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Comprehensive comparative efficacy and safety of potent $P2Y_{12}$ inhibitors in patients undergoing coronary intervention: A systematic review and *meta*-analysis

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ABSTRACT

Potent $P2Y_{12}$ receptor antagonists have been used widely for patients undergoing percutaneous coronary intervention with different results. Benefits from different regimens various between trials. Randomized controlled trials (RCTs) have restrictive inclusion and exclusion criteria; thus, they may limit the generalizability of the findings to a broader population. This study was aimed to comprehensively investigate the outcomes of potent $P2Y_{12}$ inhibitors in patients undergoing PCI, including RCTs and real-world evidence (RWE) studies.

Multiple electronic databases were systemically reviewed and searched on compared potent $P2Y_{12}$ inhibitors with clopidogrel. The primary efficacy end point was composite ischemic cardiovascular event and primary safety endpoint was major bleeding. Overall estimates of proportions and incidence rates with 95 % confidence intervals (CI) were calculated using fixed-effects models. Total 24 studies (140,986 patients) underwent coronary intervention were included in this *meta*-analysis, including 18 RCTs and 6 large cohort studies with propensity score matching. The potent $P2Y_{12}$ inhibitors including cangrelor, prasugrel, and ticagrelor, significantly decreased the risk of composite adverse cardiovascular ischemic events (95 % CI 0.89–0.96, $p < 0.001$), but increased major bleeding (95 % CI 1.15–1.33, $p < 0.001$) or any bleeding (95 % CI 1.21–1.33, $p < 0.001$) compared with Clopidogrel.

This *meta*-analysis merges RCTs and RWE studies and comprehensively evidences newer potent $P2Y_{12}$ inhibitors are significantly more effective than clopidogrel in reduction of composite adverse thrombotic events, but the incidence of major or any bleeding was higher compared with clopidogrel.

1. Main text

P2Y12 inhibitors are an essential class of antiplatelet agents that play a crucial role in the management of coronary artery disease (CAD). The incidence of bleeding and the degree of inhibition of platelet aggregation caused by P2Y12 receptor inhibitor have been of great concern in recent years [1]. Clopidogrel is a commonly used P2Y12 inhibitor recommended for the standard treatment of patients undergoing percutaneous coronary intervention (PCI). Cangrelor is an intravenous inhibitor of the adenosine diphosphate (ADP) receptor and has a role in the treatment of patients who require rapid, potent, predictable, and quickly reversible platelet inhibition [2], and another two newer ADP inhibitors, prasugrel and ticagrelor, have been associated with less interpatient variability and more potent antiplatelet aggregation response [3,4].

When comparing potent P2Y12 inhibitors with clopidogrel in randomized control trials (RCTs), some RCTs have demonstrated superiority of potent P2Y12 inhibitors in terms of efficacy, others have shown no significant difference compared to clopidogrel [5–8]. The PLATO

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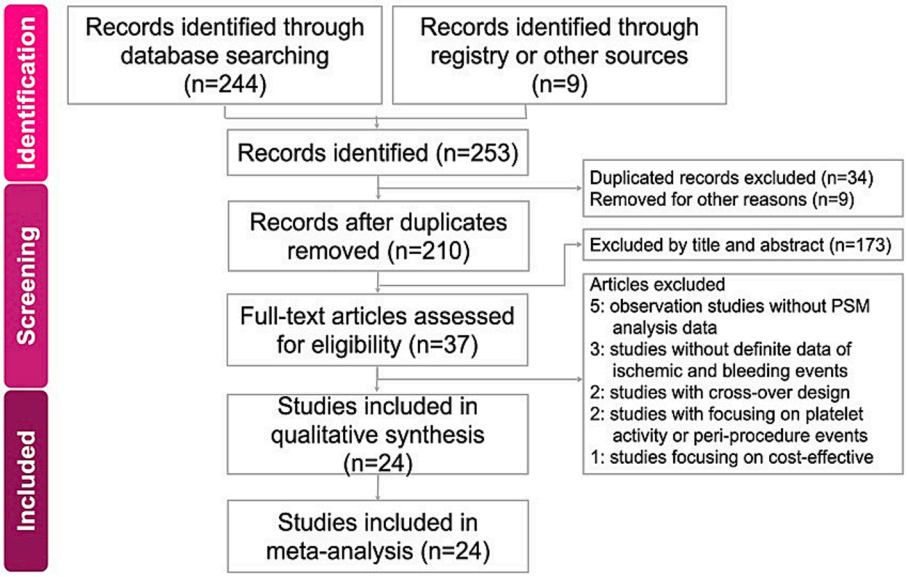

Fig. 1. PRISMA flow diagram of study selection.

(Platelet Inhibition and Patient Outcomes) trial compared ticagrelor with clopidogrel in patients with acute coronary syndrome (ACS). The trial demonstrated superiority of ticagrelor in reducing the composite endpoint of cardiovascular death, myocardial infarction, or stroke, favoring ticagrelor over clopidogrel [5]. The CURRENT-OASIS 7 trial evaluated the efficacy of two different doses of clopidogrel (standard and high) and compared them with ticagrelor in patients with ACS. The trial did not find a significant difference between ticagrelor and clopidogrel in terms of the composite endpoint of cardiovascular death, myocardial infarction, or stroke [6]. The TRITON-TIMI 38 trial compared prasugrel with clopidogrel in patients with ACS undergoing PCI. The trial showed that prasugrel was associated with a lower rate of cardiovascular events, including the composite endpoint of cardiovascular death, myocardial infarction, or stroke, but higher major bleeding risk compared to clopidogrel [7]. The ISAR-REACT 5 trial compared prasugrel with ticagrelor in patients with ACS undergoing PCI. The trial discovered that those who were administered prasugrel had a notably reduced risk of death, myocardial infarction, or stroke compared to ticagrelor group, and there was no significant disparity in the occurrence of major bleeding between the two groups [8]. These examples highlight the varying findings in different RCTs regarding the efficacy and safety of potent P2Y12 inhibitors compared to clopidogrel.

RCTs are considered the gold standard for evaluating the efficacy of interventions, but participants are typically selected based on strict inclusion and exclusion criteria, which may limit the generalizability of the findings to a broader population, while observational studies conduct in a real-world scenario of the intervention in clinical practice and all coming patients are included. Our *meta*-analysis that combines randomized controlled trials (RCTs) and real world evidence (RWE), which are well qualified and propensity score matching (PSM) cohort studies, can provide a more comprehensive overview of the effectiveness and safety of potent P2Y12 inhibitors vs. clopidogrel.

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) and the Cochrane Collaboration guidelines. It was registered on the International prospective register of systematic reviews (PRSPERO) on July 04, 2021 (ID: 265104).

2. Data Sources and Search Strategy

The search strategy aimed to find both published and unpublished trials as far back as possible. Initially, we set intuition index terms on PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases to find relative wording and Medical Subject Headings (MeSH) terms. Second, we used all identified keywords and index terms across all databases, including PubMed, MEDLINE, and Cochrane. Finally, the references listed in the selected articles were read and referred as gray articles if they met the inclusion/exclusion criteria of this review. To our background knowledge, some global trials were already published and still important in the field of cardiology. Thus, those trials were also selected if they met the inclusion criteria of this study. All potential literatures were published from 2010 to 2021 including the following major keywords: coronary intervention, percutaneous coronary intervention, clopidogrel, cangrelor, prasugrel, ticagrelor.

All retrieved studies were required to comprise two treatment arms, one of which was potent P2Y12 inhibitor (cangrelor or prasugrel or ticagrelor) and the other of which was clopidogrel. The literature was last searched on July 27, 2021. (Fig. 1).

3. Selection Criteria

3.1. *Types of participants*

The current review considered trials that included adult patients admitted with the diagnosis of ACS or CCS and planned to receive PCI after coronary angiography was done.

3.2. *Types of interventions*

We defined the intervention as prescribing potent P2Y12 inhibitor (cangrelor, prasugrel, or ticagrelor) at PCI and follow-up period. The control group was patients who received clopidogrel during PCI and follow-up period.

3.3. *Types of studies*

Randomized controlled trials or PSM cohort studies that compared outcome between high potent P2Y12 inhibitor and clopidogrel were selected into this review. Articles that published in English were enrolled.

3.4. Outcomes

The primary efficacy endpoint was the incidence of composite adverse ischemic cardiovascular events, including major adverse cardiovascular events (MACE; defined as a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke) and its individual components, as well as a composite of cardiovascular (CV) death, all-cause death, or stroke, repeat revascularization, re-admission due to ACS, and stent thrombosis. The primary safety endpoint was composite bleeding events, including major bleeding or any bleeding (major and minor bleeding).

4. Study Selection

Firstly, Endnote X9 was used to identify duplicate articles and retained only one instance of each article. Then, two reviewers examined the remaining articles with title and abstract, to determine whether the article was potentially relevant to the study purpose. Eligible literatures were listed according to the inclusion criteria and excluded articles were set apart with reasons. Finally, two reviewers read the original article together to reach an agreement. Disagreements between reviewers were resolved after well consulting a third reviewer (corresponding author).

5. Assessment of Study Quality

The quality of observational cohort studies was under assessment with the use of Newcastle-Ottawa Quality Assessment Scale [9]. RCTs were graded using the Cochrane's Risk of Bias (RoB) [10]. The quality assessment was done by two reviewers independently. Any disagreements among them were resolved after well discussion each other.

6. Data Extraction

Two investigators examined all of the retrieved articles and extracted data using a predetermined form. We recorded the trial name or the first author, year of publication, dose and method of drugs, number of patients, number of patients with cardiovascular events, follow-up time, and efficacy and safety of treatment. Between reviewer discrepancies were solved through discussions under the supervision of the corresponding author.

7. Statistical analysis

Meta-analyses were performed by using Review Manager (RevMan) 5.4.1. (RevMan; The Cochrane collaboration Oxford, United Kingdom). The treatment effect was evaluated using the odds ratio (OR) and 95 % confidence interval (CI). All the results of the study were assessed using pooled ORs and 95 % CIs by a fixed-effect model. The I^2 test was used to assess the heterogeneity of the results, with I^2 values greater than 75 % indicating that the two groups had a high heterogeneity, independence, and no significance of *meta*-analysis. The cutoff value for statistical significance for each test was set at $p = 0.05$.

Sensitivity analyses were conducted excluding the Trigger-PCI, PRASFIT-Elective, and Alpheus trials. Because these were the trials that only focus on chronic coronary syndrome (CCS), and the results were qualitatively consistent with the primary analysis.

8. Literature Search

We retrieved 210 non-duplicate citations for a review of their titles and abstracts. There were 37 full-text articles assessed, and then we excluded 13 studies due to data insufficiency, including no PSM or no definite adverse cardiac or bleeding events, 2 crossover trials, and 2 studies with only focusing on platelet activity, gene polymorphism, stent thrombosis or *peri*-procedure safety, and one study focusing on cost-effective without clinical outcomes. Finally, 24 studies involving 140,986 patients were included in the systemic review [5,11–33]. A schematic of the study selection process is presented in Fig. 1.

Table 1
Main descriptions of the studies included.

Trial Name or First Author	Type of Study	Type of Patients	Follow-up (month)	No. of Patients Randomized	
				Newer $P2Y_{12}$ Inhibitors	Clopidogrel
CHAMPION PLATFORM [14]	RCT	NSTEMI/CCS	1–12	2654 (1)	2641
CHAMPION PCI[15]	RCT	ACS/CCS	1–12	4367 (1)	4355
CHAMPION PHOENIX [18]	RCT	ACS/CCS	1	5472 (1)	5470
TRIGGER-PCI [17]	RCT	CCS	6	212 (2)	211
TRILOGY ACS [16]	RCT	ACS	30	4663 (2)	4663
TRITON-TIMI 38[13]	RCT	ACS	15	6813 (2)	6795
BASKET-PROVE[23]	RCT	ACS	2	985 (2)	1012
KAMIR-NIH, 2018[31	]Cohort (PSM +)	ACS	6*	637 (2)	637
Yun J.E. et al. [33]	Cohort (PSM +)	ACS	12–24	3097 (2)	3097
Elderly ACS [11]	RCT	ACS	12	713 (2)	730
Akita, K.[12]	Cohort (PSM +)	ACS	12	12,016 (2)	12,016
PRASFIT-ACS [19]	RCT	ACS	6–12	685 (2)	678
PRASFIT-Elective [32]	RCT	CCS	6–12	370(2)	372
PLATO[5]	RCT	ACS	12	6732 (3)	6676
PHILO[20]	RCT	ACS	12	401 (3)	400
ESTATE[21]	Cohort (PSM +)	ACS	1–12	224 (3)	224
KAMIR-NIH, 2016[22]	Cohort (PSM +)	ACS	6*	1377 (3)	1377
Li, X.Y.[24]	RCT	STEMI	12	161 (3)	281
TICAKOREA [25]	RCT	ACS	12	400 (3)	400
ALPHEUS [28]	RCT	CCS	1	941 (3)	942
POPular AGE [26]	RCT	NSTE-ACS	12	502 (3)	500
TAILOR-PCI [31]	RCT	ACS/CCS	12	903 (3)	946
Turgeon, R.D. [29]	Cohort (PSM +)	ACS	12	3711 (3)	3711
TALOS-AMI [30]	RCT	ACS	12	1348 (3)	1349
Yun J.E. et al. [33]	Cohort (PSM +)	ACS	12–24	11,402 (2)	11,402

Newer P2Y12 inhibitors: (1)Cangrelor; (2) Prasugrel; (3) Ticagrelor.
RCT, randomized clinical trial; Cohort (PSM +): propensity score matched, ACS, acute coronary syndrome; CCS, stable coronary syndrome.
*: in-hospital and 6-month cumulative clinical outcomes.

Table 2
The original data of outcome indicators.

Trial Name or First Author	Drug dose				Clinical outcome	
	Clopidogrel		New $P2Y_{12}$ Inhibitors		Main Composite Efficacy Endpoints	Main Composite Safety Endpoints
	LD	MD	LD	MD		Bleeding score
CHAMPION PLATFORM[14]	600 mg after PCI		bolus 30 ug/kg, infusion of 4 ug/kg		Death, MI, IDR	GUSTO major/minor or TIMI or ACUITY
CHAMPION PCI[16]	600 mg before PCI		bolus 30 ug/kg, infusion of 4 ug/kg		Death, MI, IDR	GUSTO major/minor or TIMI or ACUITY
CHAMPION PHOENIX[18]	600/300 mg before/after PCI		bolus 30 ug/kg, infusion of 4 ug/kg		Death, MI, IDR, ST	GUSTO major/minor or TIMI or ACUITY
TRIGGER-PCI[17]	600 mg	75 mg	60 mg	10 mg	CV death, MI	TIMI fatal, major/minor/ minimal bleeding
TRILOGY ACS[16]	300/600 mg	75 mg	30 mg	10 mg/ 5mg if age≧75 or BW < 60 kg	CV death, non-fatal MI, non-fatal stroke	GUSTO severe/moderate; TIMI major/minor
TRITON-TIMI 38 [13]	300 mg	75 mg	60 mg	10 mg	CV death, non-fatal MI, non-fatal stroke	TIMI major/minor
BASKET-PROVE [23]	300/600 mg	75 mg	60 mg	10 mg/ 5mg if age≧75 or BW < 60 kg	CV death, non-fatal MI, TVR	BARC 3–5
KAMIR-NIH, 2018 [31]	300/600 mg	75 mg	60 mg	10 mg*	CV death, non-fatal MI, stroke, TVR	TIMI major/minor
Yun J.E.[33]	300/600 mg	75 mg	60 mg	10 mg	CV death, non-fatal MI, stroke, all-cause death	Major or any bleeding
Elderly ACS[11]	300/600 mg	75 mg	60 mg	5 mg	All-cause death, MI, disabling stroke, rehospitalization for cardiovascular causes or bleeding	BARC 2,3,5
Akita, K. et al.[12]	300 mg	75 mg	20 mg	3.75 mg	In-hospital death, ST	Any bleeding
PRASFIT-ACS[19]	300 mg	75 mg	20 mg	3.75 mg	CV death, non-fatal MI, non-fatal stroke	TIMI major bleeding or any bleeding
PRASFIT-Elective [32]	300 mg	75 mg	20 mg	3.75 mg	CV death, non-fatal MI, non-fatal stroke	TIMI major bleeding or any bleeding
PLATO[5]	300/600 mg	75 mg	180 mg	90 mg bid	CV death, MI, stroke	PLATO-defined major/minor
PHILO[20]	300 mg	75 mg	180 mg	90 mg bid	CV death, MI, stroke	PLATO-defined major/minor
ESTATE[21]	300/600 mg	75 mg	180 mg	90 mg bid	CV death, MI, stroke, ST, All-cause death	PLATO-defined major/minor
KAMIR-NIH, 2016 [22]	300/600 mg	75 mg	180 mg	90 mg bid	CV death, non-fatal MI, stroke, TVR	TIMI major/minor
Li, X.Y. [24]	600 mg	75 mg	180 mg	90 mg bid	CV death, non-fatal MI, non-fatal stroke	BARC 1 (minor) BARC 2/3 (major)
TICAKOREA[25]	600 mg	75 mg	180 mg	90 mg bid	CV death, non-fatal MI, non-fatal stroke	PLATO-defined major/minor
ALPHEUS[28]	300/600 mg	75 mg	180 mg	90 mg bid	PCI-MI (type 4a or 4b) or major myocardial injury, death, MI (type 1, 4, and 5), stroke, TIA	BARC 3/5 (major) BARC 1/2 (minor) BARC 1 ~ 5 (any)
POPular AGE[26]	300/600 mg	75 mg	180 mg	90 mg bid	CV death, all-cause death, MI, stroke, ST	PLATO-defined major/minor
TAILOR-PCI[31]	300/600 mg	75 mg	180 mg	90 mg bid	CV death, MI, stroke, ST, SRI	TIMI major/minor
Turgeon, R.D.[29]		75 mg		90 mg bid	All-cause death, ACS, ischemic stroke, unplanned CR, ST	Major bleeding
TALOS-AMI[30]		75 mg		90 mg bid	CV death, MI, stroke	BARC 2/3/5
Yun J.E.[33]	300/600 mg	75 mg	180 mg	90 mg bid	CV death, non-fatal MI, stroke, all-cause death	Major or any bleeding

Newer $P2Y_{12}$ inhibitors: (1) Cangrelor; (2) Prasugrel; (3) Ticagrelor.
LD, loading dose; MD, maintenance dose; IDR, ischemia-driven revascularization; ST, stent thrombosis; TVR, target vessel revascularization; TIA, transient ischemia attack; SRI, severe recurrent ischemia; CR, coronary revascularization; GUSTO, global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries; TIMI, thrombolysis in myocardial infarction; ACUITY, acute catheterization and urgent intervention triage strategy; BARC, bleeding academic research consortium;PLATO, platelet inhibition and patient outcomes.

* Exclusion criteria: age ≧ 75 years old, body weight < 60 kg, history of stroke or TIA.

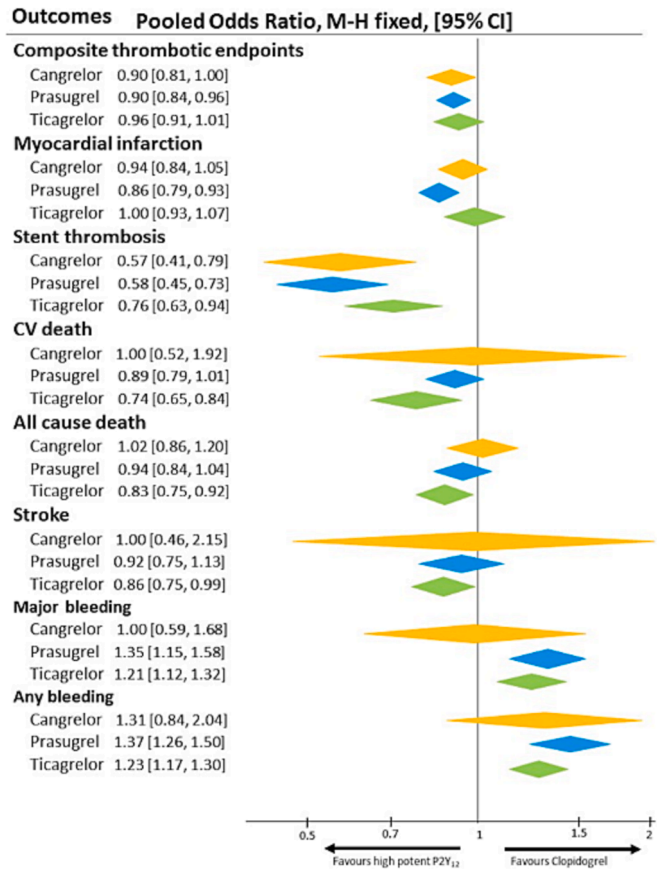

Fig. 2. Effectiveness and safety of individual potent $P2Y_{12}$ inhibitors (cangrelor, prasugrel, and ticagrelor) vs. clopidogrel by pooled odds ratios and 95% CIs. CI= confidence interval. CV= cardiovascular.

9. Methodological Quality of Studies Included

All enrolled studies are RCTs or PSM cohort studies. The methodological quality of the RCTs was determined by assessing the Cochrane's risk of biases (Supplement Table 1). and the PSM cohort studies were qualified by using the Newcastle-Ottawa Quality Assessment Scale (Supplement Table 1). Any disagreements concerning data evaluation were resolved by consensus. Three of the 24 trials are cangrelor vs. clopidogrel, nine articles are prasugrel vs. clopidogrel, eleven studies are ticagrelor vs. clopidogrel, only one paper involved ticagrelor vs. clopidogrel as well as prasugrel vs. clopidogrel. The detailed characteristics of the included 24 studies are shown in Table 1 and Table 2.

10. The Highlights of Outcomes Summary

The total pooling data with pooled odds ratios and 95 % conference intervals as showned in Central Illustation(A) discovered potent P2Y12 inhibitors have effectiveness in reducing thrombotic events compared with clopidogrel, including compositic thrombotic cardiovascular events (pooled OR = 0.93, 95 % CI, 0.89–0.96), myocardial infarction (pooled OR = 0.93, 95 % CI, 0.89–0.98) and stent thrombosis (pooled OR = 0.66, 95 % CI, 0.57–0.75), CV death (pooled OR = 0.82, 95 % CI, 0.75–0.89), All cause death (pooled OR = 0.90, 95 % CI, 0.84–0.96) and stroke (pooled OR = 0.88, 95 % CI, 0.79–0.99). On the other hand, the pooling data disclosed that potent P2Y12 inhibitors significantly increased major bleeding and any bleeding risks compared with clopidogrel. (pooled OR = 1.24, 95 % CI, 1.15–1.33; pooled OR = 1.27, 95 % CI, 1.21–1.33 respectively).

The efficacy and safety of the individual P2Y12 inhibitor (cangrelor, prasugrel, ticagrelor) vs. clopidogrel as showed in Fig. 2 as well as Central Illustration (B) and they provided consistent findings of comparable anti-ischemic efficacy with cangrelor, prasugrel and ticagrelor in comparison with clopidogrel. The classic effect of anti-thrombotic efficacy is stent thrombosis, which is consistence with the three kinds of P2Y12 inhibitors (cangrelor: pooled OR = 0.57, 95 % CI, 0.41–0.79; prasugrel: pooled OR = 0.58, 95 % CI, 0.45–0.73, and ticagrelor: pooled OR = 0.76, 95 % CI, 0.63–0.94). The oral potent P2Y12 inhibitors (prasugrel and ticagrelor) have the similar trends in all effectiveness and safety, as showed in blue diamond (prasugrel) and green one (ticagrelor) of Fig. 2. But when compared to clopidogrel, prasugrel has statistically significance in composite thrombotic endpoints, myocardial infarction and stent thrombosis, while ticagrelor is better than clopidogrel in stent thrombosis, CV death, all cause death and stroke. Both of them have higher major bleeding and any bleeding risks as shown in Central Illustration (B).

11. Quantitative Data Synthesis

11.1. Primary Efficacy End Point of Composite Ischemic Cardiovascular Events

The primary efficacy end point was a composite ischemic event and included major adverse cardiovascular events (MACE, defined as a composite of death from cardiovascular causes, non-fatal MI, or non-fatal stroke) and its individual components, and CV death, all-cause death, repeat revascularization, as well as re-admission due to ACS. The rates of primary efficacy end point of composite ischemic events were identified in all the included 24 studies. As shown in Fig. 3, the pooled OR ratio of composite ischemic event was significantly lower for high potent $P2Y_{12}$ inhibitors than that for clopidogrel (OR = 0.93, 95 % CI, 0.89–0.96, $I^2 = 52$ %, $p < 0.001$). No obvious heterogeneity among all studies were observed.

11.2. Myocardial infarction

The rates of myocardial infraction (MI) after PCI in patients with ACS or CCS were identified in 22 of all 24 studies. As shown in Supplement-Fig. 1, the risk of MI was statistically lower for potent $P2Y_{12}$ inhibitors than that for clopidogrel (OR = 0.93, 95 % CI, 0.89–0.98, $I^2 = 63$ %, $p < 0.001$). No obvious heterogeneity among all studies were observed (Supplement-Fig. 1).

11.3. Stent thrombosis

The rates of stent thrombosis after PCI in patients with ACS or CCS were also identified in 20 of all 24 studies. Potent $P2Y_{12}$ inhibitors had a significantly decreased incidence of stent thrombosis than clopidogrel group (OR = 0.66, 95 % CI, 0.57–0.75, $I^2 = 44$ %, $p < 0.001$) (Supplement-Fig. 2). The heterogeneity among studies were low.

11.4. Cardiovascular death

The rates of CV death after PCI in patients with ACS or CCS were identified in 19 of all 24 studies. Potent $P2Y_{12}$ inhibitors had a decreased pooled odds ratio of CV death after PCI than clopidogrel group (OR = 0.82, 95 % CI, 0.75–0.89, $I^2 = 27$ %, $p < 0.001$) (Supplement Fig. 3). The heterogeneity among studies were extremely low.

11.5. All-cause death

All of the 24 researches investigated the incidence of all-cause death events in patients after PCI with ACS or CCS. High potent $P2Y_{12}$ inhibitors had a decreased incidence of all-cause death after PCI than clopidogrel group (OR = 0.90, 95 % CI, 0.84–0.96, $I^2 = 27$ %, $p = 0.002$) (Supplement Fig. 4). The heterogeneity among studies were low.

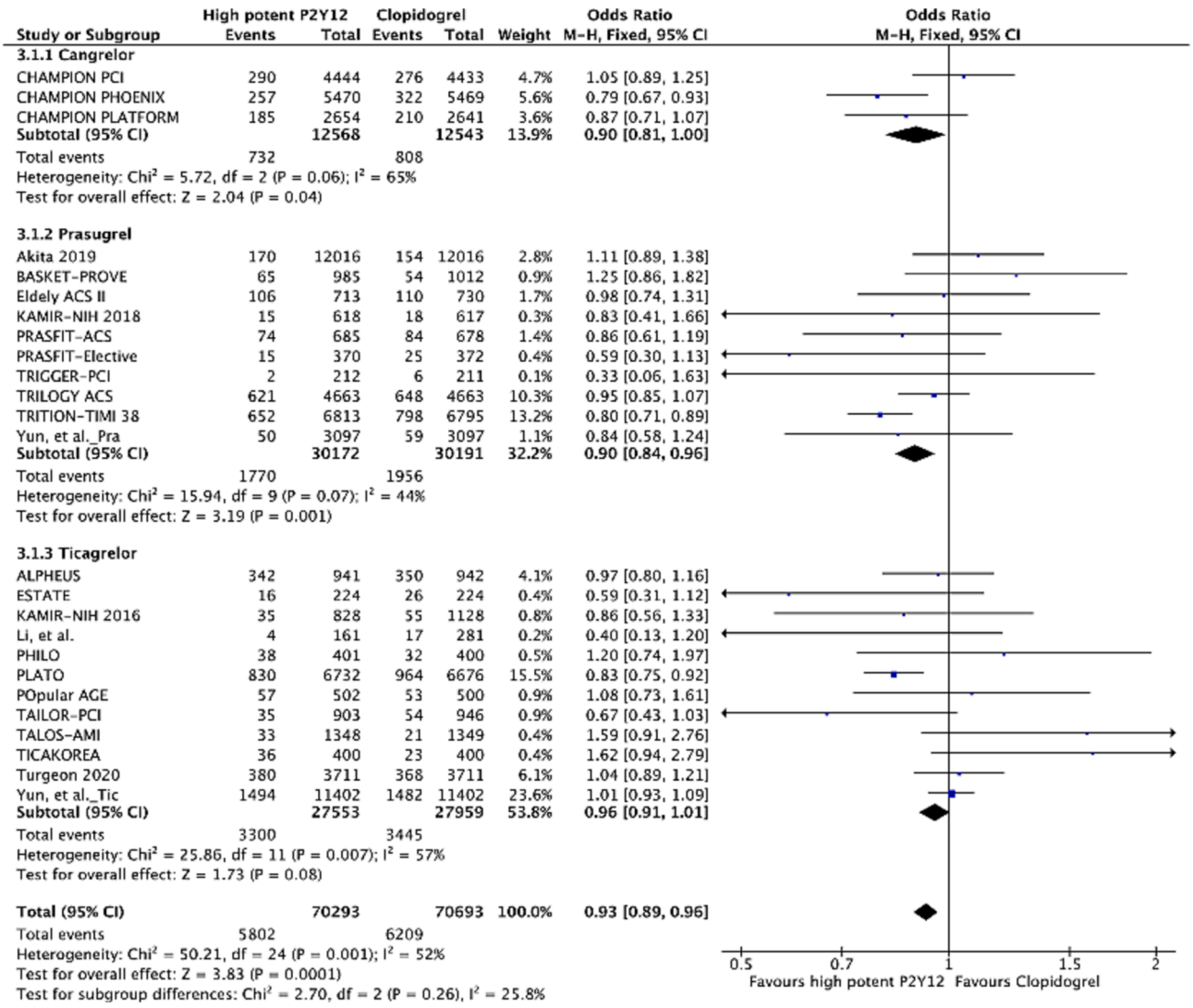

Fig. 3. Meta-analysis of the primary efficacy end point of composite thrombotic cardiovascular events.

11.6. Stroke

The rates of stroke after PCI in patients with ACS or CCS were identified in 20 of all 24 studies. The pooled odds ratio of stroke events had a trend toward reduction stroke. (OR = 0.88, 95 % CI, 0.79–0.99, I^2 = 0 %, p = 0.03) (Supplement Fig. 5). There was no heterogeneity among the 20 studies.

11.7. Primary Safety End Point of Major Bleeding

The primary safety end point of major bleeding was a composite of GUSTO severe [34], or ACUITY major [35], or TIMI major [36,37] and BARC 2,3,5 [37] and PLATO-defined major bleeding criteria [38]. The incidences of composite major bleeding events after PCI in patients with ACS or CCS were identified in 23 of all 24 articles. High potent $P2Y_{12}$ inhibitors significantly increased the risk of major bleeding compared with clopidogrel (OR = 1.24, 95 % CI, 1.15–1.33, I^2 = 50 %, $p < 0.001$) (Fig. 4).

11.8. Any Bleeding (Major and Minor Bleeding)

The safety endpoint of any bleeding includes major and minor bleeding. The same as major bleeding, the minor bleeding was a composite of GUSTO moderate/mild [34], ACUITY minor [35], TIMI minor [36,37], BARC 0,1 [37] or PLATO-defined minor bleeding criteria [38]. The incidences of any bleeding events after PCI in patients with ACS or CCS were also identified in 23 of all 24 articles. The risk of any bleeding was higher in newer P2Y12 inhibitors group compared with clopidogrel group (OR = 1.27, 95 % CI, 1.21–1.33, I^2 = 60 %, $p < 0.001$) (Fig. 5). Although possible heterogeneity between studies was found, no outliers were identified after sensitivity analysis.

11.9. Main Findings

To the best of our knowledge, this study represents the largest systemic analysis comparing the efficacy and safety of high potent P2Y12 inhibitors with clopidogrel in patients underwent coronary intervention, especially all coming patients were analysed after PSM cohort studies were involved, not only focus on RCTs. This *meta*-analysis provides evidence for the efficacy of the new P2Y12 inhibitor, cangrelor, prasugrel, and ticagrelor, relative to clopidogrel in reducing the incidence of adverse cardiovascular ischemic events in patients undergoing PCI. Total 24 studies with 140,986 patients were included in our analysis.

The highlight of the systemic review and *meta*-analysis is the summary of polled odds ratios and conference intervals of all potent P2Y12 inhibitors vs. clopidogrel, which documented the efficacy or a trend of reducing anti-thrombotic events and the safety concerns with higher bleeding risk, including major bleeding or any bleeding (Central

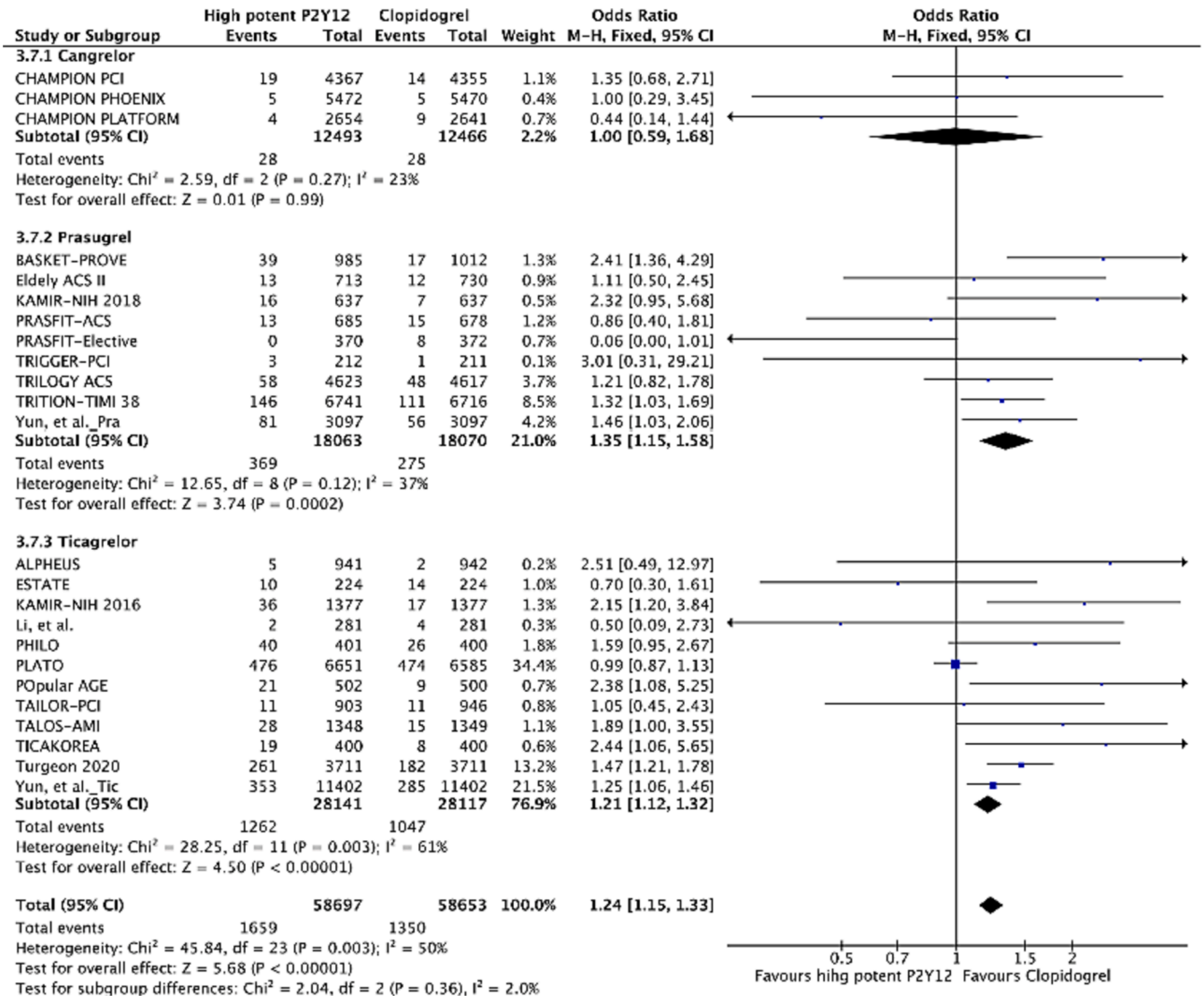

Fig. 4. Meta-analysis of the primary safety end point of major bleeding.

Illustration A).

The main findings can be summarized as follows:

(1) There was significant difference in the primary efficacy end point between patients taking potent P2Y12 inhibitors and clopidogrel. The pooled odds ratio of composite ischemic events in potent P2Y12 inhibitor groups compared with clopidogrel group was 0.93 (95 % CI: 0.89–0.96), indicating a reduced incidence of adverse composite ischemic events following potent P2Y12 inhibitor.

(2) The incidences of MI, stent thrombosis, CV death, all-cause and stroke were statistically decreased in potent P2Y12 inhibitor groups than in clopidogrel group, especially stent thrombosis (OR = 0.66, 95 % CI, 0.57–0.75, $I^2 = 44$ %, $p < 0.001$).

(3) High potent P2Y12 inhibitors were associated with a higher risk of any or major bleeding compared with clopidogrel group (Major bleeding: OR = 1.24, 95 % CI, 1.15–1.33; Any bleeding: OR = 1.27, 95 % CI, 1.21–1.33).

11.10. Clinical Significance

Clopidogrel has been a mainstay of antiplatelet therapy during PCI. However, there is recent concern for inadequate antiplatelet effect during PCI due to the delayed onset of antiplatelet activity following administration [39]. Its antiplatelet potency is closely related to the patient's CYP2C19 genotype and drug metabolism. Patients with slow metabolism (clopidogrel resistance), cardiovascular events such as death or early stent thrombosis may occur even if a preoperative high dose of clopidogrel is administered before PCI, and the risk of such events is high [40]. Clopidogrel resistance is reported to be high in Asians (>55 %), compared to that in Whites (30 %) and Blacks (40 %) [41]. Although the CYP2C19 genotype- or platelet function testing phenotype-directed individualization of $P2Y_{12}$ inhibitors seems to decrease high on-treatment platelet reactivity, but the clinical benefit and outcomes are still equivocal in the PoPular Genetics trial and TROPICAL ACS trial. (with significance in non-inferority and in-significance in superiority) [42–44]. However, the presence of clopidogrel resistance has driven the development and marketing of a new generation of antiplatelet agents, such as cangrelor, prasugrel, and ticagrelor. Compared with clopidogrel, the greatest advantage of cangrelor, ticagrelor, and prasugrel is that they have more effective antiplatelet action, faster inhibition of platelet aggregation, higher potency, more resistance to genotype variability, and fewer individual differences [39,45,46].

Cangrelor was the first intravenous and competitive P2Y12 inhibitor developed, with a reversible mode of action and a very short half-life of

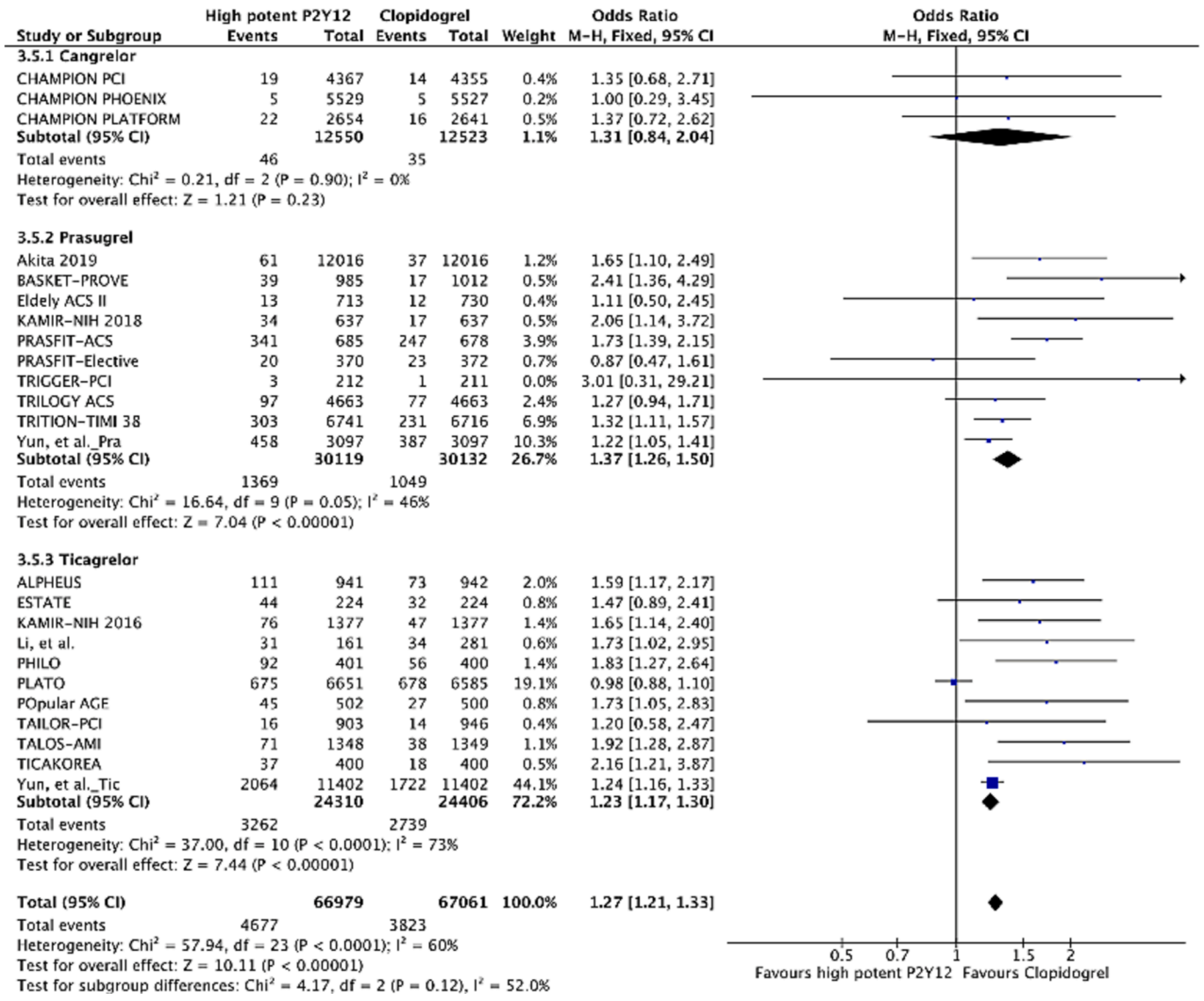

Fig. 5. Meta-analysis of the safety end point of any bleeding.

five minutes [14]. The intravenous administration may be both a benefit and a limitation. It allows for precise dosing and titration, but it requires medical personnel to administer it. The rapid onset and offset make it beneficial during PCI, its use in other clinical scenarios is relatively limited [14]. It is not commonly used for long-term antiplatelet therapy compared to other agents like clopidogrel, ticagrelor, or prasugrel.

Prasugrel, similar to clopidogrel, needs to be converted into its active metabolites to bind to the platelet P2Y12 receptor and produce an antiplatelet effect [47], but it exhibits minimal impact on the CYP2C19 gene [48,49], as it is associated with a more consistent and potent antiplatelet effect. Individuals with a CYP2C19 reduced-metabolizer genotype are estimated to have a substantial reduction in the risk of cardiovascular death, myocardial infarction, or stroke with prasugrel as compared with clopidogrel [48]. The pivotal TRITON-TIMI 38 trial showed that prasugrel significantly reduced the risk of recurrent cardiovascular events, including heart attacks, strokes, and cardiovascular death, and is associated with a higher risk of bleeding, including major bleeding, compared to clopidogrel [7]. Our *meta*-analysis reveals that prasugrel exhibits a superior composite antithrombotic effect compared to ticagrelor when compared to clopidogrel. These findings align with the results observed in the ISAR-REACT 5 trial [8]. In response to concerns about high bleeding risk, some countries such as Japan and Taiwan offer a reduced-dose prasugrel option (20 mg loading dose and 3.75 mg maintenance dose). The 2023 ESC Guidelines for the management of acute coronary syndromes suggest the following prasugrel dosing: 60 mg initial oral loading dose, followed by a 10 mg daily maintenance dose (MD). If the individual weighs less than 60 kg, consider a 5 mg daily MD. For patients 75 years or older, use caution and consider a 5 mg daily MD when necessary [50].

Ticagrelor is a new ADP receptor inhibitor, unlike other P2Y12 receptor inhibitors, it does not require in vivo activation, and its metabolites are also pharmacologically active, resulting in more rapid platelet inhibition [5]. The PLATO trial (comparing ticagrelor to clopidogrel) and the TRITON-TIMI 38 trial (comparing prasugrel to clopidogrel) were two landmark trials that evaluated the efficacy of these newer antiplatelet agents. Both ticagrelor and prasugrel were found to be similarly effective in preventing cardiovascular events, including myocardial infarction, compared to clopidogrel in their respective trials [7,38], and ticagrelor, as demonstrated in the PLATO trial, was associated with a lower risk of bleeding compared to prasugrel. However, in a recent direct comparison, the ISAR-REACT 5 trial, which pitted ticagrelor against prasugrel, showed that prasugrel carried a reduced bleeding risk when compared to ticagrelor [8]. Our *meta*-analysis indicates that both of the new oral antiplatelet medications exhibit

comparable anti-thrombotic effectiveness but come with a heightened risk of bleeding when contrasted with clopidogrel. As a result, the 2021 and 2023 ESC guidelines for ACS management do not endorse routine pre-treatment with these potent P2Y12 inhibitors in ACS patients [50].

In summary, our *meta*-analysis underscores the superior efficacy of potent P2Y12 inhibitors over clopidogrel in preventing thrombotic cardiovascular events among patients undergoing PCI. However, it also highlights the potential for an increased risk of major bleeding associated with the new generation of P2Y12 inhibitors. Therefore, the use of these potent P2Y12 inhibitors should be carefully considered by assessing an individual's bleeding and thrombotic risk following PCI. Future clinical studies, particularly well-designed, large-scale, multicenter randomized controlled trials, are needed to provide more definitive conclusions. These studies will play a pivotal role in guiding the safe and effective use of high-potency P2Y12 inhibitors as adjunctive therapy for patients undergoing PCI.

There are several limitations to this current *meta*-analysis. Firstly, this *meta*-analysis integrates a comprehensive dataset from 18 RCTs and 6 substantial cohort studies that employ propensity score matching. While these 24 studies display notable divergences in design—ranging from patient enrollment methods (RCT or RWE), blinding practices, choices of antiplatelet treatments, randomization timings, follow-up durations, to clinical outcome definitions—their populations largely align, and the main efficacy and safety outcomes are analogous. RCTs offer a structured environment, albeit with potential generalizability constraints. In contrast, cohort studies offer insights from real-world scenarios, but may be skewed by external factors. The use of propensity score matching in these cohort studies aims to reduce such biases. By amalgamating results from both study types, this *meta*-analysis seeks to provide a thorough assessment of treatment impacts across diverse research paradigms. Secondly, as is the case with any *meta*-analysis, there is the potential for publication bias, also referred to as the"file drawer problem", which cannot be entirely eliminated. Thirdly, variations in the definitions of clinical events, differences in treatment duration, diverse dosing regimens, the use of various types of coronary stents, and a lack of detailed patient characteristics, including baseline cardiovascular risk and therapy, all contribute to the heterogeneity observed in our analysis. Although random-effects pooling was employed to mitigate these disparities, it's worth noting that the heterogeneity in the analysis did not appear to be significant and did not impact the overall conclusions of the study. Of course, it should be emphasized that the field would greatly benefit from further large-scale clinical trials to ensure more precise and conclusive results in the future.

Our *meta*-analysis, encompassing data from 24 trials involving 140,986 patients, conducted a comprehensive examination comparing the efficacy and safety profiles of cangrelor, prasugrel, and ticagrelor against clopidogrel in PCI patients with ACS or CCS. The findings from this study offer compelling evidence in favor of the superior efficacy of potent P2Y12 inhibitors when compared to clopidogrel, notably in reducing the incidence of adverse cardiac thrombotic events. However, it's worth noting that these newer P2Y12 inhibitors were also associated with an increase risk of major bleeding compared to clopidogrel. As a result, the judicious selection of the appropriate P2Y12 inhibitor for dual antiplatelet therapy should be tailored to the individual patient's clinical characteristics, taking into account both ischemic and bleeding risk factors.

CRediT authorship contribution statement

Chien-Lung Huang: Conceptualization, Funding acquisition, Data curation, Writing – original draft, Visualization, Investigation, Validation, Formal analysis, Resources, Project administration. **Tien-Ping Tsao:** Writing – original draft, Writing – review & editing, Validation, Supervision, Project administration. **Wei-Hsian Yin:** Funding acquisition, Writing – review & editing, Validation, Supervision. **Wen-Bin Huang:** Writing – review & editing, Validation. **Hsu-Lung Jen:** Writing – review & editing, Validation. **Chang-Chyi Lin:** Writing – review & editing, Validation, Supervision. **Chung-Yi Chang:** Validation. **Ching-Hwa Hsu:** Conceptualization, Funding acquisition, Data curation, Writing – original draft, Visualization, Investigation, Formal analysis, Methodology, Resources, Project administration, Software.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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