ORIGINAL ARTICLE

VIA MEDICA

Invasive reperfusion after 12 hours of the symptom onset remains beneficial in patients with ST-segment elevation myocardial infarction: Evidence from a meta-analysis of published data

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Abstract

Background: *Early myocardial reperfusion therapy (< 12 h) in patients with acute myocardial infarction (AMI) can significantly improve their prognosis. However, the effect of late reperfusion (> 12 h) remains controversial. In this study, the effects of late reperfusion versus standard drug therapy on the outcomes of patients with AMI were evaluated by systematic review and meta-analysis.*

Methods: *PubMed, Embase, Medline, Cochrane, Wanfang, and CNKI databases were searched for eligible studies for the present study. Meta-analysis was performed using RevMan 5.3.3 software. Relative risk (RR) and the 95% confidence interval (CI) were used to compare the outcomes between the two groups. The main outcome measures were major adverse cardiac events (MACEs), all-cause mortality, recurrent myocardial infarction (MI), and heart failure.*

Results: *Eighteen studies were identified including 14,677 patients, of whom 5157 received late reperfusion with percutaneous coronary intervention (PCI) and 9520 received medication therapy (MT). Compared to MT, late PCI was associated with decreased all-cause mortality (RR 0.60, 95% CI 0.44–0.83; p = 0.002), MACEs (RR 0.67; 95% CI 0.50–0.89; p < 0.001), and heart failure (RR 0.76; 95% CI 0.60–0.97; p = 0.03), while there was also a trend toward decreased recurrent MI (RR 0.70; 95% CI 0.47–1.05; p = 0.08). However, subgroup analysis according to time to PCI showed that the clinical benefit was only from PCI after 12 h but not from 2 to 60 days of the onset of symptoms.*

Conclusions: *The present meta-analysis suggested that PCI performed > 12 h but not 2–60 days after AMI is associated with significant improvement in clinical outcomes. However, these results need further rigorously designed large sample size clinical trials to be validated.* (Cardiol J 2019; 26, 4: 333–342)

Key words: late reperfusion, percutaneous coronary intervention, clinical outcome, acute myocardial infarction, meta-analysis

Introduction

Acute myocardial infarction (AMI) is one of the leading causes of death worldwide [1]. Early myocardial reperfusion has become a primary therapeutic goal of ST-segment elevation myocardial infarction (STEMI) [2]. A large number of clinical practices have confirmed that the opening

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of an infarct related artery (IRA) within 12 h after onset significantly improved the prognosis of AMI patients [3–5]. However, there are two views on the treatment of patients over the reperfusion time window (> 12 h) in clinical practices. One is the standard drug treatment, including the double anti-platelet, β-blockers and statins, while another is the late reperfusion by percutaneous coronary intervention (PCI). However, the benefit of late PCI (> 12 h) has been controversial. Recent studies [6–8] have shown that late PCI may improve the cardiac function and clinical outcomes of AMI patients compared to medication therapy (MT). However, several studies reported conflicting results [9–11]. Abbate et al. [7] performed a meta-analysis including 10 randomized controlled trials (RCTs) indicating that PCI of the IRA performed late (from 12 h to 60 days) after AMI is associated with significant improvements in cardiac function and survival. However, this published meta-analysis included patients who received late PCI within 12 h–60 days. That is, patients who received PCI with 12–48 h of the onset of symptoms were included. In fact, the clinical outcomes may differ between individuals receiving PCI within 12–48 h and those receiving PCI within 2–60 days [9, 12]. Hochman et al. [9] reported that late PCI within 3–28 days (median 8 days) after AMI did not show clinical benefit. However, Gierlotka et al. [12] found late reperfusion within 12–48 h reduced the 12-month mortality rate compared to medication therapy alone in AMI patients. Therefore, although Abbate et al.'s [7] meta-analysis demonstrated that late PCI (from 12 h to 60 days) after AMI is associated with significant improvements in cardiac function and survival, the best cut-off of time window for late PCI remains uncertain.

The aim of this study was to perform an updated systematic review and meta-analysis of all eligible studies to further clarify the effect of late PCI versus MT on the prognosis of AMI patients and the best cut-off time window for late PCI.

Methods

Retrieval strategy

Eligible studies published in PubMed, Embase, Medline, Cochrane, Wanfang, and CNKI databases were searched from 1980 to November 2016 using the following keywords: "acute myocardial infarction (AMI)"; "percutaneous coronary intervention (PCI)"; "reperfusion"; "subacute myocardial infarction"; "acute coronary syndrome"; and "medication therapy".

The main outcome measures were major adverse cardiac events (MACEs), all-cause mortality, recurrent myocardial infarction, and heart failure (HF). Eligible studies published in both Chinese and English were included in the present study.

Inclusion and exclusion criteria

Randomized controlled trials were included, as well as observational studies and cohort studies in which: 1) enrolled patients with AMI received treatments of late reperfusion (> 12 h) or MT; 2) compared outcomes between treatments of MT and later reperfusion; and 3) reported clinical outcomes, such as all-cause mortality, MACEs, HF, and other outcomes.

Excluded were: 1) studies assessing the role of early reperfusion; 2) studies that only reported one therapy strategy; and 3) studies not involving human subjects.

Study selection

The procedure of eligible study selection is shown in Figure 1. Initially 1623 studies were searched. Of these, 1602 (98.7%) were excluded by title and abstract search because of irrelevant content, non-English and non-Chinese articles, animal subjects, outcomes of interest not reported, or other reasons. The remaining 21 studies were full-text reviewed, and 4 studies were excluded due to event rates not reported and outcomes of interest not reported. Finally, 18 studies [8–25] met the inclusion criteria and were included in the meta-analysis.

Data extraction

Two investigators (H.T.Y. and X.X.) carried out the data extraction using standardized data extraction forms. Discrepancies were resolved by consensus. The following information was collected from each study: name of the first author, year of publication, ethnicity or geographic location of the study subjects, study design, procedural and management strategy, ages, gender, and relevant outcomes.

Outcomes

The primary outcomes for this systematic review were MACEs and all-cause mortality. Secondary outcomes were recurrent MI and HF.

Methodological quality

The recommendations of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group were followed to perform this meta-analysis,
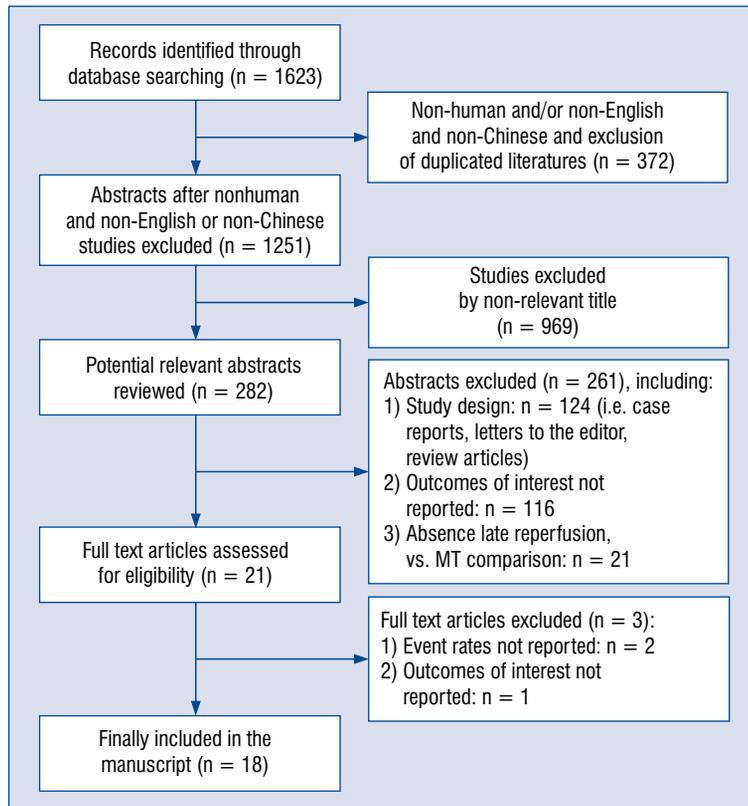
Figure 1. Flow chart of identification of eligible studies; MT — medication therapy.

including study selection, data collection, analysis, and reporting of the results.

Weighted risk ratios (RRs) were calculated and 95% confidence intervals (CIs) for categorical variables and mean difference, and 95% CI for continuous variables. Heterogeneity testing was performed using the Cochrane Q-statistic and I^2-statistic. Pooled effect sizes were determined using a fixed-effects model (the Mantel-Haenszel method) when heterogeneity was negligible ($I^2 < 50\%$) or a random-effects model (the DerSimonian and Kacker method) when significant heterogeneity was present ($I^2 \geq 50\%$). Sensitivity analysis was also performed to evaluate the effect of each study on the combined RRs by omitting each study in turn. Publication bias was visually estimated by assessing funnel plots. All analyses were performed using RevMan 5.3.3 software (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen) as described previously.

Results

Study and patient characteristics

Table 1 listed the characteristics of the 18 studies [8–25] that met eligibility criteria. Of these, 4 are observational studies [12. 14, 22, 23] and

14 are RCTs [8–11, 13, 15–21, 24, 25]. The present analysis includes 14,677 patients, of whom 5157 received late myocardial reperfusion and 9520 received MT. The mean age of study participants was 58.4 years. Mean follow-up time was 12 months.

MACEs

Thirteen of 18 studies [8, 9, 11–18, 21, 23, 24] reported 1067 MACEs during follow-up. There was significant heterogeneity among included studies ($I^2 = 81\%$, $p < 0.001$); therefore, the random-effects model were used to calculate the RR value. In all patients, the meta-analysis results suggested that late PCI was associated with a lower incidence of MACEs (RR 0.67; 95% CI 0.50–0.89; $p < 0.001$, Fig. 2A) than MT. When stratified analysis according to time to PCI was performed, the heterogeneity disappeared in the > 12 h arm ($I^2 = 0\%$) and weakened in the 2–60 days arm ($I^2 = 79\%$). Subgroup analysis showed that a decreased MACE rate was observed only in the > 12 h arm but not in the 2–60 days arm (Table 2).

All-cause mortality

Fourteen of 18 studies [8, 9, 11–17, 20, 21, 23–25] reported an outcome of all-cause mortality.

Table 1. Summary of key demographic characteristics of studies included in the meta-analysis.

First author	Publication year	Region	Sample size, n	No. of PCI/MT	Study design	Time to admission	Management strategy	Mean follow up time	Age [years]	Male sex, %	Outcomes
Freixa et al.	2012	Canada	1024	472/552	RCT	3–28 d	PCI (DES/BMS), MT	5.1 y	PCI (DES): 56.9 ± 11.3 PCI (BMS): 57.4 ± 10.6 MT: 58.7 ± 10.9	PCI (DES): 74.7 PCI (BMS): 77.4 MT: 79.0	MACEs, revascularization, death, recurrent MI, HF
Wu et al.	2012	China	146	47/44	OS	5–10 d	PCI/MT	1 m	56.2 ± 13.6	68.4	MACEs, arrhythmia, death, HF
Zeymer et al.	2003	Canada	300	149/151	RCT	8–42 d	PCI/MT	56 m	PCI: 58.2 ± 9.2 MT: 57.5 ± 9.8	PCI: 84% MT: 89%	MACEs, nonfatal reinfarction, revascularization, death
Horie et al.	1998	Japan	84	44/39	RCT	1–21 d	PTCA/MT	60 m	PTCA: 61.8 ± 11.9 MT: 61.6 ± 8.8	PTCA: 77% MT: 74%	MACEs, death/LVEF (6 m), HF, recurrent MI
Hochman et al.	2006	USA	2166	1082/1084	RCT	3–28 d	PCI/MT	34 m	PCI: 58.6 ± 10.8 MT: 58.7 ± 11.1	PCI: 78% MT: 78%	MACEs, death, HF, recurrent MI
Steg et al.	2004	France	212	109/103	RCT	2–15 d	PTCA/MT	35 m	PTCA: 56 (50–66) MT: 58 (50–66)	PTCA: 82.5% MT: 87.2%	MACEs, death, HF, revascularization, recurrent MI
Erne et al.	2007	Switzerland	201	96/105	RCT	3–58 d	PCI/MT	10.2 y	PCI: 54.4 ± 9.1 MT: 56.2 ± 8.8	PCI: 88.5% MT: 86.7%	MACEs, recurrent MI, death, revascularization
Džavik et al.	2006	USA	381	195/186	RCT	3–28 d	PCI/MT	12 m	PCI: 57.3 (34–80) MT: 57.8 (33–81)	PCI: 83.1% MT: 82.3%	LVEF
Schömig et al.	2005	German	365	182/183	RCT	12–48 h	PCI/MT	3 m	PCI: 65.7 (57.7–73.6) MT: 67.1 (551–73.7)	PCI: 74.2 MT: 74.4	LV infarct size, MACEs
Silva et al.	2005	Canada	36	18/12	RCT	12 h–14 d	PCI/MT	6 m	PCI: 56.50 ± 9.11 MT: 52.83 ± 9.50	PCI: 77.78 MT: 75	LVEF, LV volume
Dzavik et al.	1994	Canada	44	25/19	RCT	5–42 d	PTCA/MT	4 m	PTCA: 58 ± 12 MT: 59 ± 12	PTCA: 72% MT: 68%	Death
Yousef et al.	2002	England	66	32/34	RCT	3 d–4 w	PCI/MT	12 m	PCI: 59.1 ± 9.7 MT: 57.6 ± 11.2	PCI: 81% MT: 80%	MACEs, death, recurrent MI, HF, revascularization, stroke
Ellis et al.	1992	USA	87	42/45	RCT	> 4 d	PTCA/MT	12 m	PTCA: 58 ± 9 MT: 56 ± 10	PTCA: 86 MT: 82	MACEs, death, recurrent MI, LVEF

Table 1. (cont.). Summary of key demographic characteristics of studies included in the meta-analysis.

First author	Publication year	Region	Sample size, n	No. of PCI/MT	Study design	Time to admission	Management strategy	Mean follow up time	Age [years]	Male sex, %	Outcomes
Khan et al.	2014	UK	27	6/21	OS	> 12 h	PCI/MT	3 y	PCI: 54.7 ± 12.1 MT: 65.6 ± 16.2	PCI: 83.3 MT: 76.2	LVEF Infarct size
Gierlotka et al.	2011	Poland	2036	910/1126	OS	12–24 h	PCI/MT	1 y	PCI: 63.3 ± 11.8 MT: 67.2 ± 13.2	PCI: 67.6% MT: 56%	Death, MACEs, recurrent MI
Qi et al.	2006	China	84	33/51	OS	12 h–20 d	PCI/MT	3 y	PCI: 63.12 ± 10.23 MT: 67.43 ± 10.65	PCI: 76.19% MT: 70.83%	MACEs, death, recurrent MI, revascularization, HF
He et al.	2010	China	60	28/32	RCT	2–3 w	PCI/MT	1 y	PCI: 60.3 ± 8.2 MT: 61.5 ± 7.6	PCI: 92.85 MT: 87.5	MACEs, death, LVEF, HF
Elad et al.	2002	USA	7358	1631/5727	OS	> 12 h	PTCA/MT	< 1 m	PTCA: 61.1 ± 12.91 MT: 65.7 ± 13.75	PTCA: 87.7 MT: 85.0	Death Recurrent MI

BMS — bare metal stent; d — days; DES — drug eluting stent; h — hours; HF — heart failure; LV — left ventricular; LVEF — LV ejection fraction; m — months; MACEs — major adverse cardiac events; MI — myocardial infarction; MT — medication therapy; OS — observational study; PCI — percutaneous coronary intervention; PTCA — percutaneous transluminal coronary angioplasty; RCT — randomized controlled trial; w — weeks; y — years

There was significant heterogeneity among studies included (I^2 = 55%, p = 0.009). The random-effects model was used to calculate the RR value. In total patients, relative to MT, late PCI was associated with decreased all-cause mortality (RR 0.62, 95% CI 0.43–0.92; p = 0.02, Fig. 2B). When stratified analysis according to time to PCI was performed, the heterogeneity disappeared in both the > 12 h arm (I^2 = 0%) and the 2–60 days arm (I^2 = 20%). Subgroup analysis showed that decreased mortality was observed only in the > 12 h arm but not in the 2–60 days arm (Table 2).

Recurrent MI

There are 12 studies [8, 9, 11–17, 21, 23, 25] that reported the outcome of recurrent MI. Significant heterogeneity existed among the included studies (I^2 = 67%, p = 0.008). The random-effects model was used to calculate the RR value. In all patients, there was a trend toward decreased recurrent MI (RR 0.70; 95% CI 0.47–1.05; p = 0.08, Fig. 2C) in the late reperfusion group. When stratified analysis, according to time to PCI was performed, the heterogeneity disappeared in the > 12 h arm (I^2 = 0%) but remained in the 2–60 days arm (I^2 = 70%). Subgroup analysis showed late reperfusion with > 12 h was significantly associated with deceased recurrent MI (RR 0.53; 95% CI 0.39–0.72, p < 0.001). However, no difference was found between late reperfusion with 2–60 days and MT in recurrent MI (RR 0.84, 95% CI 0.46–1.51, p = 0.55, Table 2).

Heart failure

There are 8 studies [8, 9, 11, 13, 14, 16, 23, 24] that reported the outcome of HF. No significant heterogeneity existed among the studies included (I^2 = 40%, p = 0.11). The fixed-effects model was used to calculate the RR value. The meta-analysis results showed that late reperfusion was associated with decreased incidence of HF rate (RR 0.76; 95% CI 0.60–0.97; p = 0.03, Fig. 2D). Similarly, subgroup analysis showed late reperfusion PCI with > 12 h was significantly associated with decreased incidence of HF rate (RR 0.33; 95% CI 0.15–0.70; p = 0.004). However, a difference was not found between late reperfusion with 2–60 days and MT in HF (RR 0.85, 95% CI 0.66–1.10; p = 0.21, Table 2).

Sensitivity analysis

A sensitivity analysis was conducted to examine the influence of each study on the pooled RRs. The pooled RRs showed no significant change when one study was deleted individually. Further
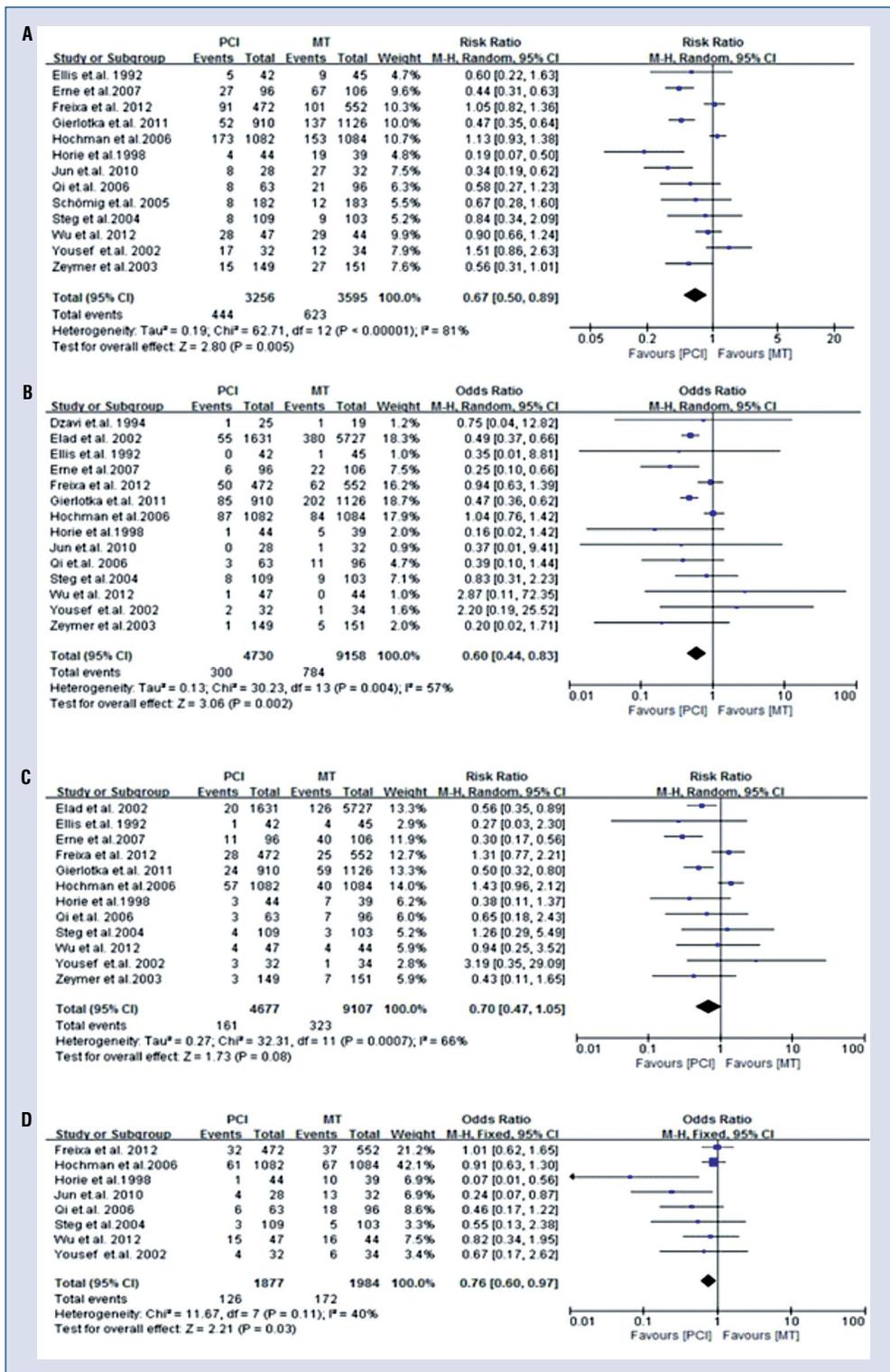
Figure 2. Forest plots of association of late percutaneous coronary intervention (PCI) versus medication therapy (MT) with clinical outcomes. **A.** major adverse cardiac events; **B.** All-cause mortality; **C.** Recurrent myocardial infarction; **D.** Heart failure; CI — confidence interval.

Table 2. Subgroup analysis according to time to percutaneous coronary intervention.

Clinical outcomes	I²	RR (95% CI)	P
All-cause mortality:			
Total	57%	0.60 (0.44–0.83)	0.002
> 12 h	0%	0.47 (0.39–0.58)	< 0.001
2–60 days	20%	0.82 (0.58–1.14)	0.24
Major adverse cardiac events:			
Total	81%	0.67 (0.50–0.89)	< 0.001
> 12 h	30%	0.46 (0.36–0.60)	< 0.001
2–60 days	79%	0.77 (0.57–1.04)	0.09
Recurrent myocardial infarction:			
Total	66%	0.70 (0.47–1.05)	0.08
> 12 h	0%	0.53 (0.39–0.72)	< 0.001
2–60 days	70%	0.84 (0.46–1.51)	0.55
Heart failure:			
Total	40%	0.76 (0.60–97)	0.03
> 12 h	61%	0.33 (0.15–0.70)	0.004
2–60 days	0%	0.85 (0.66–1.10)	0.21

CI — confidence interval; RR — relative risk

removed were the 4 observational studies in order to observe the stability of the results which also found no significant change in the pooled RRs, suggesting the results are stable and credible.

Publication bias analysis

In the present study, funnel plots were utilized to evaluate the publication bias of all included studies. No publication biases were found for this meta-analysis (Fig. 3).

Discussion

The present meta-analysis is based on the statistical pooling of 18 studies that enrolled a total of 14,677 patients, comparing late reperfusion with conservative MT in patients presenting more than 12 h after an AMI. Late PCI was reported (> 12 h) after AMI was associated with decreased MACEs, all-cause mortality, recurrent MI and HF. However, late PCI within 2–60 days after AMI is not associated with improvements in clinical outcomes. This is the first meta-analysis to not only clarify the effect of late PCI versus MT on the prognosis of AMI patients but also to answer just how late is too late for PCI after AMI. Nevertheless, there are several points to be discussed when interpreting the results.
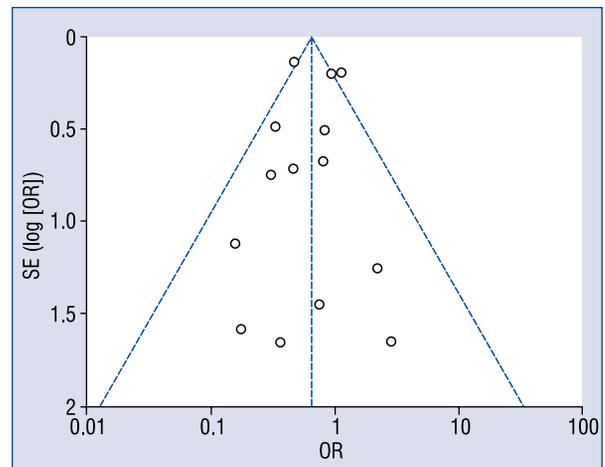

Figure 3. Funnel plot of test of publication bias; OR — odds ratio; SE — standard error.

Significant findings and clinical implications

The findings that > 12 h, but not 2–60 days of late reperfusion had a beneficial effect on the clinical outcomes of AMI patients are potentially very significant. In the real world, more than 50% of patients undergo PCI during the subacute phase after an AMI [26–29]. Specifically, the current ACC/AHA guidelines for PCI suggests that

late PCI is a class IIb (occluded artery) or class III (stenosis without evidence of spontaneous or provocable angina) indication [30]. However, the time point that is rational for PCI in the subacute phase of MI remains unclear. The present meta-analysis clarified this issue and suggested that late PCI should not be performed later than 2 days after the onset of symptoms.

Pathophysiological mechanisms

The pathophysiological mechanisms of late PCI are propitious to the prognosis of AMI and may be explained as follows: Firstly, opening of an IRA is beneficial to the salvaging of "hibernating" myocardium from death, even if late and beyond the time limit set for salvaging from myocardial necrosis [31]. Second, late reperfusion may favorably affect the apoptotic cascade, subsequently resulting in heart function protection [32]. In addition, opening of an IRA may interrupt the progression from hibernating myocardium to necrotic/apoptotic myocardium [33]. Busk et al. [34] observed the infarct size and myocardial salvage after primary angioplasty in patients presenting with symptoms for < 12 h vs. 12–72 h and supported that reducing time to treatment is pivotal because 'time is muscle'. However, Busk et al. [34] also demonstrated that substantial salvage was observed despite pain-to-balloon intervals of 12–72 h, even in patients with total occlusion of the IRA. Busk et al.'s [34] findings challenge the 12 h limit in primary angioplasty and suggest angioplasty of occluded IRAs should be performed within 48–72 h after AMI. Schömig et al. [18] also reported that primary angioplasty within 12–48 h reduced final infarct size and increased the salvage index when compared with MT. In the present data, clinical benefit was found from reperfusion with a > 12 h interval but not from a 2–60 day interval. The results are in line with the views of Busk et al. [34] and Schömig et al. [18].

Validity and potential limitations of the meta-analysis

This study has two advantages compared with Abbate et al.'s [8] meta-analysis published in 2008. The present study enrolled clinical trials that included a total of 14,677 AMI patients. Thus, results may be credible and stable. Identified patients received late PCI of > 12 h or 2–60 days, respectively and a concrete conclusion was made.

Several potential limitations are worth mentioning. First, in meta-analysis, many of the studies included had different entry criteria, study popula-tions, clinical outcomes, time to PCI, and follow-up time. This is a source of increased heterogeneity that may limit the generalizability of the conclusions to a broader AMI population. Therefore, a subgroup analysis was made and found heterogeneity disappeared or decreased. Second, there are 4 studies designed not as randomized trials, and therefore different study designs may influence results. Third, the participants in some studies including both PCI of within 12–48 h and within 2–60 days could not be divided into two groups to perform meta-analysis because of absence of stratification in the original studies. Thus, there is a proportion of 2–60 days PCI patients mixed in the > 12 h PCI subjects. Therefore, the results need to be verified by further rigorously designed large sample size clinical trials.

Conclusions

This meta-analysis of data from 18 studies shows beneficial outcomes in performing PCI late (> 12 h) in the course of an AMI. However, PCI performed later than 2 days after onset of AMI may be unnecessary in clinical practice.

Conflict of interest: None declared

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