Systematic Review and Meta-Analysis

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P2Y12 inhibitor pretreatment in patients with nonST-segment elevation acute coronary syndrome

A meta-analysis

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Abstract

Background: The 2020 European Society of Cardiology guidelines do not recommend pretreatment for nonST-segment elevation myocardial infarction (NSTEMI) patients with unclear coronary anatomy, which is inconsistent with our routine preoperative approach to loading P2Y12 receptor inhibitors (e.g., preoperative loading of 300 mg of clopidogrel).

Objectives: The purpose of our study was to compare the safety and effectiveness of P2Y12 inhibitors administered before coronary angiography or at least before percutaneous coronary intervention (PCI) with during or after PCI.

Methods: Cochrane, PubMed, and Embase databases were searched. The primary effect endpoint and safety endpoint were any-cause death and major bleeding, respectively. Major adverse cardiovascular events, myocardial infarction and revascularization were also analyzed.

Results: Our search identified 9 trials. P2Y12 inhibitor pretreatment was associated with lower death from any cause (OR 0.62, 95% CI 0.53–0.72, $P < 0.00001$) without increasing the risk of bleeding (OR 1.02, 95% CI 0.80–1.30, $P = 0.89$). However, prasugrel or ticagrelor pretreatment was not associated with a lower risk of mortality (OR 0.70, 95% CI 0.31–1.59, $P = 0.40$) and increased the risk of bleeding (OR 1.67, 95% CI 1.10–2.54, $P = 0.02$).

Conclusions: In summary, clopidogrel pretreatment was associated with significantly lower mortality, major adverse cardiovascular events, myocardial infarction and revascularization with no increase in major bleeding. However, these advantages were not observed with prasugrel or ticagrelor pretreatment.

Abbreviations: CAG = coronary angiography, CI = confidence interval, MACE = major adverse cardiovascular events, MI = myocardial infarction,NSTE-ACS = nonST-segment elevation acute coronary syndrome, NSTEMI = nonST-segment elevation myocardial infarction, OR = odds ratio, PCI = percutaneous coronary intervention, TIMI = thrombolysis in myocardial infarction,TVR = target vessel revascularization.

Keywords: meta-analysis, NSTE-ACS, pretreatment, P2Y12 inhibitor

1. Introduction

Dual antiplatelet therapy is the cornerstone of conservative and invasive treatments for acute coronary syndrome. Pretreatment generally refers to the initiation of dual antiplatelet therapy (aspirin and P2Y12 receptor inhibitor) before coronary angiography.[1] The theory of pretreatment is based on a sufficient antiplatelet effect prior to PCI and clopidogrel-mediated delay of action, providing low and slow platelet inhibition.[2–4] CURE and CREDO trials have demonstrated that P2Y12 receptor inhibitor loading (300 mg clopidogrel) before percutaneous coronary intervention is beneficial for reducing major adverse cardiovascular events but slightly increase bleeding events.[5,6] Subsequent observational studies have reached similar conclusions, but large-scale randomized controlled studies of routine clopidogrel pretreatment are lacking. According to these studies, the guidelines from the European Society of Cardiology and the American College of Cardiology/American Heart Association made a Class I recommendation for clopidogrel pretreatment.[7,8] Compared with clopidogrel, ticagrelor or prasugrel are more potent P2Y12 inhibitors with faster onset[9,10] and represent the first choice among ACS patients.[11] the ACCOST study, which enrolled 4033 patients with NSTE-ACS. In the pretreatment group, received prasugrel (30 mg) before the angiography and when PCI was indicated, an additional 30 mg of prasugrel

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was given. The results suggested pretreatment with prasugrel did not reduce the rate of ischemic events while the rate of major bleeding complications was increased.[12] In a post hoc analysis of patients with nonST-segment elevation acute coronary syndrome (enrolled 2365 patients) from the ISAR-REACT 5 trial, Ticagrelor 180 mg was started before coronary angiography and prasugrel 60 mg loaded postponed until the coronary anatomy was known.[13] Prasugrel significantly reduced cardiovascular events compared with ticagrelor, implying no apparent benefit of the ticagrelor pretreatment strategy. Taking into account patients who were undiagnosed or did not require PCI, pretreatment may delay the process of coronary artery bypass graft (CABG) and increase the risk of bleeding. The 2020 ESC guidelines did not recommend routine pretreatment with P2Y12 inhibitors for NSTE-ACS patients with unclear coronary anatomy.[11] In the era of prasugrel and ticagrelor, the optimal timing of P2Y12 receptor inhibitor administration remains controversial. Therefore, we performed a meta-analysis comparing pretreatment with P2Y12 inhibitors with without pretreatment in patients with NSTE-ACS.

2. Method

2.1. Search strategy and eligibility criteria

The present meta-analysis was performed met PRISMA guidelines.[14] Two researchers (Longhui Yan and Yan Zhou) independently used "Acute Coronary Syndrome" or "nonST-segment elevation acute coronary syndrome" or "Myocardial Infarction" as the subject terms and corresponding free terms in combination with "Antiplatelet" or "Antiplatelet therapy" or "Antiplatelet treatment" or "P2Y12 receptor inhibitor" or "P2Y12 receptor antagonist" or "clopidogrel" or "prasugrel" or "ticagrelor" or "elinogrel" or "cangrelor" and "pretreatment" or "pre-treatment" or "loading dose" or "preload" or "timing" or "upstream", systematically searched PubMed, Embase, Cochrane and the references of retrieved studies were checked to identify additional trials. Selected full-text articles and no language restrictions. Preliminary screening of relevant literature was performed based on title and abstract. Trials met our following criteria were included in the analysis: (1) studies including >50% of patients with NSTE-ACS; (2) studies comparing pretreatment with P2Y12 receptor inhibitor with no pretreatment in NSTE-ACS patients; (3) observational or randomized studies; (4) data on loading dose and timing of P2Y12 inhibitors were available; and (5) data reporting any data of interest, including at least any cause mortality, major bleeding. The following exclusion criteria were adopted: (1) ongoing studies; (2) the lack of a control group; and (3) duplicate reports. In our study, the primary efficacy endpoint was death from any cause, and the primary safety endpoint was major bleeding. Secondary end points included major adverse cardiovascular events (MACEs), myocardial infarction (MI) and revascularization (as defined in each trial). Pretreatment was defined as P2Y12 inhibitor loading preCAG or at least prePCI. The event rate was considered the shortest follow-up available in each study. For the studies included in the analysis, 2 researchers extracted relevant data and assessed the quality of the studies. Any disagreements were discussed or resolved by a third researcher (BuYun Xu). For the studies included in the analysis, data extraction tables and extraction methods were standardized for each study. The study was a reanalysis of a published paper and therefore does not require ethics committee approval or consent.

2.2. Quality assessment and statistical analysis

Randomized controlled trials were evaluated based on the Cochrane Collaboration guidelines.[15] Through sequence generation, allocation concealment, blinding (of participants, investigators, and outcome assessment), incomplete outcome data, and selective outcome reporting. Nonrandomized controlled studies were evaluated using the Newcastle-Ottawa Scale (NOS) by analyzing the selection of patients, comparability and outcome (Table 1). Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were reported as the results, and probability values were 2 tailed with $P < 0.05$ considered significant. Heterogeneity tests were performed using the Cochran Q test and Higgins I^2 test. Cochran Q $P < 0.10$ and $I^2 \geq 50\%$ were considered to be heterogeneous. $I^2 \geq 50\%$, random-effects model was applied; otherwise, fixed-effects model was adopted. Sensitivity analysis was conducted by excluding trials with the largest sample size. Subgroup analyses were performed according to study types and drugs (clopidogrel vs prasugrel or ticagrelor). All analyses were performed using ReviewManager5.3.

3. Results

3.1. Characteristics of the included studies

A total of 2457 articles were searched, of which 38 articles were potentially eligible. Upon further reviewing the studies, we excluded 12 studies that included patients with STEMI or the majority of patients underwent elective surgery, 2 dose comparison (300 vs 600 mg) trials and 3 articles that lacked a control group or had an inappropriate control group. In addition, 10 trials did not have available data, and an additional 2 studies examined the effect of glycoprotein IIb/IIIa and pretreatment duration. Eventually, 9 studies were included (Fig. 1), including 2 randomized controlled studies,[12,16] 2 post hoc analyses of randomized trials[17,18] and 5 nonrandomized controlled studies.[19–23] The included randomized controlled studies were high-quality studies, and nonrandomized controlled studies had a score of at least 6 (Fig. 2 and Table 1). Prasugrel or ticagrelor pretreatment was adopted in the ACCOST and DUBIUS studies. Three P2Y12 inhibitors (clopidogrel, prasugrel, and ticagrelor) were used in SCAAR

Table 1

Risk of bias of included nonrandomized studies.

Study		SCAAR 2020	MIG 2015	ARIAM 2015	Feldman 2010	ACUITY 2008	TARGET 2003	Assali 2001
Selection	Representativeness of the exposed cohort	*	*	*	*	*	*	*
	Selection of the nonexposed cohort					*	*	*
	Ascertainment of exposure	*	*	*	*	*	*	*
	Demonstration outcome of interest not present at the study	*	*	*	*	*	*	*
Comparability	cohorts on the basis of the design			**		**	**	
Outcomes	Assessment of outcome	*	*	*	*	*	*	*
	Was follow-up sufficiently long for outcomes to occur	*	*	*	*	*	*	*
	Adequacy of follow-up	*	*	*	*	*	*	*

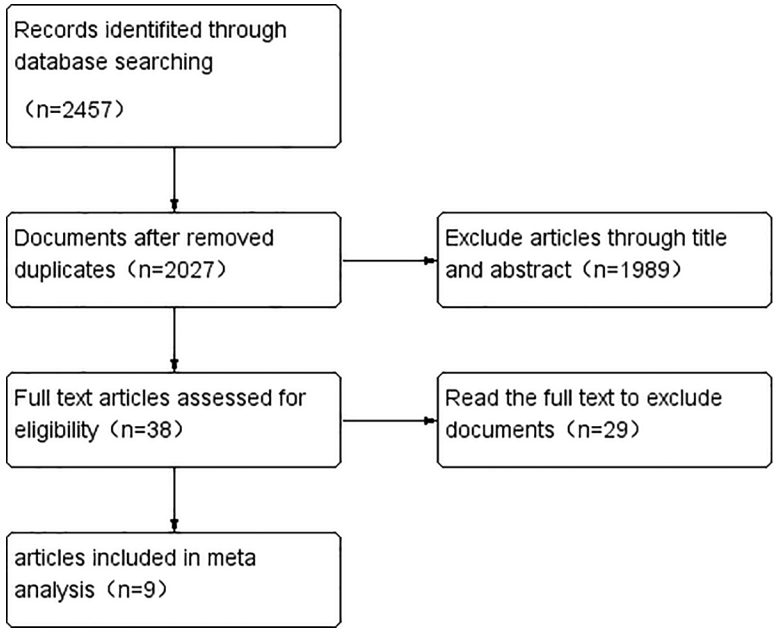

Figure 1. Literature screening process.

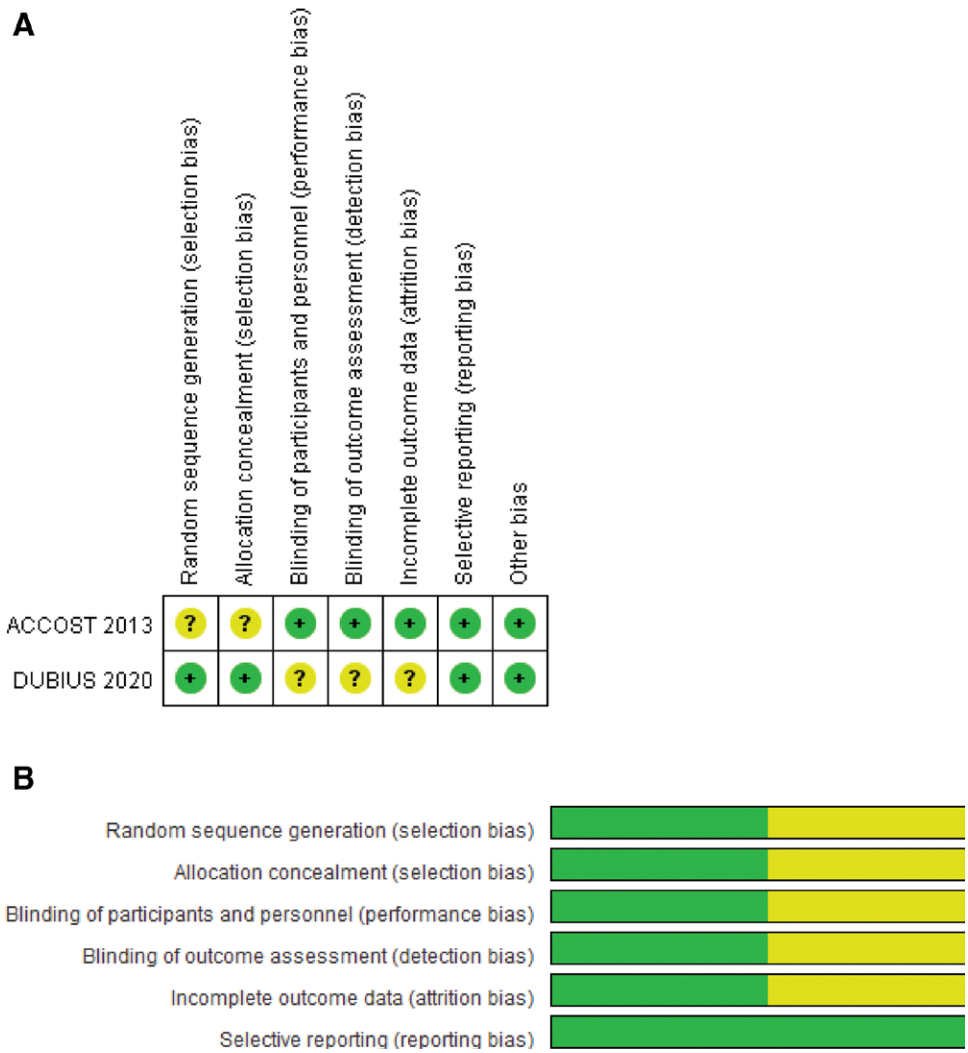

Figure 2. Risk of bias assessment for the included trials: A. Summary of the risk of bias for each individual trial. B. Overall risk of bias.

trials, and clopidogrel was applied in the remaining 6 studies. GP IIb/IIIa inhibitors were widely used in nonrandomized controlled studies. A total of 94,506 NSTE-ACS patients were enrolled, and 80,272 patients received P2Y12 inhibitor pretreatment. A total of 51,922 patients (55.6%) were treated with clopidogrel, and 41,389 (44.4%) were treated with prasugrel or ticagrelor. The majority of patients were diagnosed with NSTEMI and underwent PCI. The characteristics of the included study, P2Y12 inhibitor loading dose and timing are summarized in Tables 2 and 3.

3.2. Impact on primary outcomes

Mortality was reported in 9 studies. Pretreatment before CAG was related with lower incidence of mortality in NSTE-ACS patients (OR 0.62, 95% CI 0.53–0.72, $P < 0.00001$, Fig. 3).

Table 2

Characteristics of included studies.

Study	Design	Population (*P* vs N)	Pretreatment	No pretreatment	Primary outcomes
DUBIUS 2020	Randomized	1449 717 vs 732	180 mg ticagrelor after randomization	180 mg ticagrelor or 60 mg prasugrel at the start of PCI or after PCI	CV death, nonfatal MI, nonfatal stroke and BARC ≥type 3
SCAAR 2020	Registry Retrospective	64,857 59,894 vs 4963	Clopidogrel, ticagrelor or prasugrel (NA) before CAG	Clopidogrel, ticagrelor or prasugrel (NA) at the start of PCI	Mortality, bleeding during the index hospitalization
MIG 2015	Registry Retrospective	6817 3866 vs 2951	Clopidogrel (NA) before CAG	Clopidogrel (NA) load during or after PCI	Death, MI, and/or TVR
ARIAM-Andaluci 2015	Retrospective	3572 2797 vs 775	300/600-mg clopidogrel load prior to CAG or PCI or 75 mg for chronically treated patients	300/600 mg clopidogrel either before (<6 h) or during PCI	CV death, and nonfatal reinfarction or stroke/TIA
ACCOAST 2013	Randomized	4033 2037 vs 1996	30 mg prasugrel 2–48 h before PCI (median 4.4 hours), 30 mg at the time of PCI	60 mg prasugrel after angiography only in patients undergoing PCI	CV death, MI, stroke, urgent revascularization, major and minor bleeding (TIMI criteria)
Feldman 2010	Registry Observational	1,041467 vs 574	75 mg/d clopidogrel > 5 days, 300 mg >12 hr or 600 mg > 6 hr before PCI	600 mg clopidogrel <2 h or after PCI (within 30 min)	MI and MACE (postPCI death, post-PCIMI, emergency cardiac surgery, emergency PCI, or a cerebral vascularaccident)
TARGET 2003	Registry Observational	4809 4477 vs 332	300 mg clopidogrel before PCI (mean: 2.1 hours)	300 mg clopidogrel load immediately after PCI	Death, nonfatal MI or urgent TVR within 30 d
ACUITY 2008	Registry Observational	7646 6703 vs 943	300 mg clopidogrel before or <30 min after PCI	300 mg clopidogrel >30 min after PCI or not receive at any time	Death, MI, or revascularization
Assali 2001	Registry	299,235 vs 64	75 mg clopidogrel within 5 days or 300-mg load plus glycoprotein IIb/IIIa inhibitor before PCI	300 mg clopidogrel load after stent	Q-wave or nonQ-wave MI, urgent TVR, CV death

BARC = bleeding academic research consortium, CV = cardiovascular, MACE = major adverse cardiovascular events, MI = myocardial infarction, N = no pretreatment, NSTE ACS = nonST-segment elevation acute coronary syndrome, P = pretreatment, PCI = percutaneous coronary intervention, TIMI = thrombolysis in myocardial infarction, TVR = target vessel revascularization, NA = not available.

Table 3

Basic characteristics of the included patients.

Study		Age	Male (%)	DM (%)	UA (%)	NSTE MI (%)	GPIIb/IIIa inhibitor ues(%)	UFH Heparin use (%)	PCI (%)	Follow-up
DUBIUS 2020	P	64 (56–73)	74.7	23.5	21.4	78.6	5.0	94.0	70.1	30 d
	N	65 (56–73)	76.4	24.1	20.7	79.3	7.0	93.0	68.3	
SCAAR 2020	P	68 ± 10	72.1	22.2	22.1	77.9	2.6	89.1	100	30 d 1 y
	N	69 ± 10	72.6	23.9	38.1	61.9	1.9	90.4	100	
MIG 2015	P	64.9 ± 12.3	73.1	27.9	38.1	68.2	22.5	NA	100	30 d 1 y
	N	65.4 ± 12.1	72.4	26.4	29.2	70.8	26.5	NA	100	
ARIAM-Andaluci 2015	P	64 ± 12	73.0	35.0	27.5	72.5	28.0	2.7	81.0	In-hospital
	N	62 ± 11	72.0	38.0	35.0	65.0	33.0	8.2	77.5	
ACCOAST 2013	P	63.8	72.9	20.3	100%		NA	65.4	68.7	7, 30 d
	N	63.6	72.0	20.4	NSTE-ACS		NA	65.5		
Feldman 2010	P	67.1 ± 12.2	66.2	37.7	100%		46.7	NA	100	In-hospital 1 y
	N	67.3 ± 11.7	71.4	25.8	NSTE-ACS		52.6	NA	100	
ACUITY 2008	P	NA	73.3	27.2	100%		65.9	32.7	100	30 d 1 y
	N	NA	71.9	30.4	NSTE-ACS		69.2	33.6	100	
TARGET 2003	P	62.3 ± 10.9	73.6	23.3	46.9	15.8	100	100	100	30 d 6 mo 1 y
	N	62.5 ± 11.3	71.7	22.0	51.5	14.7	100	100	100	
Assali 2001	P	61.1 ± 11.8	66.0	34.0	66.0	0	100	100	100	In-hospital
	N	59.4 ± 12.1	67.0	30.0	80.0	0	100	100	100	

P = pretreatment, N = No pretreatment, DM = diabetes mellitus, UA = unstable angina, NSTEMI = nonST-segment elevation myocardial infarction, NSTE-ACS = nonST-Segment Elevation acute coronary syndrome, NA = not available.

Major bleeding events were described in 9 studies. No significant difference in the incidence of major bleeding was detected (OR 1.02, 95% CI 0.80–1.30, P = 0.89, Fig. 4).

3.3. Impact on MACE, MI, and revascularization

For MACE, difference was not noticed between the pretreatment group and no pretreatment group (OR 0.83, 95% CI 0.68–1.01, P = 0.07, Fig. 5A). This conclusion was similar to MI (OR 0.74, 95% CI 0.54–1.00, P = 0.05, Fig. 5B) and revascularization (OR 0.82, 95% CI 0.67–1.00, P = 0.05, Fig. 5C).

3.4. subgroup analyses

3.4.1. Prasugrel or ticagrelor versus clopidogrel. SCAAR trials (the data pretreatment by Prasugrel, ticagrelor or clopidogrel cannot be extracted separately) were excluded from this analysis. No striking differences in mortality (OR 0.70, 95% CI 0.31–1.59, P = 0.40, Fig. 3), MACE, MI, and revascularization were noted for prasugrel or ticagrelor pretreatment, whereas major bleeding events were significantly increased (OR 1.67, 95% CI 1.10–2.54, P = 0.02, Fig. 4). Clopidogrel pretreatment was related with lower incidence of mortality (OR 0.61, 95% CI 0.52–0.72,

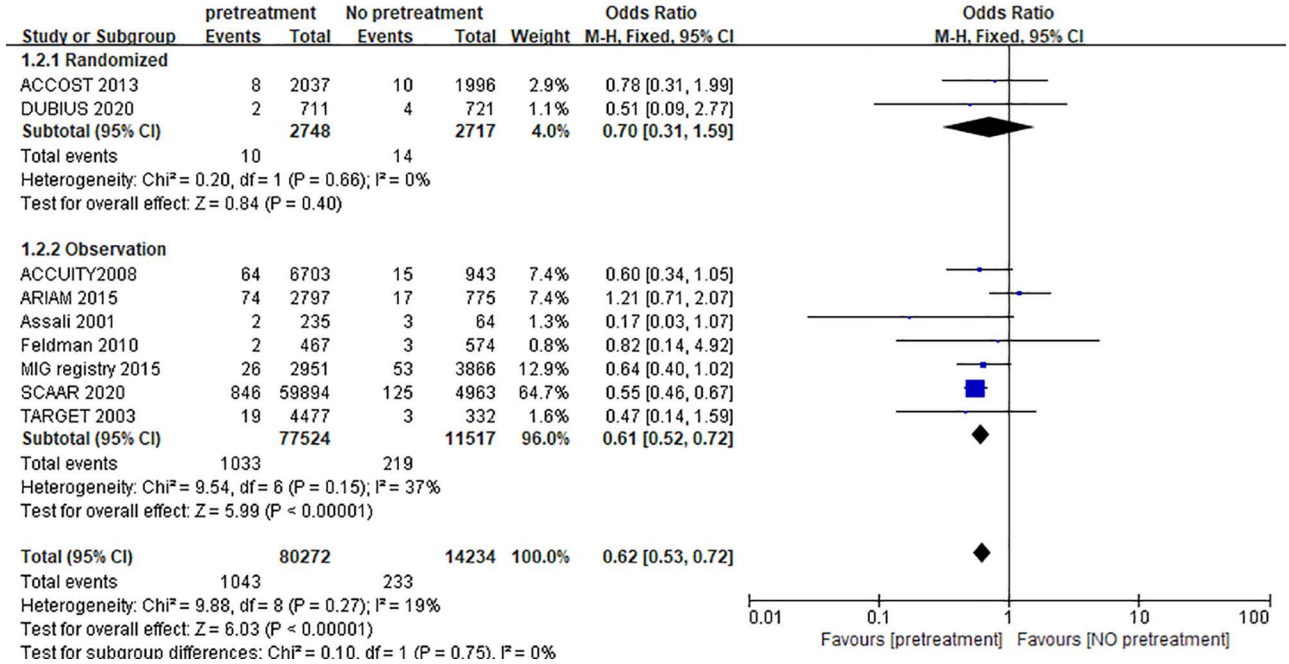

Figure 3. Forest plot of the death in patients administered P2Y12 inhibitor loading before CAG vs after CAG.

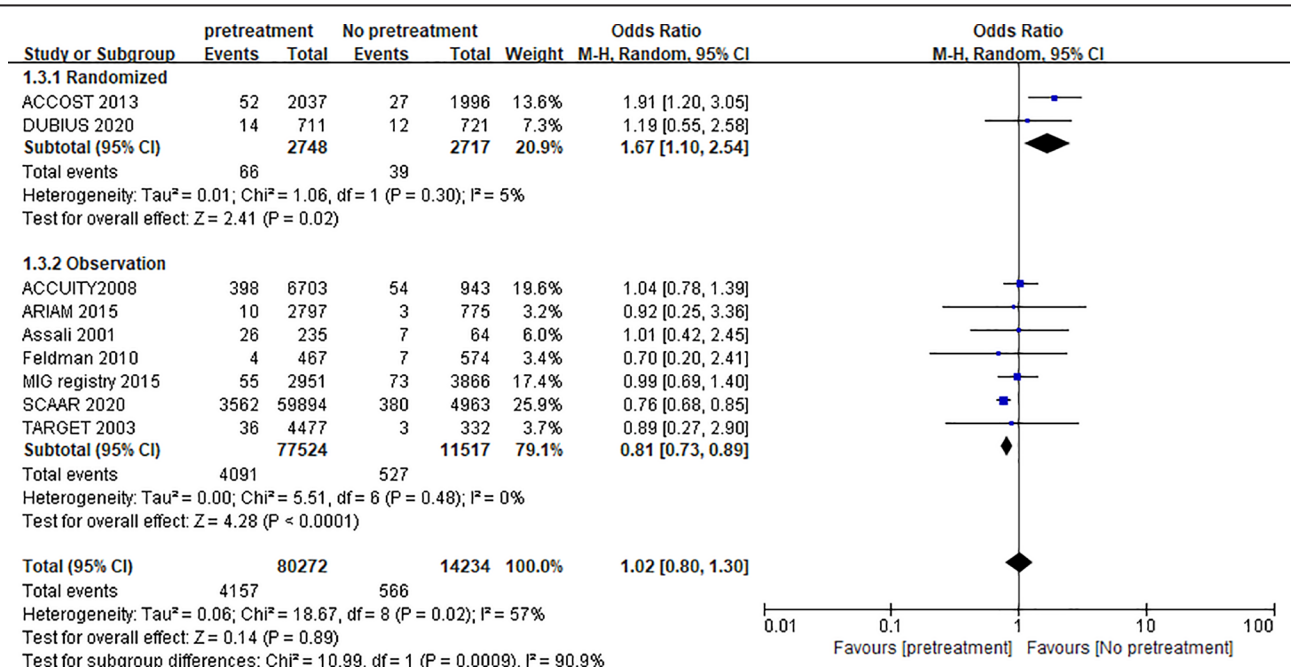

Figure 4. Forest plot of the major bleeding in patients administered P2Y12 inhibitor loading before CAG vs after CAG.

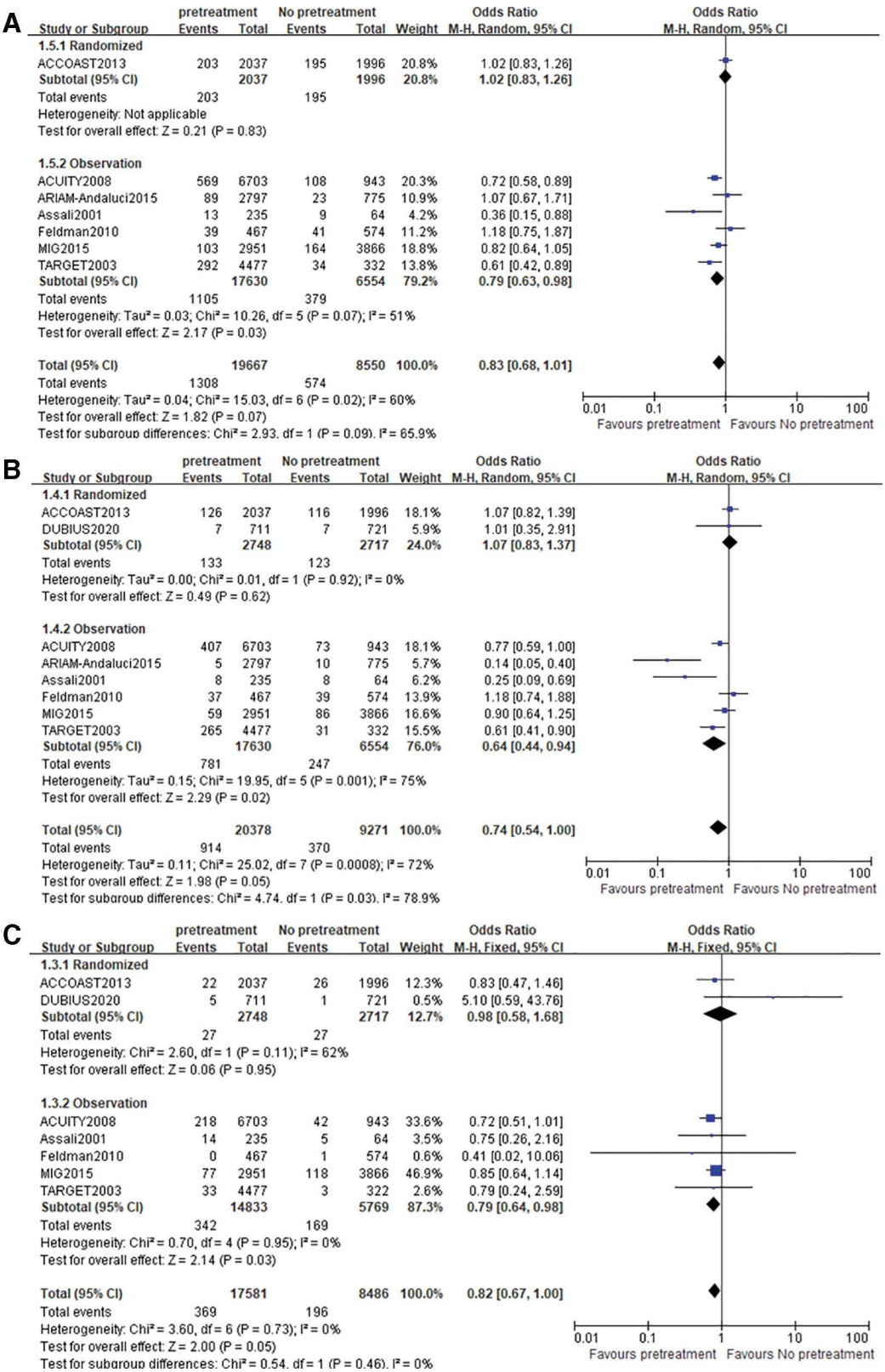

Figure 5. Forest plot of MACE, MI and revascularization in patients administered P2Y12 inhibitor loading before CAG vs after CAG.

$P < 0.0001$, Fig. 3), MACE, MI, and revascularization without increasing major bleeding.

3.4.2. Randomized versus nonrandomized. When randomized studies were analyzed alone, the results suggested that pretreatment with P2Y12 inhibitors was not relevant to lower mortality (OR 0.70, 95% CI 0.31–1.59, $P = 0.40$, Fig. 3), MACE, MI or revascularization (Fig. 5). However, major bleeding events were significantly increased (OR 1.67, 95% CI 1.10–2.54, $P = 0.02$, Fig. 4). In contrast, in nonrandomized controlled studies, pretreatment was significantly associated with lower mortality, and ischemic protection was observed.

3.5. Sensitivity analysis and reporting bias

After excluding the study with the largest number of patients, the results remained unchanged. Ticagrelor and prasugrel were approved by the FDA in 2011 and 2009, respectively, and were recommended by major guidelines in 2011. We evaluated the results related to the guideline change by comparing the relevant research results before (before 2011) and after the change (after 2011). The heterogeneity between the 2 groups in all-cause death, major bleeding, MACE, MI, and revascularization were $P = 0.57$, $I^2 = 0\%$; $P = 0.8$, $I^2 = 0\%$; $P = 0.13$ $I^2 = 53.6\%$; $P = 0.34$ $I^2 = 0\%$; $P = 0.93$ $I^2 = 0\%$, respectively. On the whole, there was no obvious heterogeneity in the research results of different era. The included literature was limited, and publication bias was not assessed.

4. Discussion

In the current meta-analysis, we found that pretreatment with P2Y12 inhibitors could reduce any-cause mortality without increasing the risk of major bleeding with no distinction in myocardial infarction, revascularization and MACE. However, subgroup analysis revealed that significant benefits were detected with clopidogrel pretreatment, prasugrel or ticagrelor pretreatment lacked ischemic protection and caused major bleeding events.

PLATO and TRITON–TIMI 38 trials showed that ticagrelor or prasugrel pretreatment could significantly reduce ischemic events compared with clopidogrel.[9,10] Clopidogrel is no longer the first-line antiplatelet recommendation[11,24] due to bleeding risk, contraindications and onset time, but it is still extensively employed in clinical practice. Clopidogrel is an irreversible platelet inhibitor that exerts its maximum antiplatelet effect after 2–6 hours of being metabolized by the human body. It seemed reasonable for clopidogrel pretreatment to inhibit platelets completely and effectively. Early randomized controlled trials assessing clopidogrel preload included the CURE and CREDO trials.[5,6] In the CURE study, clopidogrel preload could reduce major cardiovascular events by 20% (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke) compared with placebo without increasing fatal bleeding. In the PCI subset of the CURE,[25] NSTE-ACS patients were preloaded with clopidogrel before PCI (median 6 days). Major cardiovascular events were decreased 30%, and MI, urgent revascularization was all decreased. The Clopidogrel for the Reduction of Events During Observation (CREDO) also confirmed that clopidogrel loading at least 6 hours before PCI could lower major adverse cardiovascular events. Loading was confirmed to be reasonable according to the 2 older studies mentioned above, and the possible benefits of pretreatment were suggested. The advantages of clopidogrel pretreatment were further verified in subsequent nonrandom studies[17,21] and meta-analyses.[26,27] Our study emphasizes the profit from clopidogrel pretreatment in patients with NSTE-ACS. Nevertheless, it was noteworthy that trials adopted in this meta-analysis about clopidogrel pretreatment were all nonrandomized controlled trials, which compromises the credibility of the research. The results of nonrandomized controlled studies were more susceptible to various potential biases. In clinical practice, physicians were more likely to choose patients with low bleeding and high ischemic risk for loading. That may be one of the reasons why we found inconsistency between nonrandomized controlled studies and randomized controlled studies in our subgroup analysis. The current randomized controlled studies for prasugrel and ticagrelor do not recommend pretreatment, and our study suggest that pretreatment with clopidogrel was an option when potent P2Y12 receptor inhibitors were not available. In the retrieved published literature, no large randomized controlled trials on clopidogrel pretreatment have been performed in NSTE-ACS patients. Subsequent large randomized controlled studies are needed.

This study was novel compared to previous research because we included 2 randomized controlled studies on prasugrel or ticagrelor pretreatment. As the first-line recommended drugs in the guidelines, faster onset (approximately 0.5–2 hours) and stronger antiplatelet effects were noticed. Routine pretreatment strategies were challenged with the development of new drugs, construction of chest pain centers and progress in stent technology. The ACCOST study included 4033 NSTE-ACS patients who were scheduled to undergo angiography. The pretreatment group received a 30-mg prasugrel before coronary angiography followed by 30 mg prasugrel after definitive PCI. The control arm received a 60 mg prasugrel during PCI. The study confirmed that prasugrel pretreatment was not associated with lower ischemic events and increased major bleeding events.[12] A previous meta-analysis including the ACCOST trials did not observe clinical advantages of pretreatment.[28] Recently, 30-day follow-up data from the DUBIUS study have been released.[16] A total of 1449 NSTE-ACS patients undergoing invasive management were included in the study. The pretreatment group received 180 mg ticagrelor immediately after randomization, and the control group received 180 mg ticagrelor (50%) and 60 mg prasugrel (47%) before PCI after angiography. No difference detected in ischemic and bleeding events. A predefined subgroup of NSTE-ACS patients from the randomized trial ISAR-REACT 5[13] showed that prasugrel deferred loading was superior to ticagrelor pretreatment in reducing MACEs without increasing the risk of bleeding. The subgroup analysis of prasugrel or ticagrelor pretreatment in our research found no significant differences in mortality, MACE, MI or revascularization, whereas major bleeding events were significantly increased. A lower incidence of bleeding was observed in nonrandomized controlled studies. A possible explanation was that the bleeding risk of the SCAAR study included minor bleeding, and ticagrelor was applied extensively in the control group (78.8%). In contrast, the bleeding risks noted for ticagrelor and clopidogrel in the pretreatment group were 52.9% and 45.3%, respectively. With the exception of the SCAAR trials, difference in major bleeding was not observed. Current randomized controlled trials on ticagrelor pretreatment in NSTE-ACS were not identified. However, pretreatment with ticagrelor before hospital admission in STEMI showed no difference between ischemic and bleeding events.[29]

Another concern of P2Y12 inhibitor pretreatment was that it would delay the timing of CABG. It remains unclear whether P2Y12 receptor inhibitors should be stopped before CABG surgery, and the best time to stop is unknown. A small randomized controlled study showed that stopping clopidogrel on the day of surgery overtly increased the risk of bleeding and blood transfusion.[30] The meta-analysis included 34 studies suggested that continuous dual antiplatelet until the day of CABG could reduce the risk of recurring ischemic in ACS patients. However, mortality and reoperation rates were increased.[31] One limitation was that this meta-analysis only included 2 small sample studies on clopidogrel within 24 hours by timing CABG in ACS patients, and most studies stopped clopidogrel at least 2 days before surgery. The NCDR (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get with the Guidelines) reported no difference in in-hospital mortality and the composite ischemic outcome between early and late CABG.[32] Among the potent P2Y12 receptor inhibitors, the prospective, multicenter clinical trial of ticagrelor noted that continuing ticagrelor up to the time of surgery increased the incidence of severe bleeding.[33] Subgroup analysis of PLATO prompted termination of ticagrelor 24 hours before surgery seemed to increase total mortality.[34] The current research is more focused on the optimal stopping time before surgery and dual antiplatelet therapy after surgery.

According to the current data, clopidogrel pretreatment in NSTE-ACS patients was associated with reduced death, MACE, MI, and revascularization without increasing bleeding, but most of the research data were from nonrandomized controlled studies. Further randomized controls are needed for verification. Prasugrel and ticagrelor pretreatment did not reduce ischemic events but increased the risk of major bleeding.

5. Limitations

The meta-analysis presents several limitations. (1) Most of the included studies were nonrandomized controlled studies with many inherent biases and confusions. (2) Obvious heterogeneity in myocardial infarction and MACE was observed, which may be caused by differences definitions used in various studies. (3) The definition of pretreatment as well as the time from P2Y12 inhibitor load to PCI differed in various studies. (4) The analysis of the potency of P2Y12 was limited due to a lack of data.

6. Conclusions

Based on existing data, clopidogrel pretreatment was associated with a lower risk of MACE, MI, death, and revascularization without increasing bleeding in NSTE-ACS patients. However, prasugrel or ticagrelor pretreatment was not related to ischemic events, whereas the risk of major bleeding events was increased. The feasibility of the pretreatment strategy requires further evaluation.

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