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Original Article

Intracoronary versus intravenous administration of abciximab during percutaneous coronary intervention for acute coronary syndrome: grading the evidence through a meta-analysis of randomized controlled trials

Chuan-Nan Zhai[1,2,3], Ying Zhang[2], Yu-Jie Liu[2], Xian-Feng Liu[1], Hao Zhang[1], Zhi-Jing Ren[1], Hong-Liang Cong[2]

[1]Department of Cardiology, Tianjin Gongan Hospital, Tianjin, China; [2]Department of Cardiology, Tianjin Chest Hospital, Tianjin, China

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Abstract: The efficacy and safety of intracoronary (IC) abciximab administration were conflicting in patients undergoing percutaneous coronary intervention (PCI) compared with intravenous (IV) therapy. The purpose of the present study was to evaluate the effect between IC and IV administration of abciximab based on a meta-analysis of previous all RCTs and grading of evidence. We assembled the relevant published RCTs studies that compared the efficacy of IC with IV administration of abciximab in ACS patients undergoing PCI. Furthermore, we appraised the evidence from a meta-analysis that evaluate the differences in clinical effect between IC and IV administration of abciximab in patients undergoing PCI and conducted to explicit grading of evidence. In short-term outcome, the finding of our meta-analysis was that IC administration of abciximab has not a significant improvement in TIMI grade 3 flow and TMPG compare with IV administration. IC administration was also not significantly reduced the risk of reinfarction, the rate of TVR, mortality and the incidence of bleeding more than in the IV therapy. There was no significant difference in long-term outcomes when comparing efficacy of IC with IV administration of abciximab. The GRADE evidence quality was high in short-term outcomes and very low in long-term. Compared to IV administration, IC administration of abciximab does not have favorable effects on short- and long-term outcomes based on the current evidence. High GRADE evidence quality will strengthen the confidence in any recommendations in short-term follow-up. However, High-quality RCTs with long-term follow-up are still required.

Keywords: Abciximab, acute coronary syndrome, intracoronary, intravenous, percutaneous coronary intervention

Introduction

Previous clinical studies confirmed that percutaneous coronary intervention (PCI) could quickly and effectively open infarction related artery (IRA), retrieve myocardial early reperfusion and decrease mortality and major adverse cardiac events (MACE) [1]. Therefore, PCI is established as the most effective treatment of acute coronary syndrome (ACS) [2, 3]. The application of abciximab in the perioperative period has been incorporated into the ACS preferred treatment strategy [4], because several trials reported that the final common pathway of platelet aggregation was blocked by the glycoprotein IIb/IIIa receptor inhibitor and it was demonstrated reduce the occurrence of no-reflow after PCI [5].

Several studies indicated the efficacy and safety of intravenous (IV) administration of abciximab in patients undergoing PCI. In recent years, more cardiology experts concentrated on the intracoronary (IC) administration that is considered to have better treatment results and the reduction of postoperative adverse events [6], which can be achieved high local drug concentrations of antibody inside coronary arteries [7]. Some relevant meta-analyses compared the different effects between IC and IV administration of abciximab. A previous meta-analysis [8] included two non-randomized controlled trials that added the heterogeneity of the studies and influenced comparative conclusions. Another meta-analysis [9] attracted not only abciximab administration, but also included tirofiban and eptifibatide, with the result that

the evaluation of efficacy and safety of abciximab has limitation. Furthermore, although some studies conducted incorporative analyses aim at previous several single trials, there is no evidence rank evaluation and recommendation based on the results.

Therefore, the aim of the present study is to appraise the evidence from an meta-analysis that evaluate the differences in clinical effect between IC and IV administration of abciximab in patients undergoing PCI and to develop Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) based recommendations for comparing IC and IV administration of abciximab in patients undergoing PCI.

Materials and methods

Search strategy

We systematically collected the relevant published studies, OVID, ScienceDirect, EMBASE, PRISMA compliant searches of PubMed, the Cochrane library database and Google scholar were conducted for all studies published through January 2014 that investigate the effect of IC and IV administration of abciximab in patients undergoing PCI. The databases of our study searched from American Heart Association (http://www.aha.org), American College of Cardiology (http://www.acc.org), European Percutaneous Coronary Revascularization (http://www.europcr.com). The following search terms were used to maximize the search sensitivity and specificity: abciximab, the glycoprotein IIb/IIIa receptor inhibitor, intracoronary, intravenous, percutaneous coronary intervention, PCI, acute coronary syndrome, ACS, myocardial infarction, randomized controlled trials. We also searched ongoing or completed randomized controlled trials in the Clinical Trials.

Inclusive and exclusive criteria

Studies were included if they estimated the effect of intracoronary and intravenous abciximab administration in patients undergoing PCI. Studies were eligible for inclusion in the present meta-analysis if the following criteria were met: (1) type of the studies were RCTs; (2) the trial evaluated the effect of intracoronary and intravenous abciximab administration in patients undergoing PCI; (3) the studies were included enough follow-up time after PCI; (4) the studies reported the results of mortality, reinfarction, TIMI 3 flow, TVR, any bleeding and MACE. Single case reports, review articles, and non-comparable studies were excluded.

Study selection

Two reviewers independently screened the titles and/or abstracts of the individual studies for the eligibility criteria. Moreover, the full text of the studies which potentially met the inclusion criteria was reviewed to determine the final included studies. A controversy was resolved through discussion if we had no agreements on the process of study selection.

Date extraction

The data from all included studies was extracted independently by two authors (H.Z and CN.Z) using a preliminary data extraction forum. The data included the title, years, authors, study design, ACS classification, sample size, drug protocol, follow-up time, and outcomes parameters. The corresponding authors of the included studies were contacted to obtain any required information that was missing. The extracted data were confirmed completely by HL.C.

Outcomes

The following items were the outcomes of the present study: the studies reported the results of mortality, reinfarction, TIMI 3 flow, TVR, any bleeding and MACE.

Assessment of methodological quality

Each study was assessed for methodological quality by Cochrane Handbook for Systematic Reviews of Interventions 5.3. The above assessment was independently conducted by two authors (H.Z. and CN.Z.). Any dispute was settled by discussion. When no consensus could be achieved, we can resort to the adjudicator (HL.C.) aiming to uniformity.

Data analysis

All of the meta-analyses were performed with the Review Manager software (RevMan Version 5.1; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) and Stata software (Stata Version 12.0; StataCorp

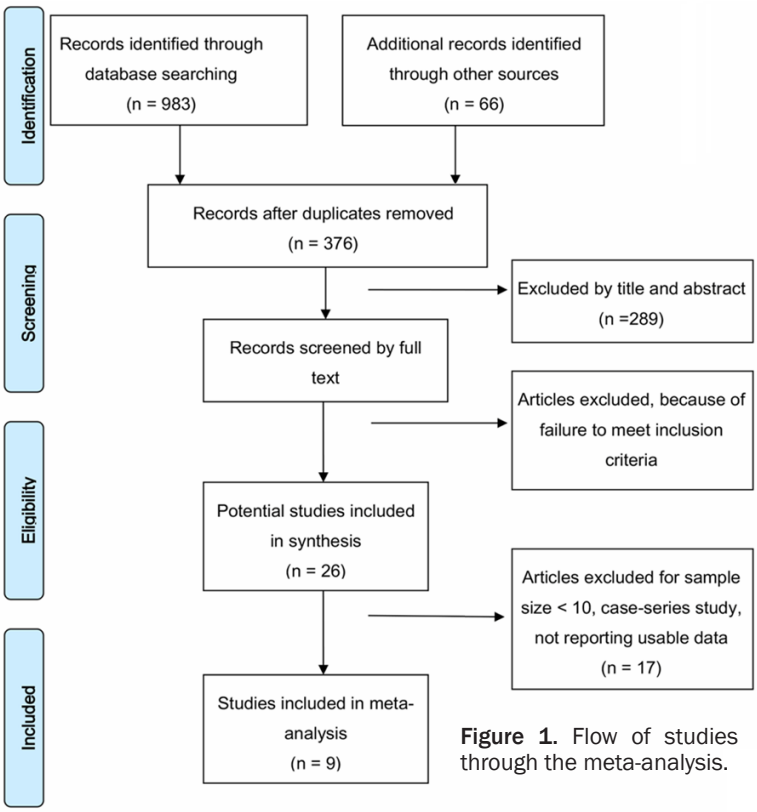

Figure 1. Flow of studies through the meta-analysis.

LP, TX, USA). The odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the dichotomous outcomes, such as the incidence of reinfarction and target vessel revascularization (TVR). To combine the separate statistics, the inverse variance and Mantel-Haenszel techniques were used. The heterogeneity was investigated by the use of the Q statistics, and P values < 0.05 was regarded as statistically significance. A fixed-effects model was used when the effects were assumed to be homogenous ($P > 0.05$). $P < 0.05$ was regarded as statistical heterogeneity, and a random effects model was used in above circumstances. Data were pooled and stratified into short (1 month to 3 months) and mid-/long-term (> 6 months) follow-up durations.

Publication bias was evaluated statistically using Begg funnel plots and Egger's bias test using STATA 12.0 software (Statacorp, college station, Tex). The above methods measure the degree of funnel plot asymmetry statistically [10, 11]. The Begg adjusted rank correlation test was used to evaluate the relationship between the test accuracy estimates and their variances. The deviation of Spearman's rho values from zero provides an estimate of the funnel plot asymmetry. Positive values indicate a trend towards higher levels of test accuracy in studies with smaller sample sizes. Egger's bias test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision values.

Evidence synthesis

The evidence grade was determined by the use of the guidelines of the GRADE working group [12]. The GRADE system uses a sequential assessment of the evidence quality that is followed by an assessment of the risk-benefit balance and a subsequent judgment on the strength of the recommendations. The evidence grades are divided into the following categories: (1) high grade, which indicates that further research is unlikely to change confidence in the effect estimate; (2) moderate grade, which indicates that further research is likely to significantly alter confidence in the effect estimate and may change the estimate; (3) low grade, which indicates that further research is likely to significantly alter confidence in the effect estimate and to change the estimate; and (4) very low grade, which indicates that any effect estimate is uncertain. Uniformity of the estimated effects across studies and the extent to which the patients, interventions, and outcome measures are similar to those of interest may lower or raise the evidence grade [13-17]. The reasons for increasing the quality of evidence include presentation of a dose-response gradient, a large effect and plausible confounders that would decrease an apparent treatment effect [18]. As recommended by the GRADE working group, the lowest evidence quality for any of the outcomes was used to rate the overall evidence quality. The evidence quality was graded using the GRADEpro Version 3.6 software. The

Table 1. Characteristics of the clinical studies

Study	Year	No. of pateints		ACS classification	Mean age, y		Sex (male)	Time of randomization	Drug protocol	
		IC	IV		IC	IV			IC	IV
Bellandi F [19]	2004	22	23	STEMI	62.4	61.4	78%	After CAG	IC bolus below occlusion, then 12-hour IV infusion	IV bolus, then 12-hour IV infusion
Thiele H [21]	2008	77	77	STEMI	64	66	80%	After CAG	IC bolus before balloon dilation, then 12-hour IV infusion	IV bolus, then 12-hour IV infusion
Dominguez-Rodriguez A [22]	2009	25	25	STEMI	66	70	76%	After CAG	IC bolus after thrombectomy, then 12-hour IV infusion	IV bolus after thrombus aspiration, then 12-hour IV infusion
Gu YL [24]	2010	271	263	STEMI	64	64	74%	After CAG	IC bolus proximal to lesion, then no 12-hour IV infusion	IV bolus during PCI, then no 12-hour IV infusion
Iversen AZ [25]	2011	185	170	STEMI	62	62	81%	Before CAG	IC bolus, then 12-hour IV infusion	IV bolus, then 12-hour IV infusion
Thiele H [27]	2012	1032	1033	STEMI	63	62	75%	Before CAG	IC bolus, then 12-hour IV infusion	IV bolus, then 12-hour IV infusion
Galache Osuna JG [20]	2006	72	65	ACS	63	59.8	82%	After CAG	IC bolus, then 12-hour IV infusion	IV bolus, then 12-hour IV infusion
Bertrand OF [23]	2010	53	52	STEMI	59	59	80%	After CAG	IC bolus, then 12-hour IV infusion	IV bolus, then 12-hour IV infusion
Eitel I [26]	2011	77	77	STEMI	64	66	61%	After CAG	IC bolus, then 12-hour IV infusion	IV bolus, then 12-hour IV infusion

STEMI: ST-segment elevation myocardial infarction; IC: intracoronary; IV: intravenous; ACS: acute coronary syndrome; CAG: coronary angiography.

Table 2. Study outcomes in randomized controlled trials comparing IC to IV administration of abciximab

Study	No. of patients		TIMI 3 Flow After PCI		TMPG 2-3 flow		TVR		Reinfarction		Death		Any bleeding	
	IC	IV	IC	IV	IC	IV	IC	IV	IC	IV	IC	IV	IC	IV
Bellandi F 2004 [19]	22	23	22	20	21	15	-	-	-	-	1	1	-	-
Thiele H 2008 [21]	77	77	65	66	71	62	0	2	0	2	2	3	4	5
Dominguez-Rodriguez A 2009 [22]	25	25	22	17	-	-	-	-	0	0	0	0	2	3
Gu YL 2010 [24]	271	263	241	226	202	174	9	10	3	4	5	7	31	27
Iversen AZ 2011 [25]	185	170	149	124	-	-	7	16	5	8	2	9	21	28
Thiele H 2012 [27]	1032	1033	877	870	-	-	-	-	17	17	42	34	131	129
Galache Osuna JG 2006 [20]	72	65	72	64	72	64	-	-	4	2	2	3	-	-
Bertrand OF 2010 [23]	53	52	50	47	44	38	-	-	0	0	-	-	-	-
Eitel I 2011 [26]	77	77	65	66	-	-	2	4	0	2	4	4	4	5

TIMI: Thrombolysis in myocardial infarction; PCI: percutaneous coronary intervention; IC: intracoronary; IV: intravenous; TMPG: TIMI myocardial perfusion grade; TVR: target vessel revascularization.

strengths of the recommendations were according to the quality of the evidence.

Results

Search results

We initially identified 376 potential articles from electronic search, and after screened titles and abstracts, among which most were excluded for irrelevant to our analysis. Seventeen articles then were removed because small number cases, unusable data, especially observational and retrospective studies. Through the above retrieve strategy, nine RCTs [19-27] from 3522 patients including the comparative results between IC and IV abciximab administration eventually satisfied our eligibility criteria (**Figure 1**).

Characteristics of included studies

Table 1 presents characteristics of the included studies. A total of nine studies were involved in presence meta-analysis comparing IC to IV administration (including 1814 IC administra-

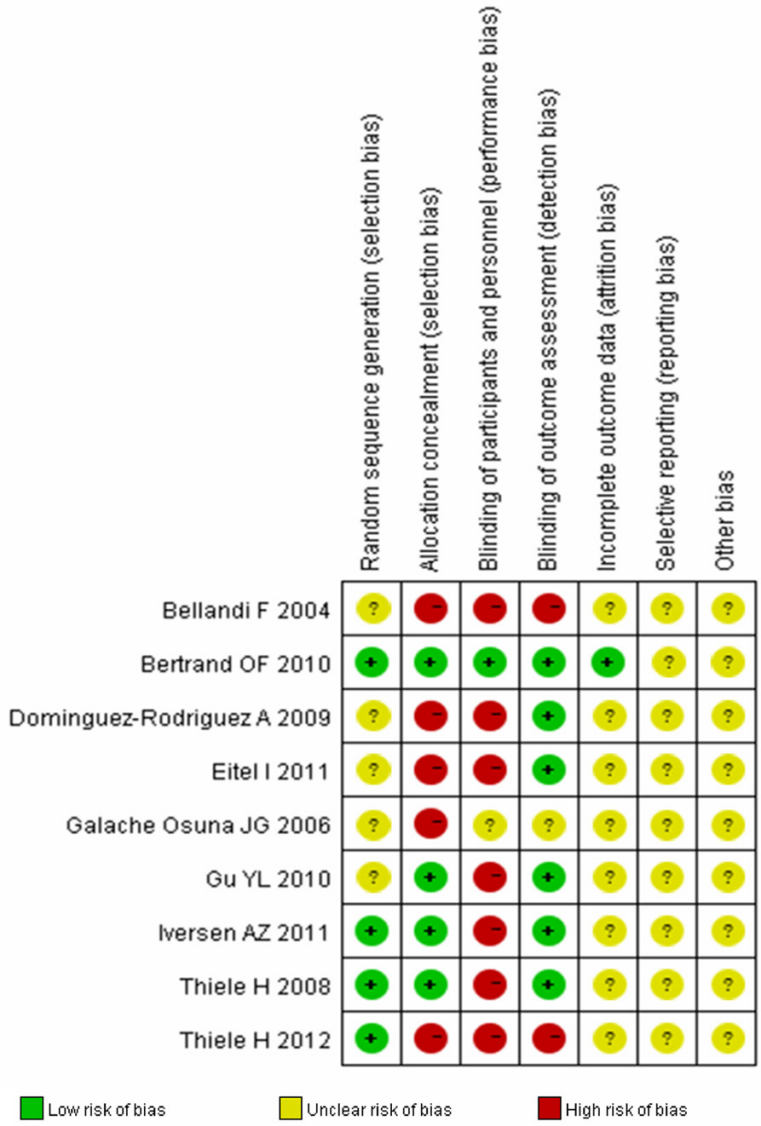

Figure 2. Methodological quality of included studies. This risk of bias tool incorporates assessment of randomization (sequence generation and allocation concealment), blinding (participants, personnel and outcome assessors), completeness of outcome data, selection of outcomes reported and other sources of bias. The items were scored with 'yes', 'no', 'unsure'.

tion patients and 1708 IV administration patients). The glycoprotein IIb/IIIa receptor inhibitor Abciximab was used in all included RCTs. Randomization was performed before diagnostic coronary angiography in 3 studies, while randomization was performed after diagnostic coronary angiography in others. PCI was initiated within 12 hours from the onset of chest pain symptom in all studies. The number of subjects in each RCT ranged from 22 to 1033, and length of follow-up ranged from 1 to ≥ 6 months. Participants were predominantly men (ranging from 61% to 82% men), with mean age ranging from 59 to 64 years. Six studies [19, 21, 22, 24, 25, 27] reported the short-term (1-3 months) outcomes comparing IC to IV administration after PCI, while other three studies [20, 23, 26] reported the mid-/long-term (≥ 6 months) comparative outcomes between IC and IV therapy.

The outcomes of the individual studies were present in **Table 2**, including TIMI 3 flow, TMPG 2-3 flow after PCI, TVR, reinfarction, mortality and incidence of bleeding (**Table 2**).

Quality assessment

Among the 9 included studies, 4 RCTs reported adequate generation of allocation sequence, and 4 trials reported allocation concealment. Whilst surgeon blinding would have been inappropriate in this study design, 3 studies did not blind their assessors to patients group. One RCT performed the single-blinding to participants. Five trials performed the single-blinding to assessors. The methodological quality of included studies was presented in **Figure 2**. Judgment about each risk of bias item presented as percentages across all included studies in **Figure 3**.

Short-term pooled outcomes after PCI with IC versus IV abciximab administration

In 6 studies providing TIMI grade 3 flow between IC and IV administration, the pooled RR was 1.01 (95% CI: 0.96-1.07). There was no significant difference between the both groups. The TMPG 2-3 flow after PCI was calculated for only 3 studies. The available data demonstrated that TMPG 2-3 flow after PCI was not significantly reduced in IC compared with IV administration (RR=1.08 95% CI: 0.95-1.23). Further-

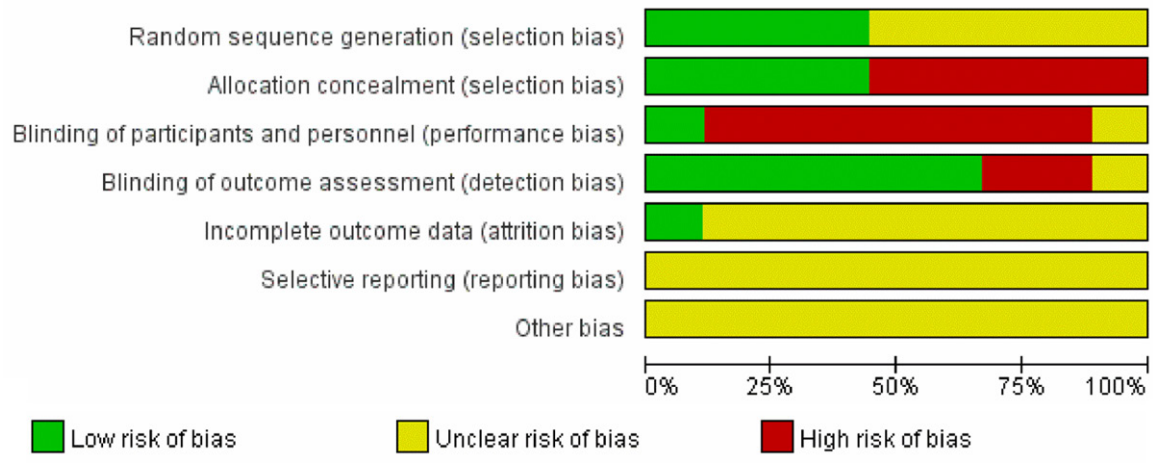

Figure 3. Risk of bias. Each risk of bias item presented as percentages across all included studies, which indicated the proportion of different level risk of bias for each item.

Table 3. Meta-analysis for short- and long-term follow-up comparing IC to IV administration of abciximab

Outcomes	No of studies	Heterogeneity		RR	95% CI
		I-squared	*P* value		
Short-term outcomes					
TIMI 3 Flow After PCI	6 [19, 21, 22, 24, 25, 27]	0.0%	0.98	1.01	0.96-1.07
TMPG	3 [19, 21, 24]	0.0%	0.86	1.08	0.95-1.23
TVR	3 [21, 24, 25]	51.9%	0.13	1.17	0.57-2.40
Reinfarction	5 [21, 22, 24, 25, 27]	0.0%	0.67	0.80	0.48-1.34
Death	6 [19, 21, 22, 24, 25, 27]	26.3%	0.25	0.95	0.66-1.39
Bleeding	5 [21, 22, 24, 25, 27]	0.0%	0.60	0.97	0.81-1.18
Long-term outcomes					
TIMI 3 Flow After PCI	3 [20, 23, 26]	0.0%	0.99	1.01	0.87-1.17
TMPG	2 [20, 23]	0.0%	0.76	1.03	0.85-1.25
TVR	1 [26]	-	-	0.51	0.10-2.72
Reinfarction	2 [20, 26]	34.7%	0.22	0.93	0.25-3.43
Death	2 [20, 26]	0.0%	0.67	0.83	0.29-2.41
Bleeding	1 [26]	-	-	0.81	0.23-2.91

TIMI: Thrombolysis in myocardial infarction; PCI: percutaneous coronary intervention; IC: intracoronary; IV: intravenous; TMPG: TIMI myocardial perfusion grade; TVR: target vessel revascularization; RR: risk ratio; CI: confidence interval.

more, there was no statistically significant difference between the IC and IV administration in TVR (RR=1.17 95% CI: 0.57-2.40), reinfarction (RR=0.80 95% CI: 0.48-1.34), mortality (RR= 0.95 95% CI: 0.66-1.39) and incidence of bleeding (RR=0.97 95% CI: 0.81-1.18) (**Table 3**).

Long-term pooled outcomes after PCI with IC versus IV abciximab administration

As shown in **Table 3**, there was no significant difference between the both groups in mid-/long-term TIMI grade 3 flow, TMPG 2-3 flow after PCI, TVR, reinfarction, mortality and incidence of any bleeding.

Quality of the evidence and recommendation strengths

The short-term and mid-/long-term pooled outcomes in this meta-analysis were evaluated using the GRADE system. The evidence quality for short-term outcomes was high (**Table 4**). However, the evidence quality for mid-/long-term outcomes was very low (**Table 5**). Therefore, this finding may strengthen the confidence in any recommendations in short-term adminis-

Table 4. The GRADE evidence quality for short-term outcomes

Outcomes	Illustrative comparative risks (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk		
	Control	Short		
TIMI3 flow	Study population		3203 (6 studies)	⊕⊕⊕⊕ high
	832 per 1000	856 per 1000 (832 to 881)		
	Moderate			
	850 per 1000	875 per 1000 (850 to 901)		
TMPG	Study population		733 (3 studies)	⊕⊕⊕⊕ high
	691 per 1000	795 per 1000 (733 to 864)		
	Moderate			
	662 per 1000	761 per 1000 (702 to 827)		
TVR	Study population		1043 (3 studies)	⊕⊕⊕⊕ high
	25 per 1000	30 per 1000 (15 to 61)		
	Moderate			
	26 per 1000	30 per 1000 (15 to 62)		
Reinfarction	Study population		3158 (5 studies)	⊕⊕⊕⊕ high
	20 per 1000	16 per 1000 (9 to 26)		
	Moderate			
	17 per 1000	13 per 1000 (8 to 23)		
Death	Study population		3203 (6 studies)	⊕⊕⊕⊕ high
	34 per 1000	32 per 1000 (22 to 47)		
	Moderate			
	36 per 1000	34 per 1000 (24 to 50)		
Bleeding	Study population		3158 (5 studies)	⊕⊕⊕⊕ high
	122 per 1000	119 per 1000 (98 to 143)		
	Moderate			
	125 per 1000	121 per 1000 (100 to 146)		

GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

tration, while lower the confidence in any recommendations in mid-/long-term administration.

Publication bias

The publication bias test was performed for short-term TIMI 3 flow. Significant publication bias was not shown for short-term studies by the Begg rank correlation method (P=0.26) and the Egger weighted regression method (P=0.10).

Discussion

Our meta-analysis was designed to compare the effect of abciximab IC therapy with IV administration in patients undergoing PCI. The outcomes of our study were divided into two subgroups, including the short (1-3 months) and mid-/long-term (≥ 6 months). In short-term, the finding of our meta-analysis was that IC administration of GPIs (abciximab) has not a significant improvement in TIMI grade 3 flow and TMPG compare with IV administration. IC administration was also not significantly reduced the risk of reinfarction, the rate of TVR, mortality and the incidence of bleeding more than in the IV therapy. The evidence quality for short-term outcomes was high, which will strengthen our confidence in recommendation. Similarly, the same meta-analysis results were found in the long-term subgroup. However, the very low evidence quality of long-term results will lower our confidence in any recommendations.

Recently, a meta-analysis [8] demonstrated that IC administration of abciximab can reduce the risk of MACE, reinfarction and heart failure when compared with IV therapy. However, two observational studies [6, 28] were included in the above mentioned meta-analysis, which

Table 5. The GRADE evidence quality for long-term outcomes

Outcomes	Illustrative comparative risks (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk		
	Control	Long		
TIMI 3 flow		Study population	396 (3 studies)	⊕⊖⊖⊖ very low
	912 per 1000	921 per 1000 (867 to 976)		
		Moderate		
	904 per 1000	913 per 1000 (859 to 967)		
TMPG		Study population	242 (2 studies)	⊕⊖⊖⊖ very low
	872 per 1000	924 per 1000 (750 to 1000)		
		Moderate		
	858 per 1000	909 per 1000 (738 to 1000)		
TVR		Study population	154 (1 study)	⊕⊖⊖⊖ very low
	52 per 1000	26 per 1000 (5 to 138)		
		Moderate		
	52 per 1000	26 per 1000 (5 to 138)		
Reinfarction		Study population	291 (2 studies)	⊕⊖⊖⊖ very low
	28 per 1000	26 per 1000 (7 to 97)		
		Moderate		
	28 per 1000	26 per 1000 (7 to 96)		
Death		Study population	291 (2 studies)	⊕⊖⊖⊖ very low
	49 per 1000	40 per 1000 (14 to 118)		
		Moderate		
	49 per 1000	40 per 1000 (14 to 117)		
Bleeding		Study population	154 (1 study)	⊕⊖⊖⊖ very low
	65 per 1000	52 per 1000 (14 to 186)		
		Moderate		
	65 per 1000	52 per 1000 (14 to 187)		

GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

introduced methodological bias to the pooled results. Therefore, the positive results were obtained in this study. Two meta-analyses [9, 29] were conducted to compare clinical effects between IC and IV administration of GPIs in patients undergoing PCI. However, these studies did not perform subgroup analysis according to the type of GPIs (abciximab, epitifibatide and tirofiban). Thus, the above clinical heterogeneity influenced the stability of the pooled results. Subgroup analysis is needed in the present analysis. Owing the limited number of relevant studies reporting the clinical effect of epitifibatide and tirofiban, we only conducted meta-analysis of abciximab in the present study. Furthermore, the previous meta-analyses were not included the explicit GRADE evidence classification. We, therefore, evaluate the evidence from a meta-analysis that appraise the differences in clinical effect between recommendations.

The application of the glycoprotein IIb/IIIa receptor inhibitors is considered to be the main strategy of ACS patients during the preoperative period and two kinds of administration routs including intravenous and intracoronary were adopted in treatment process. In recent years, several studies [19, 30] were identified that IC bolus administration was availed to superior myocardial salvage and was more safe, effective and good tolerance. However, the previous conclusions were not consistent. Abciximab [31, 32] is one type of GPIs, which is Fab fragment of human-mouse chimeric monoclonal antibody that can reversibility blockade platelet receptor. It is demonstrated that Activation and aggregation of platelet play vital role in the pathological process of ACS. Different from the small molecule GPIs, the binding site of abciximab is located in β3 subunit of the glycoprotein IIb/IIIa receptor [33]. Therefore, abciximab can also act on other inte-

grin receptors containing β3 subunits, such as glassy protein of vascular smooth muscle cells and Mac-1 receptors of leucocytes. These components are considered to play a vital role in preventing microvascular damage which mediated by leucocytes. The clinical efficacy, safety and the choice of administration routes of abciximab are more focused on clinical practice in recent years. Consequently, it is necessary for us to conduct a meta-analysis again about GPIs abciximab.

Theoretically, IC administration of GPIs could increase the concentration at the culprit lesion and in the distal bed of the culprit vessel compared with IV therapy. However, the present meta-analysis revealed that the effect of abciximab administration via IC or IV was similar in short- and long-term outcomes. The results of the current study were inconsistent with several previous meta-analyses [8, 9]. The reasons for the variance among these individual meta-analyses included the following items as sample size of trials, types of GPIs, trials design, ACS classification and the difference in ischemia time. Retrospective trials were included in previous meta-analyses, which will introduce higher risk of selective bias. Furthermore, other studies did not conduct subgroup analysis based on types of GPIs. Therefore, the present study only included the restrict RCTs which were performed with abciximab administration. Although there was no positive outcome found in the present study, the conclusion was more stable because of the religious inclusion criteria and quality supervision in procedure of study.

Meta-analysis is used as a method in the research paper about interventional effects. It is in high accuracy and reliability than that in regression analysis or original papers. Meta-analysis can promote statistical power and amplify sample size via combination of original studies, which could provide more stable evidence. However, the methodological quality assessment identified several shortages in methodological quality assessment. (1) Only four included studies used sealed envelopes for allocation concealment. Four reported the specific generation of randomization sequence. Five of the included studies reported blinding of the assessors, but one of dual-blinding, allowing for assessor and expectation bias and the potential for type II statistical errors regarding these outcomes. The efficacy of the statistics could be improved in the future by including high quality RCTs. The studies with a high risk of bias included in this meta-analysis would overestimate the treatment effects. (2) Clinical heterogeneity may be caused by the preexisting conditions of the patients, different dosage, ACS classification, and medical commodities. The above confounding factors might have an impact on the present outcomes. (3) Meta-analyses are subject to bias and provide inappropriate estimates for the effect of treatment when compared to successive large RCTs [34].

Some degree of clinical heterogeneity was induced by the different dosage, ACS classification, different PCI technologies used, transfemoral/transradial intervention, medical co-morbidities, nutritional status of patients, duration of ischemia, time of randomization, admission to the hospital from a healthcare facility, conditions of ischemia-reperfusion injury, pre-PCI medical status, physicians' experience, deliver drug time and utility of aspiration thombectomy. Heterogeneity may have been caused by study design. Because of limited information got from original studies, heterogeneity cannot be completely resolved. Accordingly, although the results of the meta-analysis should be considered appropriate, methodological quality defects and clinical heterogeneity should be considered when interpreting the findings.

The present study showed that the evidence quality of outcome in the short-term subgroup was high and the long-term outcome was very low. Therefore, we considered that evidence quality of the short-term outcomes will strength our confidence in recommendation for short-term efficacy and safety after IC or IV administration of abciximab. However, very low evidence quality of long-term outcomes may lower the confidence in any recommendations. It suggests that further RCTs with longer follow-up should be continually performed about comparison of IC and IV administration of abciximab in patients with ACS.

The several potential limitations of this meta-analysis include the following: (1) The number of previous studies which appraised the effect of abciximab between IC and IV therapy were insufficient, sample size was few, especially the studies with longer follow-up. (2) Some sources of heterogeneity could not be com-

pletely resolved, for instance, different dosage or ACS classification might lead to several bias in the outcomes of previous trials. (3) Particularly, individual studies existed potential conflict if these studies were funded by relative pharmaceutical business. (4) In spite of evaluation the evidence quality and recommendation strengths by GRADE system, the GRADE classification method inevitably contained the subjective factor of researchers. Therefore, in the process of treatment, we also required actual judgments based on the clinical practice and features of individual patients.

Conclusions

From our meta-analysis and grading of the evidence, the present study offers available conclusions and demonstrates that IC bolus administration of abciximab could not significantly improve TIMI grade 3 flow and TMPG comparing with IV administration. Furthermore, IC administration was not associated in reduction of the risk of reinfarction, the rate of TVR, mortality and the incidence of bleeding more than in the IV therapy. The short-term GRADE evidence quality was high, which will improve our confidence in recommendations strengths. However, the very low evidence quality of long-term results will lower our confidence in any recommendations. It showed that further high-quality studies are still constantly required to confirm the long-term results because of the several primary limitations of current studies.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hong-Liang Cong, Department of Cardiology, Tianjin Chest Hospital, 291 Taierzhuang South Road, Jinnan District, Tianjin 300350, China. E-mail: hl_cong@126.com

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