-analysis was feasible because the inclusion criterion and grouping methods were similar to the other randomized trials. On the other hand, both of the two retrospective studies belonged to the subgroup of facilitated PCI with in-hospital fibrinolysis and did not interfere the analysis of the facilitated PCI with prehospital fibrinolysis. The highlight of our analysis lied in the non-inferiority and even potential superiority of facilitated PCI with prehospital fibrinolysis compared with primary PCI. Second, no randomized trials were designed merely to compare facilitated PCI with prehospital fibrinolysis with primary PCI. Even in the STREAM trial [32], which had the highest weight in the meta-analysis for prehospital strategy subgroup, 81% (764 of 939) of the patients assigned to the facilitated PCI group received prehospital fibrinolysis, while 29% (175 of 939) of the patients receiving fibrinolytic agent after hospital admission. In the analysis of the subgroups according to the place of randomization, the prehospital treatment group had more potential clinical benefits compared with in-hospital treatment group [32]. If all the facilitated PCI approaches could be initiated with prehospital fibrinolysis, the advantages of this strategy would be more visible in all probability. Finally, our study focused on the short-term clinical endpoints (up to 90 days), the prolonged follow-up duration was necessary for most trials to assess the long-term prognosis of

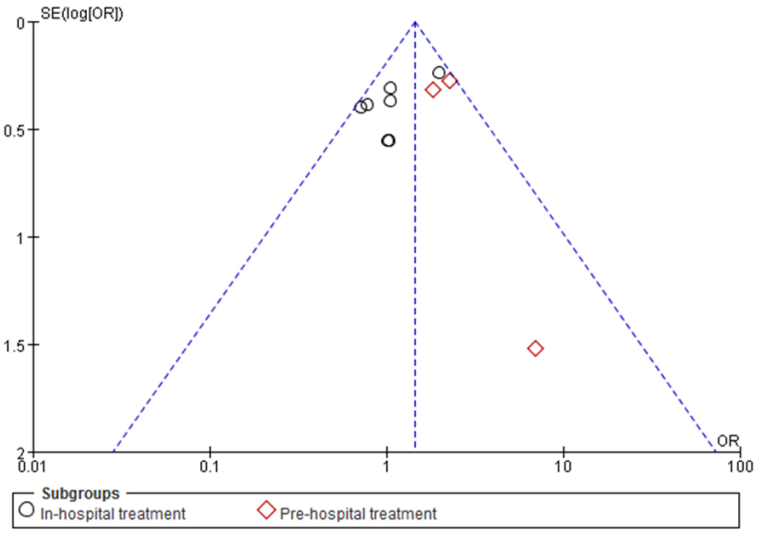

Figure 11. Funnel plot of all individual studies in the meta-analysis of short-term urgent target vessel revascularization in patients receiving facilitated PCI and primary PCI.

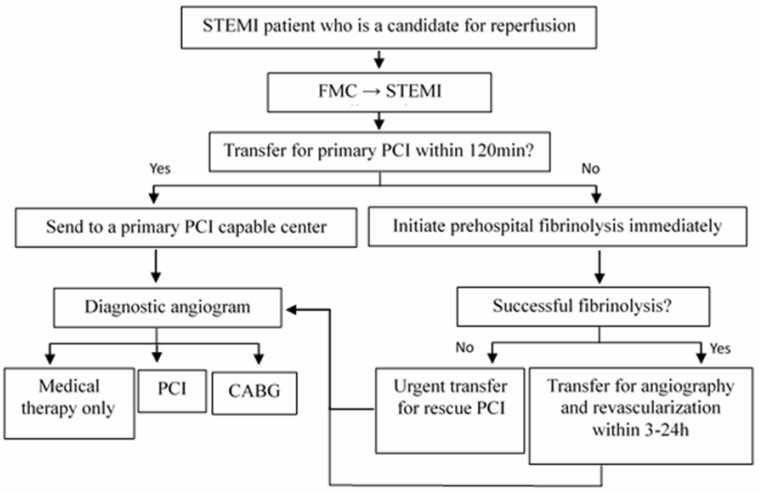

Figure 12. Organization of STEMI patient disposal. FMC = first medical contact. CABG = coronary artery bypass graft. Organization of STEMI patient disposal. STEMI = ST-segment elevation myocardial infarction. FMC = first medical contact. PCI = percutaneous coronary intervention. CABG = coronary artery bypass graft.

this treatment strategy, although the 5-year mortality was lower with facilitated PCI with prehospital fibrinolysis compared and primary PCI in the CAPTIM trial [28] and FAST-MI (French Registry on Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction; n=1030) trial [55].

Conclusions

Despite of the limitations, our analysis reveals that compared with primary PCI, facilitated PCI could result in early effective reperfusion in patients with STEMI. Facilitated intervention with prehospital fibrinolysis provides potential benefits for the treatment of patients with STEMI due to its association with potential decreased rates of short-term mortality, cardiogenic shock, heart failure and major bleeding. However, the facilitated approach with fibrinolysis after hospital admission should be avoided because of its potential risks for increasing the endpoints above.

Disclosure of conflict of interest

None.

Authors' contribution

Dr. Yang: contributed to design, data analysis, writing and revision of the manuscript. Dr. Guan: contributed to data analysis. Dr. Wan: contributed to statistical analysis supervision and revised the manuscript. Dr. Kang: contributed to design, data analysis and revision of the manuscript and had full access to all the data in this study and the final responsibility for the decision to submit for publication.

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