Immediate versus deferred percutaneous coronary intervention for patients with acute coronary syndrome: A meta-analysis of randomized controlled trials

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Abstract

Inconsistent results exist regarding the treatment effectiveness of immediate versus deferred percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS). This meta-analysis aimed to evaluate the efficacy and safety of immediate versus deferred PCI in ACS patients. PubMed, EMBASE, and Cochrane Library electronic databases were systematically searched from their inception up to August 2019. Random-effects models were employed to calculate pooled relative risks (RRs) and weight mean differences (WMDs) with 95% confidence intervals (CIs). A total of 10 randomized controlled trials (RCTs) that recruited 3350 patients were selected for inclusion in the final meta-analysis. Four trials included patients with non-ST elevation ACS (NSTEACS), whereas the remaining six trials included patients with ST elevation myocardial infarction (STEMI). There were no significant differences between immediate versus deferred PCI for the risk of major adverse cardiovascular events (NSTEACS patients: RR, 0.76, 95%CI, 0.33–1.75, P = 0.513; STEMI patients: RR, 1.24, 95%CI, 0.80–1.92, P = 0.335), myocardial infarction (NSTEACS patients: RR, 0.88, 95%CI, 0.27–2.81, P = 0.826; STEMI patients: RR, 0.86, 95%CI, 0.43–1.74, P = 0.678), all-cause mortality (NSTEACS patients: RR, 0.85, 95%CI, 0.38–1.88, P = 0.686; STEMI patients: RR, 1.16, 95%CI, 0.82–1.66, P = 0.407), target vessel revascularisation (NSTEACS patients: RR, 1.26, 95%CI, 0.29–5.43, P = 0.756; STEMI patients: RR, 1.01, 95%CI, 0.51–1.97, P = 0.988), or major bleeding (NSTEACS patients: RR, 0.99, 95%CI, 0.64–1.54, P = 0.972; STEMI patients: RR, 0.90, 95%CI, 0.45–1.77, P = 0.753). Although patients who underwent immediate PCI may experience increased incidences of cardiac death (RR, 1.19, 95%CI, 0.69–2.07, P = 0.525) and no or slow reflow (RR, 1.60, 95%CI, 0.91–2.84, P = 0.105), these increases were not statistically significant. We noted that immediate versus deferred PCI was associated with a reduced incidence of myocardial brush grade 3 (RR, 0.70, 95%CI, 0.56–0.88, P = 0.002); however, no significant differences were observed between immediate and deferred PCI for TIMI III flow (RR, 0.98, 95%CI, 0.93–1.03, P = 0.453), complete ST-segment resolution (RR, 0.93, 95%CI, 0.75–1.17, P = 0.548), and ejection fraction (WMD, −1.05, 95%CI, -2.58 to 0.49, P = 0.182). The findings of this study suggested that deferred PCI did not yield significant benefits for
clinical endpoints. Further large-scale RCTs should be conducted to verify the findings of this study.

Introduction

Acute coronary syndrome (ACS) includes unstable angina and myocardial infarction (MI) and is characterized by decreased perfusion of the heart muscles, which is associated with high risks of cardiovascular morbidity and mortality [1, 2]. Studies have illustrated baseline angiographic markers of disease burden, calcification, and lesion severity with significant predictive values for short- and long-term ischemic outcomes in ACS patients treated with early invasive strategies [3]. Currently, patients discharged after ACS treatment should be managed by lifestyle modification (e.g., physical activity planning, smoking cessation, and adherence to a healthy diet) and pharmacotherapy (e.g., acetylsalicylic acid, P2Y12-receptor inhibitors, beta-blockers, statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers) [4]. Although invasive strategies are widely introduced in combination with conservative treatment approaches, the treatment effectiveness and optimal timing of such approaches remain unclear [5–8].

Previous studies have illustrated differences between non-ST elevation ACS (NSTEACS) and ST elevation MI (STEMI) for ruptured plaques with a large necrotic core and abundant thrombus, with STEMI patients showing poor vascular healing processes and high risk of stent thrombosis [9–11]. Moreover, although the average daily ischemic risk and bleeding risk were similar within 1 year after percutaneous coronary intervention (PCI), we noted the incidence of average daily ischemic risk was higher than average daily bleeding risk within 2 weeks after PCI, especially for patients with STEMI or undergoing incomplete revascularization. Furthermore, the incidence of average daily ischemic risk was greater than average daily bleeding risk for patients with incomplete revascularization, while average daily bleeding risk was significantly higher than average daily ischemic risk for NSTEACS patients treated with ticagrelor [12]. Therefore, the risks of intervention for unstable plaque and ischemic events should be balanced with waiting for an invasive procedure. However, studies have reported inconsistent results regarding the effects of the use of early interventions on the risk of ischemic events and levels of cardiac injury biomarkers [13–15]. The current meta-analysis was conducted to evaluate the efficacy and safety of immediate versus deferred PCI in NSTEACS and STEMI patients on the basis of published randomized controlled trials (RCTs).

Materials and methods

Data sources, search strategy, and selection criteria

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement issued in 2009 [16]. Studies designed as RCTs and that investigated the treatment effectiveness of immediate versus deferred PCI in NSTEACS or STEMI patients were eligible for inclusion in this meta-analysis, with no restrictions placed on publication status or language. PubMed, EMBASE, and Cochrane Library electronic databases were systematically searched from their inception up to August 2019; we used the keywords “immediate” AND (“deferred” OR “delayed”) AND (“stenting” or “percutaneous coronary intervention” or “PCI” or “percutaneous coronary angioplasty”) AND (“acute coronary syndrome” or “myocardial infarction”) as the core search terms. Moreover, the website http://clinicaltrials.gov/ (US NIH) was reviewed for ongoing trials that registered their trial
results but were not yet published. The reference lists of the collected articles were also manually reviewed to select any other RCTs that met the inclusion criteria.

The literature search and study selection were conducted by two authors following a standardized flow, and any conflicts were resolved by an additional author who read the original article. The inclusion criteria of this study included the following: (1) Patients: those diagnosed with NSTEACS or STEMI; (2) Intervention: immediate PCI; (3) Control: deferred PCI, which defined as the performed of PCI from within few hours up to 1 week and not restricted the timing of the second coronary angiogram; (4) Outcomes: the study should have reported at least one of following outcomes: major adverse cardiovascular events (MACEs), MI, all-cause mortality, target vessel revascularisation (TVR), major bleeding, cardiac death, no or slow reflow, myocardial brush grade 3 (MBG 3), TIMI III flow, complete ST-segment resolution, or ejection fraction level; and (5) Study design: RCT.

Data collection and quality assessment

The collected data from individual trials included study, publication year, country, sample size, age, percentage of males, hypertension, diabetes mellitus, dyslipidemia, smoking, previous PCI, disease status, intervention, control, follow-up duration, and reported outcomes. The study quality was assessed using the Jadad scale, which was based on randomization, blinding, allocation concealment, withdrawals and dropouts, and the use of an intention-to-treat analysis [17]. The scoring system of the Jadad scale ranges from zero to five points with scores of four or more points considered to indicate high quality. Two authors conducted data collection and quality assessment, and the inconsistencies were settled by an additional author by referring to the original article.

Statistical analysis

The treatment effectiveness of immediate versus deferred PCI for ACS patients was divided into categories and continuous data. The pooled relative risk (RR) and weighted mean difference (WMD) values with corresponding 95% confidence intervals (CIs) were calculated using a random-effects model, because of the true underlying effect varies across included trials were considered [18, 19]. Heterogeneity among included trials for each pooled outcome was assessed using $I^2$ and Q statistics, and $I^2 > 50.0\%$ or $P < 0.10$ was considered to indicate significant heterogeneity [20, 21]. Subgroup analyses were conducted based on disease status (NSTEACS or STEMI). Publication biases for investigated outcomes were calculated using funnel plots and Egger [22] and Begg [23] tests. All inspection levels for pooled effect estimates were two-sided, and $P < 0.05$ was considered statistically significant. STATA version 10.0 software (StataCorp, Texas, United States of America) was used for all statistical analyses.

Results

Literature search

The initial electronic search yielded 746 records, of which 142 were excluded for being duplicates. The titles and abstracts of the remaining 604 articles were reviewed, and 567 were further excluded because of irrelevant topics. A total of 37 studies were retrieved for further full-text evaluations, of which 27 studies were excluded because of an observational design ($n = 13$), being a review or meta-analysis ($n = 8$), or having no appropriate control groups ($n = 6$). The results of the manual reference list searches did not yield any other articles. Thus, a total of 10 RCTs were selected for final quantitative analysis (Fig 1) [14, 15, 24–31].
Study characteristics

A total of 3350 patients from 10 RCTs were included in the final analysis. Four of these trials included 1219 patients with NSTEACS, whereas the remaining six trials included 2131 patients with STEMI. The baseline characteristics of the included studies and patients are summarized in Table 1. The duration of follow-up ranged from 30.0 days to 42.0 months, and 101–1215 patients were included in each trial. The mean age of the included patients ranged from 57.7 to 72.4 years, and the percentage of males ranged from 67.7% to 83.3%. Eight trials were conducted in Europe, one trial was conducted in the United States, and one trial was conducted in Korea. Seven of the included trials were of high quality, whereas the remaining three trials were of low quality.

Major adverse cardiovascular events

Data for the effects of immediate versus deferred PCI on the risk of MACEs were available in three and four studies of NSTEACS and STEMI patients, respectively. There were no significant differences between immediate and deferred PCI for the risk of MACEs in NSTEACS (RR: 0.76, 95% CI: 0.33–1.75; P = 0.513) and STEMI (RR: 1.24, 95% CI: 0.80–1.92; P = 0.335) patients (Fig 2). Significant heterogeneity was noted for MACEs in NSTEACS patients, whereas moderate heterogeneity was noted for MACEs in STEMI patients. No significant
Table 1. Baseline characteristics of the included studies.

| Study        | Country    | Sample size | Age (years) | Percentage male (%) | Hypertension (%) | DM (%) | Dyslipidemia (%) | Smoking (%) | Previous PCI (%) | Disease status | Intervention | Control | Follow-up duration | Study quality |
|--------------|------------|-------------|-------------|---------------------|------------------|--------|------------------|-------------|------------------|---------------|-------------|----------|------------------|---------------|
| van’t Hof 2003 [14] | Netherlands | 220 | 64.0 | 70.5 | 41.8 | 14.5 | NA | 34.5 | 14.5 | Non-ST ACS | Immediate PCI | Deferred PCI (>12 h) | 30 days | 3 |
| Riezebos 2009 [15] | Netherlands | 142 | 62.5 | 71.8 | 43.7 | 19.7 | 35.2 | 38.7 | 23.2 | Non-ST ACS | Immediate PCI | Deferred PCI (24–48 h) | 30 days | 4 |
| Badings 2013 [24] | Netherlands | 534 | 72.4 | 67.7 | 56.2 | 22.1 | NA | 23.8 | 19.5 | Non-ST ACS | Immediate PCI | Deferred PCI (>48 h) | 30 days | 3 |
| Milosevic 2016 [25] | Serbia | 323 | 61.7 | 68.1 | 68.7 | 26.9 | 74.3 | 45.2 | 9.9 | Non-ST MI | Immediate PCI (<2 h) | Deferred PCI (2–72 h) | 30 days | 4 |
| Pasquale 2006 [26] | Italy | 451 | 59.0 | 72.9 | 29.0 | 18.2 | 37.3 | 33.7 | 8.9 | STEMI | Immediate PCI (<2 h) | Deferred PCI (12–72 h) | 6 months | 3 |
| Carrick 2014 [27] | US | 101 | 59.6 | 69.3 | NA | 12.9 | NA | NA | 4.0 | STEMI | Immediate stenting | Deferred stenting (4–16 h) | 6 months | 5 |
| Kim 2016 [28] | Korea | 114 | 59.6 | 83.3 | 50.0 | 30.7 | 35.1 | 52.6 | 1.8 | STEMI | Immediate stenting | Deferred stenting (3–7 days) | 30 days | 5 |
| Kelbaek 2016 [29] | Denmark | 1215 | 61.5 | 75.0 | 41.0 | 9.0 | NA | 52.5 | NA | STEMI | Immediate stenting | Deferred stenting (>48 h) | 42 months | 5 |
| Belle 2016 [30] | France | 140 | 57.7 | 81.4 | 30.0 | 11.4 | NA | 67.1 | 4.3 | STEMI | Immediate stenting | Deferred stenting (24–48 h) | 6 months | 5 |
| Janssens 2019 [31] | Netherlands | 110 | 61.7 | 70.9 | 33.6 | 9.1 | 27.3 | 46.4 | 6.4 | STEMI | Immediate PCI | Deferred PCI (24–48 h) | 12 months | 4 |

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publication bias was detected for the risk of MACEs (P value for Egger = 0.598 and P value for Begg = 1.000; S1 Fig).

### Myocardial infarction

Data for the effects of immediate versus deferred PCI on the risk of MI were available in four and three studies of NSTEACS and STEMI patients, respectively. The summary RR indicated that immediate versus deferred PCI did not yield significant effects on the risk of MI in NSTEACS (RR: 0.88, 95% CI: 0.27–2.81; P = 0.826) and STEMI (RR: 0.86, 95% CI: 0.43–1.74; P = 0.678) patients (Fig 3). Significant heterogeneity was noted for MI in NSTEACS patients, whereas moderate heterogeneity was noted for MI in STEMI patients. No significant publication bias was observed for the risk of MI (P value for Egger = 0.892 and P value for Begg = 1.000; S2 Fig).

### All-cause mortality

Data for the effects of immediate versus deferred PCI on the risk of all-cause mortality were available in three and five studies of NSTEACS and STEMI patients, respectively. No significant differences were noted between immediate and deferred PCI for the risk of all-cause mortality in NSTEACS (RR: 0.85, 95% CI: 0.38–1.88; P = 0.686) and STEMI (RR: 1.16, 95% CI: 0.82–1.66; P = 0.407) patients (Fig 4). There was no evidence of heterogeneity for all-cause mortality in NSTEACS and STEMI patients. No significant publication bias for the risk of all-cause mortality was observed (P value for Egger = 0.158 and P value for Begg = 0.386; S3 Fig).
### Target vessel revascularisation

Data for the effects of immediate versus deferred PCI on the risk of TVR were available in one and three studies of NSTEACS and STEMI patients, respectively. There were no significant differences between immediate and deferred PCI for the risk of TVR in NSTEACS (RR: 1.26, 95% CI: 0.29–5.43; P = 0.756) and STEMI (RR: 1.01, 95% CI: 0.51–1.97; P = 0.988) patients (Fig 5). Moreover, significant heterogeneity was noted for TVR in STEMI patients. No significant publication bias was observed for TVR (P value for Egger = 0.900 and P value for Begg = 1.000; S4 Fig).

### Major bleeding

Data for the effects of immediate versus deferred PCI on the risk of major bleeding were available in three and two studies of NSTEACS and STEMI patients, respectively. Compared with deferred PCI, immediate PCI was not associated with a risk for major bleeding in NSTEACS (RR: 0.99, 95% CI: 0.64–1.54; P = 0.972) and STEMI (RR: 0.90, 95% CI: 0.45–1.77; P = 0.753) patients (Fig 6). No significant heterogeneity was detected for NSTEACS and STEMI patients. Moreover, no significant publication bias was observed for major bleeding (P value for Egger = 0.402 and P value for Begg = 0.221; S5 Fig).

### Cardiac death and no or slow reflow

Data on the incidences of cardiac death and no or slow reflow in STEMI patients who underwent immediate PCI were available in two and four studies, respectively (Fig 7). The summary RRs indicated that immediate or deferred PCI was not associated with the incidences of cardiac death (RR: 1.19, 95% CI: 0.69–2.07; P = 0.525) and no or slow reflow (RR: 1.60, 95% CI: 0.95–2.69; P = 0.086) patients (Fig 7). No significant heterogeneity was noted for cardiac death and no or slow reflow in STEMI patients. No significant publication bias was observed for cardiac death and no or slow reflow (P value for Egger = 0.579 and P value for Begg = 0.762; S6 Fig).

| Study            | Risk ratio (95% CI) | % Weight |
|------------------|---------------------|----------|
| NSTEACS          |                     |          |
| van Hout 2003    | 1.43 (0.47, 4.36)   | 17.9     |
| Riezebos 2009    | 0.95 (0.06, 14.82)  | 4.6      |
| Badings 2013     | 2.46 (0.48, 12.58)  | 10.9     |
| Milosevic 2016   | 0.25 (0.08, 0.73)   | 18.7     |
| Subtotal         | 0.88 (0.27, 2.81); P=0.826 (I-square: 59.7%; P=0.059) | 52.0     |
| STEMI            |                     |          |
| Carrick 2014     | 0.21 (0.03, 1.75)   | 7.3      |
| Kelbaek 2016     | 0.94 (0.62, 1.43)   | 34.8     |
| Janssens 2019    | 2.09 (0.19, 22.50)  | 6.0      |
| Subtotal         | 0.86 (0.43, 1.74); P=0.678 (I-square: 14.1%; P=0.312) | 48.0     |
| Overall          | 0.83 (0.44, 1.55); P=0.549 (I-square: 39.9%; P=0.125) | 100.0    |

Fig 3. Immediate versus deferred PCI for myocardial infarction.

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Fig 4. Immediate versus deferred PCI for all-cause mortality.

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| Study         | Risk ratio (95% CI) | % Weight |
|---------------|---------------------|----------|
| NSTEMI        |                     |          |
| van't Hof 2003| 0.61 (0.15, 2.49)   | 5.3      |
| Badings 2013  | 0.99 (0.20, 4.84)   | 4.1      |
| Milosevic 2016| 0.99 (0.29, 3.37)   | 7.0      |
| Subtotal      | 0.85 (0.38, 1.88); $P=0.686$ (I-square: 0.0%); $P=0.857$ | 16.5     |

| STEMI         |                     |          |
| Pasquale 2006 | 1.17 (0.40, 3.43)   | 9.1      |
| Carrick 2014  | 0.35 (0.01, 8.47)   | 1.0      |
| Kelbaek 2016  | 1.19 (0.81, 1.74)   | 71.3     |
| Belle 2016    | 2.76 (0.11, 66.53)  | 1.0      |
| Janssens 2019 | 0.35 (0.01, 8.39)   | 1.0      |
| Subtotal      | 1.16 (0.82, 1.66); $P=0.407$ (I-square: 0.0%); $P=0.847$ | 83.5     |
| Overall       | 1.10 (0.80, 1.53); $P=0.553$ (I-square: 0.0%); $P=0.948$ | 100.0    |

Fig 5. Immediate versus deferred PCI for TVR.

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Fig 6. Immediate versus deferred PCI for major bleeding.

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Fig 7. Immediate versus deferred PCI for cardiac death and no or slow reflow.

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0.91–2.84; $P = 0.105$). Furthermore, there was no significant heterogeneity for cardiac death, whereas potential significant heterogeneity for no or slow reflow was noted.

**Myocardial brush grade 3, TIMI III flow, and complete ST-segment resolution**

Data on the incidences of MBG 3, TIMI III flow, and complete ST-segment resolution for STEMI patients who underwent immediate PCI were available in two, four, and three studies, respectively (Fig 8). Immediate versus deferred PCI was associated with a reduced incidence of MBG 3 (RR: 0.70, 95% CI: 0.56–0.88; $P = 0.002$); however, no significant differences between groups were noted for the incidences of TIMI III flow (RR: 0.98, 95% CI: 0.93–1.03; $P = 0.453$) and complete ST-segment resolution (RR: 0.93, 95% CI: 0.75–1.17; $P = 0.548$). No significant heterogeneity was detected for MBG 3 and complete ST-segment resolution, whereas significant heterogeneity was observed for TIMI III flow.

**Ejection fraction**

Data for the effect of immediate versus deferred PCI on ejection fraction level were available in three trials. The pooled results suggested that no significant differences existed between immediate and deferred PCI for ejection fraction (WMD: $-1.05$, 95% CI: $-2.58$ to $0.49$; $P = 0.182$), and no significant heterogeneity was detected across the included trials (Fig 9).

| Study                        | Risk ratio (95% CI)                  |
|------------------------------|-------------------------------------|
| **MBG 3**                    |                                     |
| Carrick 2014                 | 0.69 (0.51, 0.93)                   |
| Kim 2016                     | 0.72 (0.52, 0.99)                   |
| Subtotal                     | 0.70 (0.56, 0.88); $P = 0.002$      |
| (I-square: 0.0%; $P = 0.858$) |                                     |
| **TIMI III flow**            |                                     |
| Carrick 2014                 | 0.83 (0.71, 0.96)                   |
| Kim 2016                     | 1.02 (0.96, 1.08)                   |
| Kelbaek 2016                 | 1.00 (0.98, 1.02)                   |
| Belle 2016                   | 0.96 (0.87, 1.06)                   |
| Subtotal                     | 0.98 (0.93, 1.03); $P = 0.453$      |
| (I-square: 61.7%; $P = 0.050$) |                                     |
| **complete ST-segment resolution** |                                   |
| Carrick 2014                 | 0.78 (0.50, 1.21)                   |
| Kim 2016                     | 0.84 (0.54, 1.32)                   |
| Belle 2016                   | 1.08 (0.79, 1.48)                   |
| Subtotal                     | 0.93 (0.75, 1.17); $P = 0.548$      |
| (I-square: 0.0%; $P = 0.423$) |                                     |

Fig 8. Immediate versus deferred PCI for MBG 3, TIMI III flow and complete ST-segment resolution. 

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The current study provides updated results regarding immediate versus deferred PCI for STEMI patients and is the first study to pool the treatment effectiveness of immediate versus deferred PCI in NSTEACS patients. The current quantitative meta-analysis recruited 1219 NSTEACS patients and 2131 STEMI patients from 10 RCTs with a broad range of patient characteristics. The results of this study indicated that no significant differences existed between immediate and deferred PCI for the incidences of MACEs, MI, all-cause mortality, TVR, and major bleeding, irrespective of NSTEACS or STEMI status. Moreover, immediate or deferred PCI was not associated with cardiac death, no or slow reflow, TIMI III flow, complete ST-segment resolution, or ejection fraction in STEMI patients; however, compared with deferred PCI, immediate PCI was associated with a reduced incidence of MBG 3 in STEMI patients.

Several systematic reviews and meta-analyses have been conducted to evaluate the treatment effectiveness of immediate versus deferred PCI. Desch et al conducted a meta-analysis of nine RCTs and found that patients treated with immediate or early PCI showed reduction in all-cause mortality risk; however, the risk of stroke or major bleeding between groups was not statistically significantly different [32]. Freixa et al included five non-RCTs and one RCT in their study and found that delayed stent implantation may lead to beneficial angiographic outcomes in patients with acute MI [33]. Liu et al conducted a meta-analysis including 16 studies and found that STEMI patients treated with early PCI, as opposed to primary PCI alone, after fibrinolysis displayed similar results, which were better than those observed with ischemia-guided or delayed PCI [34]. A meta-analysis of three RCTs and seven non-RCTs suggested that deferred stenting provided beneficial outcomes for periprocedural composite events and abnormal flow in STEMI patients; however, no significant difference between immediate and deferred stenting for MACEs was noted [35]. Qiao et al conducted a meta-analysis including...
three RCTs and six non-RCTs and suggested that deferred stenting was associated with an improved left ventricular function; however, no significant differences between groups were noted in clinical endpoints [36]. Mahmoud et al conducted a meta-analysis including four RCTs and suggested that deferred stent implantation was associated with a lower incidence of no or slow reflow and improved MBG 3; however, association between the clinical endpoints in deferred and immediate stenting was not statistically significant [37]. Cassese et al conducted a meta-analysis including four RCTs and suggested that deferred stent implantation was associated with a lower incidence of no or slow reflow and improved MBG 3; however, association between the clinical endpoints in deferred and immediate stenting was not statistically significant [38].

Therefore, the current meta-analysis was conducted to evaluate the efficacy and safety of immediate versus deferred PCI for NSTEACS and STEMI patients.

The summary results indicated that immediate versus deferred PCI did not yield any significant effects on MACEs, MI, all-cause mortality, TVR, and major bleeding, irrespective of NSTEACS or STEMI status. Although no significant differences between groups were noted for cardiac death, no or slow reflow, TIMI III flow, complete ST-segment resolution, and ejection fraction, we noted that deferred PCI may have a beneficial effect on MBG 3. Several reasons could help interpret the above results: (1) deferred PCI allows for a better sizing of the lesion and artery, which is associated with optimized stent selection [39]; (2) patients treated with deferred PCI require better evaluations of the revascularization strategy, which could avoid unnecessary stenting for nonsignificant residual stenosis [40]; and (3) deferred PCI strategy always involves repeated angiograms, which could detect nonculprit arteries in patients with multivessel lesions [41]. However, smaller number of included trials could be the reason behind no significant differences between immediate and deferred PCI for the incidences of clinical endpoints, and the power may not have been sufficient to detect potential differences between immediate and deferred PCI. Moreover, treatment with deferred PCI strategy is associated with higher costs, prolonged hospitalization, and high risk of reocclusion.

Although the results of our study did not reveal any significant differences between immediate and deferred PCI, our findings suggested that deferred PCI is safe for the treatment of NSTEACS and STEMI patients. However, several limitations of this study should be mentioned: (1) variations in disease status and background therapies could affect the prognosis of NSTEACS and STEMI patients; (2) several investigated outcomes were reported in few trials, and the results regarding immediate versus deferred PCI were variable; and (3) this meta-analysis was based on published study levels; thus, publication bias was inevitable and detailed analysis results were not obtained.

**Conclusion**

The results of this study indicated that compared with deferred PCI, immediate PCI may be associated with poor MBG 3 outcomes; however, no significant differences between the groups were noted for other clinical endpoints. Our results are stable and were not affected by the inclusion of NSTEACS or STEMI patients. The results of this study should be verified by further large-scale RCTs in accordance with patients’ characteristics.

**Supporting information**

S1 Fig. Funnel plot for major adverse cardiovascular events. (TIF)
S2 Fig. Funnel plot for myocardial infarction. (TIF)
S3 Fig. Funnel plot for all-cause mortality. (TIF)
S4 Fig. Funnel plot for TVR. (TIF)
S5 Fig. Funnel plot for major bleeding. (TIF)
S1 Checklist. PRISMA 2009 checklist. (DOC)

Author Contributions
Conceptualization: Weijun Li.
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References
1. Fanaroff AC, Rymer JA, Goldstein SA. JAMA Patient Page. Acute Coronary Syndrome. Jama. 2015; 314:1990. https://doi.org/10.1001/jama.2015.12743 PMID: 26547478
2. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. The New England journal of medicine. 2004; 350:1495–1504. https://doi.org/10.1056/NEJMoa040583 PMID: 15007110
3. Lansky AJ, Gotto K, Cristea E, Fahy M, Parise H, Feit F, et al. Clinical and angiographic predictors of short- and long-term ischemic events in acute coronary syndromes: results from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. Circulation Cardiovascular interventions. 2010; 3:308–316. https://doi.org/10.1161/CIRCINTERVENTIONS.109.887604 PMID: 20647564
4. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segm ent Elevation of the European Society of Cardiology (ESC). European heart journal. 2016; 37:267–315. https://doi.org/10.1093/eurheartj/ehv320 PMID: 26320110
5. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. The New England journal of medicine. 2001; 344:1879–1887. https://doi.org/10.1056/NEJM200106213442501 PMID: 11419424
6. Mehta SR, Cannon CP, Fox KA, Wallentin L, Boden WE, Skaczk R, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. Jama. 2005; 293:2908–2917. https://doi.org/10.1001/jama.293.23.2908 PMID: 15956654
7. Wallentin L, Lagerqvist B, Husted S, Kontry F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. Lancet (London, England). 2000; 356:9–16. https://doi.org/10.1016/s0140-6736(00)02427-2
8. O’Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. Jama. 2008; 300:71–80. https://doi.org/10.1001/jama.300.1.71 PMID: 18594042
9. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. JACC Cardiovascular interventions. 2013; 6:1267–1274. https://doi.org/10.1016/j.jcicin.2013.06.015 PMID: 23455117

10. Nakazawa G, Finn AV, Joner M, Ladich E, Kutsys R, Mont EK, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation. 2008; 118:1138–1145. https://doi.org/10.1161/CIRCULATIONAHA.107.762047 PMID: 18725485

11. Gonzalo N, Barlis P, Serruys PW, Garcia-Garcia HM, Onuma Y, Ligthart J, et al. Incomplete stent apposition and delayed tissue coverage are more frequent in drug-eluting stents implanted during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction than in drug-eluting stents implanted for stable/unstable angina: insights from optical coherence tomography. JACC Cardiovascular interventions. 2009; 2:445–452. https://doi.org/10.1016/j.jcicin.2009.01.012 PMID: 19463469

12. D’Ascenzo F, Biolo C, Raposeiras-Roubin S, Gaido F, Abu-Assi E, Kinnaird T, et al. Average daily ischemic versus bleeding risk in patients with ACS undergoing PCI: Insights from the BleemACS and RENAMI registries. American heart journal. 2020; 220:108–115. https://doi.org/10.1016/j.ahj.2019.10.001 PMID: 31809991

13. Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, et al. Evaluation of prolonged antithrombotic pretreatment (“cooling-off” strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. Jama. 2003; 290:1593–1599. https://doi.org/10.1001/jama.290.12.1593 PMID: 14506118

14. van’t Hof AW, de Vries ST, Dambrink JH, Miedema K, Suryapranata H, Hoornije JC, et al. A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unStable Angina (ELISA) pilot study. 2b/3a upstream therapy and acute coronary syndromes. European heart journal. 2003; 24:1401–1405. https://doi.org/10.1016/s0195-668x(03)00259-8 PMID: 12909068

15. Riezebos RK, Ronner E, Ter Bals E, Slagboom T, Smits PC, ten Berg JM, et al. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. Heart. 2009; 95:807–812. https://doi.org/10.1136/hrt.2008.154815 PMID: 19085085

16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009; 6:e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072

17. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled clinical trials. 1996; 17:1–12. https://doi.org/10.1016/0169-209x(95)00134-4 PMID: 8721797

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986; 7:177–188. https://doi.org/10.1016/0197-2456(86)90046-2 PMID: 3802833

19. Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. Medical decision making: an international journal of the Society for Medical Decision Making. 2005; 25:646–654. https://doi.org/10.1177/0272989x05282643 PMID: 16282215

20. Deeks J. Analysing Data and Undertaking Meta-Analyses: Higgins JPT. Green S, Cochrane handbook for systematic reviews of interventions: cochrane book series [Internet]. The Cochrane Collaboration, 2008: 243–96. 2008.

21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003; 327:557–560. https://doi.org/10.1136/bmj.327.7414.557 PMID: 12958120

22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed). 1997; 315:629–634. https://doi.org/10.1136/bmj.315.7109.629 PMID: 9310563

23. Beggb CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50:1088–1101. PMID: 7786990

24. Badings EA, The SH, Dambrink JH, van Wijngaarden T, Tjeerdumga M, Rasoul S, et al. Early or late intervention in high-risk non-ST-elevation acute coronary syndromes: results of the ELISA-3 trial. EuroIntervention; journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2013; 9:54–61. https://doi.org/10.4244/eijv91a19 PMID: 23685295

25. Milasinovic D, Milosevic A, Vasiljevic-Pokrajac Z, Marinkovic J, Vukcevic V, Stefanovic B, et al. Three-Year Impact of Immediate Invasive Strategy in Patients With Non-ST-Segment Elevation Myocardial Infarction (from the RIDDLE-NSTEMI Study). The American journal of cardiology. 2018; 122:54–60. https://doi.org/10.1016/j.amjcard.2018.03.006 PMID: 29705375

26. Di Pasquale P, Cannizzaro S, Parrinello G, Giambanco F, Vitale G, Fusullo S, et al. Is delayed facilitated percutaneous coronary intervention better than immediate in reperfused myocardial infarction?
Immediate versus deferred percutaneous coronary intervention for patients with acute coronary syndrome

Six months follow up findings. Journal of thrombosis and thrombolysis. 2006; 21:147–157. https://doi.org/10.1007/s11239-006-5733-z PMID: 16622610

Carrick D, Oldroyd KG, McEntegart M, Haig C, Petrie MC, Eteiba H, et al. A randomized trial of deferred stenting versus immediate stenting to prevent no- or slow-reflow in acute ST-segment elevation myocardial infarction (DEFER-STEMI). Journal of the American College of Cardiology. 2014; 63:2088–2098. https://doi.org/10.1016/j.jacc.2014.02.530 PMID: 24583294

Kim JS, Lee HJ, Woong Yu C, Kim YM, Hong SJ, Park JH, et al. INNOVATION Study (Impact of Immediate Stent Implantation Versus Deferred Stent Implantation on Infarct Size and Microvascular Perfusion in Patients With ST-Segment-Elevation Myocardial Infarction). Circulation Cardiovascular interventions. 2016; 9: https://doi.org/10.1161/circinterventions.116.004101 PMID: 27965296

Kelbaek H, Hofsten DE, Kober L, Helqvist S, Klovgaard L, Holmvang L, et al. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial. Lancet (London, England). 2016; 387:2199–2206. https://doi.org/10.1016/s0140-6736(16)30072-1

Belle L, Motreff P, Mangin L, Range G, Marcaggi X, Marie A, et al. Comparison of Immediate With Delayed Stenting Using the Minimalist Immediate Mechanical Intervention Approach in Acute ST-Segment-Elevation Myocardial Infarction: The MIMI Study. Circulation Cardiovascular interventions. 2016; 9:e003388. https://doi.org/10.1161/CIRCINTERVENTIONS.115.003388 PMID: 26957418

Janssens GN, van der Hoeven NW, Lemkes JS, Everaars H, van de Ven PM, Marques KMJ, et al. 1-Year Outcomes of Delayed Versus Immediate Intervention in Patients With Transient ST-Segment Elevation Myocardial Infarction. JACC Cardiovascular interventions. 2019. https://doi.org/10.1016/j.jcaicardiointerv.2019.07.018 PMID: 31488353

Desch S, Eitel I, Rahimi K, de Waha S, Schuler G, Thiele H. Timing of invasive treatment after fibrinolysis in ST elevation myocardial infarction—a meta-analysis of immediate or early routine versus deferred or ischemia-guided randomised controlled trials. Heart. 2010; 96:1695–1702. https://doi.org/10.1136/htert.2010.193862 PMID: 20736192

Freixa X, Belle L, Joseph L, Tanguay JF, Souteyrand G, PL LA, et al. Immediate vs. delayed stenting in acute myocardial infarction: a systematic review and meta-analysis. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2013; 8:1207–1216. https://doi.org/10.4244/eijv8i10a18 PMID: 23425545

Liu F, Guo Q, Xie G, Zhang H, Wu Y, Yang L. Percutaneous Coronary Intervention after Fibrinolysis for ST-segment elevation myocardial infarction: A Collaborative Meta-analysis of Randomized trials. The Canadian journal of cardiology. 2018; 34:1573–1580. https://doi.org/10.1016/j.cjca.2018.07.480 PMID: 30523834

Lee JM, Rhee TM, Chang H, Ahn C, Park TK, Yang JH, et al. Deferred versus conventional stent implantation in patients with acute ST-segment elevation myocardial infarction: An updated meta-analysis of 10 studies. International journal of cardiology. 2017; 230:509–517. https://doi.org/10.1016/j.ijcard.2016.12.071 PMID: 28057364

Qiao J, Pan L, Zhang B, Wang J, Zhao Y, Yang R, et al. Deferred Versus Immediate Stenting in Patients With ST-Segment Elevation Myocardial Infarction: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2017; 6: https://doi.org/10.1161/jaha.116.004838 PMID: 28275065

Mahmoud AN, Saad M, Elgendi AY, Mentias A, Elgendi IY. Deferred or immediate stent implantation for primary percutaneous coronary intervention: A meta-analysis of randomized trials. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions. 2018; 91:260–264. https://doi.org/10.1002/ccd.27240 PMID: 28799712

Cassese S, Belle L, Ndrepepa G, Bosson JL, Fusaro M, Lonborg J, et al. Deferred vs Immediate Stenting in Primary Percutaneous Coronary Intervention: A Collaborative Meta-analysis of Randomized Trials With Cardiac Magnetic Resonance Imaging Data. The Canadian journal of cardiology. 2018; 34:1573–1580. https://doi.org/10.1016/j.cjca.2018.07.480 PMID: 30527145

Harbaoui B, Motreff P, Lantelme P. Delayed versus immediate stenting during STEMI: Towards a "tailored" strategy for primary PCI? Arch Cardiovasc Dis. 2016; 109:373–375. https://doi.org/10.1016/j.acvd.2016.03.001 PMID: 27173055

Meneveau N, Seronde MF, Descotes-Genon V, Dutheil J, Chopard R, Ecarnot F, et al. Immediate versus delayed angioplasty in infarct-related arteries with TIMI III flow and ST segment recovery: a matched comparison in acute myocardial infarction patients. Clinical research in cardiology: official journal of the German Cardiac Society. 2009; 98:257–264. https://doi.org/10.1007/s00392-009-0756-z PMID: 19205776

Meliga E, Fiorina C, Valgimigli M, Belli R, Gagnor A, Sheiban I, et al. Early angio-guided complete revascularization versus culprit vessel PCI followed by ischemia-guided staged PCI in STEMI patients with multivessel disease. Journal of interventional cardiology. 2011; 24:535–541. https://doi.org/10.1111/j.1540-8183.2011.00666.x PMID: 22010970