Systematic Review with Meta-analysis: The Risk of Gastrointestinal Bleeding in Patients Taking Third-Generation P2Y12 Inhibitors Compared with Clopidogrel

Running title: GIB risk of prasugrel or ticagrelor

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Summary

Background: Ticagrelor and prasugrel are two third-generation oral $P2Y_{12}$ receptor antagonists with rapid onset and pronounced platelet inhibition. However, higher overall bleeding rates have been reported for these agents when compared with clopidogrel.

Aims: To compare the risk of gastrointestinal bleeding (GIB) among users of third-generation $P2Y_{12}$ inhibitors with clopidogrel.

Methods: We systematically searched published randomized control trials of ticagrelor or prasugrel versus clopidogrel until September 2018. The primary outcome was the risk of GIB among users of third-generation $P2Y_{12}$ inhibitors when compared to clopidogrel, expressed as risk ratio (RR) and 95% confidence interval (CI). The rates of non-coronary artery bypass graft (CABG) major bleeding, life-threatening bleeding, fatal bleeding, and intracranial bleeding were analyzed as secondary outcomes.

Results: Forty-one studies were included in the analysis of non-CABG major bleeding, of which twelve studies were included in the analysis of GIB including 58,678 patients. Third-generation P2Y12 inhibitors were associated with higher risk of GIB as compared with clopidogrel (RR 1.28, 95% CI 1.13-1.46). The findings were consistent for upper (RR 1.32, 95% CI 1.05-1.67)) and unspecified GIB (RR 1.25, 95% CI 1.01-1.53)), but not lower GIB (RR 1.25, 95% CI 0.95-1.65). Subgroup analysis showed higher GIB risk in prasugrel studies (RR 1.40, 95% CI 1.10-1.77) than in ticagrelor studies (RR 1.15, 95% CI 0.94-1.39). Third-generation $P2Y_{12}$ inhibitors also increased the risk of non-CABG major bleeding (RR 1.18, 95% CI 1.08-1.28).

Conclusion: Third-generation P2Y12 inhibitors were associated with increased risk of GIB and non-CABG major bleeding when compared with clopidogrel.

Key words: ticagrelor, prasugrel, gastrointestinal bleeding, meta-analysis

Introduction

Dual-antiplatelet treatment with aspirin and clopidogrel is the usual primary therapy for patients with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention.[1,2] However, the delayed onset and the modest antiplatelet effect are important limitations of clopidogrel. Additionally, platelet responses after clopidogrel are variable due to potential drug interactions which could be associated with adverse clinical outcomes.[3] Ticagrelor and prasugrel are two third-generation oral inhibitors of the adenosine diphosphate receptor $P2Y_{12}$ that inhibit platelets more rapidly and consistently than clopidogrel.[4,5] The superiority of third-generation $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) over clopidogrel in preventing ischemic vascular events have been confirmed in patients with acute coronary syndromes, stable coronary artery disease or peripheral artery disease both in clinical trials as well as in recent meta-analyses.[6-11] Moreover, ticagrelor and prasugrel have demonstrated more effective platelet inhibition in patients with high on-treatment platelet reactivity as compared with clopidogrel.[12,13]

On the other hand, there are data suggesting that the third-generation oral $P2Y_{12}$ inhibitors are associated with a higher risk of non-CABG (coronary artery bypass graft) related major bleeding[7,9-11]. Of which, gastrointestinal tract was the most common source. In the PLATO trial, ticagrelor was observed to have a higher rate of non-CABG-related bleeding, although it was not significant for overall major bleeding.[7,14] Prasugrel was also found to be associated with a significant increase of TIMI (Thrombolysis In Myocardial Infarction) major bleeding in the TRITON-TIMI 38 study (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction).[9] In contrast, higher bleeding risk was not observed in other studies [8,15,16] and the results remained conflicting in the literature.

Thus far, there is no study that focused on gastrointestinal bleeding (GIB) related to use of the third-generation oral $P2Y_{12}$ inhibitors as the primary outcome. Herein, we performed a meta-analysis of randomized control trials (RCTs) to determine the risk of GIB of the third-generation $P2Y_{12}$ inhibitors (ticagrelor or prasugrel) as compared with clopidogrel. We also evaluated the risk of major GIB, all-cause non-CABG major

bleeding, life-threatening bleeding, fatal bleeding or intracranial bleeding of these agents as the secondary outcomes.

METHODS

Search strategy and study selection

This meta-analysis was reported according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses).[17] We systematically searched PubMed, Cochrane library, ClinicalTrials.gov and Web of Science to identify RCTs comparing the safety of ticagrelor or prasugrel with clopidogrel published until September 2018. The following terms were used for the retrieval: prasugrel or Cs-747 or Ly640315 or Ticagrelor or Azd6140; and randomized controlled trial or random* or controlled clinical trial; and bleeding or bleed* or hemorrhag* or haemorrhag*. After the initial search, titles and abstracts were reviewed to exclude irrelevant citations, and then full-text assessments were performed. Reference lists of the relevant studies, reviews and meta-analyses were also checked manually to avoid missing related references.

Studies were included according to the following criteria: 1) RCTs; 2) comparing ticagrelor or prasugrel with clopidogrel; 3) bleeding was one of the outcomes; 4) published in English; and 5) with full text available. Studies which met the following criteria were excluded: 1) original data were incomplete including number of patients or events in any intervention arm; 2) bleeding definition or severity of bleeding events were not specified; 3) studies drugs were accompanied by anticoagulants; 4) including non-human subjects or healthy subjects only; 5) studies included patients with sickle cell anemia or chronic renal disease only; 6) subgroup analysis or reanalysis of previous RCTs. Selection was performed by two reviewers independently and discrepancies were resolved by discussion.

Data extraction and quality assessment

Data of the included studies including year of publication, country, indications for antiplatelet agents, doses of antiplatelet agents, duration of therapy, follow-up duration, number of patients, definition of bleeding, number of patients who developed bleeding and severity of bleeding were extracted by two authors independently. As GIB data was not available in most published papers, we checked the results of published or unpublished studies posted in ClinicalTrials.gov, in which GIB events were reported as

serious adverse events or other adverse events. All randomized patients, or patients who received at least one dose of study drug if it was specified in the study, were included in the meta-analysis. If the data of bleeding outcomes were incomplete, authors would be contacted for more information. The Cochrane Collaboration's tool was used to assess the risk of bias in included studies.[18]

Outcome measures

The primary outcome was the risk of GIB associated with third-generation oral $P2Y_{12}$ inhibitors when compared with clopidogrel, in which all reported GIB were included. Secondary outcomes included major GIB, all-cause non-CABG major bleeding, life-threatening bleeding, fatal bleeding, and intracranial bleeding.

We adopted the PLATO definition of major bleeding events that occurred in the gastrointestinal tract as major GIB, including life-threatening bleeding, bleeding that caused significant disability, and associated drop in hemoglobin of 3 to 5 g/dl or requiring transfusion of two or more units of whole blood or pack red blood cells.[7,19] All-cause non-CABG major bleeding was any bleeding events that met the major bleeding definition but not met CABG-related bleeding definition, which was defined as perioperative intracranial bleeding within 48 hours of the CABG surgery, reoperation after closure of sternotomy for the purpose of controlling bleeding, transfusion of ≥5 U whole blood or pack red blood cells within 48-hour period, or chest tube output ≥2L within a 24-hour period. Life-threatening bleeding included fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, bleeding that caused hypovolemic shock or severe hypotension, bleeding associated with decrease in hemoglobin > 5 g/dl, and bleeding requiring transfusion of ≥4 U whole blood or packed red blood cells. Fatal bleeding was defined as bleeding that directly resulted in death. The severity of bleeding based on other bleeding definitions in the original RCTs such as TIMI definition, Bleeding Academic Research Consortium (BARC) definition, or study defined definitions, were transferred into that of the PLATO definition accordingly.[19] For example, both TIMI major and minor bleeding, and BARC type 3-5 were regarded as PLATO major bleeding. TIMI bleeding requiring medical attention and BARC type 2 bleeding were regarded as PLATO minor bleeding.

Statistical methods

Pooled estimates of the bleeding risk of third-generation oral $P2Y_{12}$ inhibitors were calculated with risk ratios (RRs) for major GIB, all non-CABG major bleeding, life-threatening bleeding, fatal bleeding and intracranial bleeding. Pooled RRs were estimated using random effects model, and fixed effects model was also performed as sensitivity analysis. The presence of heterogeneity among studies was tested using chi-square test. Heterogeneity with *P* value <0.1 would be regarded as significant. The I^2 statistic was calculated to measure the proportion of total variation in study estimates which was due to heterogeneity.[20] The I^2 values of less than 25%, 25-75%, and over 75% indicated low, moderate, and high heterogeneity, respectively. Funnel plots were plotted to search for potential publication bias, of which symmetric funnel indicates no publication bias.[21] To test the symmetry of funnel plot, the Begg's rank correlation test and the Egger's linear regression test were performed.[22,23]

Subgroup analyses were performed on individual drug (ticagrelor or prasugrel), studies with duration of therapy more than one month, studies involving Asian subjects, and studies with standard dosage of ticagrelor (loading dose of 180mg once and maintenance does of 90mg twice per day) or prasugrel (loading dose of 60mg once and maintenance does of 10mg once per day). Subcategory analyses of GIB locations into upper, lower or unspecified GIB were also performed. In addition, subgroups involving low-risk patients, <75 years old or body weight ≥60 kg, as defined in TRITON-TIMI 38, or data of these patients reported separately, were analyzed as sensitivity analysis for all-cause major bleeding. TIMI major bleeding was also evaluated as another sensitivity analysis with studies using TIMI as the bleeding classification. The sensitivity analysis was also performed after excluding studies with high risk of bias. All statistical analyses were performed using R software, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria, 2017).[24]

RESULTS

Included studies and study quality

After initial search in PubMed, Cochrane library and Web of Science, 1,649 citations were included after excluding duplicated citations. By screening the titles and abstract, 1,566 citations were excluded. A total of 80 potential eligible studies were then

reviewed for full-text evaluations, of which 39 articles were excluded because they did not meet the inclusion criteria (**Supplementary Table 1**). Finally, 41 RCTs were included in the meta-analysis with 23 trials comparing ticagrelor with clopidogrel[6-8,13,25-43] and 18 trials comparing prasugrel with clopidogrel[9,12,15,44-58], in which bleeding data from ClinicalTials.gov was used for the study of Ge 2010[48]. The selection steps and specific excluding reasons were shown in **Figure 1**. Twelve studies were included in the analyses of GIB, in which the GIB data of TRITON-TIMI 38 study was from a post hoc analysis[59], and GIB data was available for 5 studies in ClinicalTials.gov[7,8,12,15,48]. In all-cause major bleeding analysis, all 41 studies were included with a total of 69,727 patients who were randomized to receive third-generation oral $P2Y_{12}$ inhibitors or clopidogrel. The characteristics of the included RCTs were presented in **Table 1** and **Table 2**. PLATO, TIMI and BARC were the main bleeding definitions in the included trials.

Studies were evaluated using the Cochrane Risk Bias tool and the bias risk of each study was present in **Supplementary Table 2**. High risk bias was present in a few trials, but selection bias was unclear in most studies as the generation of random sequence and allocation concealment were not reported. Other biases were low in most studies.

Gastrointestinal bleeding risk of third-generation P2Y12 inhibitors

In the analysis of GIB, seven ticagrelor[7,8,29,35,36,39,42] and five prasugrel studies[9,12,15,48,52] were included with a total of 58,678 patients (ticagrelor 17,329 vs clopidogrel 16,798; prasugrel 12,407 vs clopidogrel 12,144). GIB occurred in 541 (1.8%) patients treated with third-generation $P2Y_{12}$ inhibitors and 411 (1.4%) patients with clopidogrel. Among these GIB, 81.9% (780/952) were reported as PLATO major GIB or serious adverse event. Overall, higher risk of GIB was found with the third generation $P2Y_{12}$ inhibitors than clopidogrel (RR 1.28, 95% CI 1.13-1.46; **Figure 2**). Similar result was also observed in analyses including studies with follow-up duration over one month (RR 1.28, 95% CI 1.13-1.46) and studies with standard dosage (RR 1.27, 95% CI 1.05-1.54). The elevated risk of GIB was significant in prasugrel studies (RR 1.40, 95% CI 1.10-1.77), but not in ticagrelor studies (RR 1.15, 95% CI 0.94-1.39). In subcategory analysis of GIB location, third generation P2Y12 inhibitors were associated with higher

risk of upper GIB (RR 1.32, 95% CI 1.05-1.67) and unspecified GIB (RR 1.25, 95% CI 1.01-1.53), but not lower GIB (RR 1.25, 95% CI 0.95-1.65). In studies involving Asian patients, no difference was found between the third generation $P2Y_{12}$ inhibitors and clopidogrel (RR 1.06, 95% CI 0.40-2.78). Low to moderate heterogeneity was observed in these analyses (**Table 3**).

Six studies were included in the analysis of major GIB[9,29,35,36,39,52], which involved 15,943 patients. Major GIB occurred in 127 (1.5%) patients treated with third-generation $P2Y_{12}$ inhibitors and 94 (1.2%) patients with clopidogrel (RR 1.28, 95% CI 0.98-1.67). Subgroup analyses of individual drug showed similar results (ticagrelor RR 1.16, 95% CI 0.40-3.35; prasugrel RR 1.19, 95% CI 0.65-2.15). No significant difference in risk of major GIB was also observed in analyses including studies with follow-up duration over 1 month (RR 1.28, 95% CI 0.98-1.68) and studies involving Asian users (RR 0.71, 95% CI 0.07-6.74).

Other bleeding risks

For all-cause major bleeding, analysis of all 41 RCTs showed that major bleeding occurred in 3.3% (1,190/35,660) of patients in the third-generation $P2Y_{12}$ inhibitors group and 2.9% (967/34,067) in the clopidogrel group (ticagrelor 3.4% [697/20,374] vs clopidogrel 2.9% [580/19,688]; prasugrel 3.2% [493/15,286] vs clopidogrel 2.7% [387/14,379]). The risk of major bleeding was higher in third-generation $P2Y_{12}$ inhibitors when compared to clopidogrel (RR 1.18, 95% CI 1.08-1.28; **Figure 3**). Subgroup analyses of individual drug also showed higher risk of major bleeding associated with ticagrelor (RR 1.15, 95% CI 1.03-1.28) and prasugrel (RR 1.23, 95% CI 1.08-1.40). Similar result was observed in studies with duration of therapy more than one month and studies with standard dosage (**Table 3**). However, increased bleeding risk was not found in Asian users of third-generation $P2Y_{12}$ inhibitors as compared with clopidogrel (RR 1.08, 95% CI 0.84-1.39). In low-risk patients, third-generation $P2Y_{12}$ inhibitors still increased the risk of non-CABG major bleeding (RR 1.26, 95% CI 1.02-1.55). In the analysis of TIMI major bleeding, increased risk was also observed for third-generation $P2Y_{12}$ inhibitors (RR 1.17, 95% CI 1.04-1.32). The result was

consistent in analysis after excluding studies with high risk of bias (RR 1.19, 95% CI 1.09-1.29).

Thirteen studies[7-9,12,15,25,29,39,44,48,52,54,55] were included in the analysis of life-threatening bleeding, in which no significant difference was observed in life-threatening bleeding between third-generation $P2Y_{12}$ inhibitors and clopidogrel (RR 1.06, 95% CI 0.94-1.20). Similarly, the results were not significant in the analysis of fatal bleeding or intracranial bleeding (**Table 3)**.

Publication bias

Publication biases were neither detected in the analysis of GIB including 12 studies (*P* value for Begg's test: 0.493; *P* value for Egger's test: 0.188; **Supplementary Figure 1**), nor all-cause major bleeding of all 41 studies (*P* value for Begg's test: 0.243; *P* value for Egger's test: 0.116; **Supplementary Figure 2**).

DISCUSSION

While GIB is one of the common sources of major bleedings in patients using antiplatelet drug,[14] antiplatelet drug is also an important risk factors of GIB.[60] In this meta-analysis, we determined the risk of GIB in patients using third-generation $P2Y_{12}$ inhibitors and found that the risk of GIB was increased (RR 1.28, 95% CI 1.13-1.46) when compared to clopidogrel. Subgroup analysis of bleeding locations showed that third generation P2Y12 inhibitors were associated with higher risk of upper GIB (RR 1.32, 95% CI 1.05-1.67) and unspecified GIB (RR 1.25, 95% CI 1.01-1.53).

Gastrointestinal tract was the most common site of major bleeding of ticagrelor or prasugrel in the PLATO and TRITON-TIMI 38 studies.[14,59] However, data on GIB were only reported in 12 of the 41 RCTs which compared the efficacy and safety of ticagrelor or prasugrel versus clopidogrel, in which data on GIB were actually extracted from the ClinicalTrials.gov in 5 of them and separate data of major GIB was only available in 6 studies. In this meta-analysis, we found that the elevated risk of GIB was significant in prasugrel studies (RR 1.40, 95% CI 1.10-1.77), but not in ticagrelor studies (RR 1.15, 95% CI 0.94-1.39). On the other hand, ticagrelor appears to have a higher risk of gastrointestinal diseases, including overall gastrointestinal or anal bleeding and

spontaneous GIB events, nausea, vomiting, dyspepsia and diarrhea, according to Food and Drug Administration (FDA) secondary reviews of ticagrelor.[61] In contrast to the comprehensive FDA safety review of ticagrelor, there are few data on the gastrointestinal adverse events of prasugrel, and it was unquestionable that prasugrel increased the risk of GIB.[61] However, most of the previous conclusions were based on the data from PLATO and TRITON-TIMI 38 studies. The current meta-analysis of RCTs would add more updated evidences of the risk of GIB of the third-generation $P2Y_{12}$ inhibitors.

When compared to the limited data on GIB, more studies were available for the analysis of all-cause non-CABG major bleeding, in which higher risk of non-CABG major bleeding was found in patients taking third-generation $P2Y_{12}$ inhibitors. In addition to RCTs, the elevated bleeding risk of third-generation $P2Y_{12}$ inhibitors was also observed in the real-world setting where there were no stringent inclusion or exclusion criteria for the use of $P2Y_{12}$ inhibitors. A prospective cohort study including 45,073 ACS patients from the SWEDEHEART (Swedish Web system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies) registry showed that ticagrelor increased the risk of re-admission with bleeding (adjusted hazard ratio [HR] 1.20, 95% CI 1.04-1.40) as compared with clopidogrel.[62] Similarly, prasugrel was also associated with a higher risk of bleeding (odds ratio [OR] 1.47, 95%CI 1.06-2.02) in a propensity score matching analysis of the Swiss national ACS registry involving 7,621 patients.[63] However, increased risk of bleeding among third-generation oral $P2Y_{12}$ inhibitors users when compared with clopidogrel was not found in other studies.[64-66] In addition, a meta-analysis of RCTs found that switching to ticagrelor was associated with similar bleeding and ischemic outcomes as compared to continuation of clopidogrel.[67]

Considering the relative higher bleeding risk in patients ≥75 years old and/or <60 kg body weight, or patients with prior transient ischemic attack or stroke, reduced dose of prasugrel were recommended. In this setting, increased bleeding rate with reduced dose prasugrel was not observed.[68-70] Nonetheless, in a Korean study, in which high-risk patients mentioned above were excluded, prasugrel was still associated with a significantly higher risk of in-hospital TIMI major or minor bleeding (OR 2.02, 95%

CI 1.10-3.71).[71] Our finding in low-risk patients (<75 years old or body weight ≥60 kg) was therefore consistent with this study that third-generation $P2Y_{12}$ inhibitors still increased the risk of non-CABG major bleeding in low-risk patients (RR 1.26, 95% CI 1.02-1.55).

Although it is generally believed that the risk of bleeding might be increased in Asian patients using antiplatelet or antithrombotic drugs, this meta-analysis showed that the third-generation $P2Y_{12}$ inhibitors did not increase the bleeding risk as compared to clopidogrel in Asian users for both GIB and all-cause non-CABG major bleeding. This is different from a meta-analysis of ticagrelor, which found that ticagrelor was associated with a higher risk of major bleeding in East Asian patients with ACS,[72] but only 3 RCTs were included in this study. An analysis of the National inpatient sample database of the USA showed that Asian ethnicity was an independent predictor for major bleeding in patients with ST-segment elevation myocardial infarction (STEMI).[73] However, study also reported that patients in East Asian countries have a lower rate of in-hospital bleeding than European patients taking new P2Y12 inhibitors agents (4% vs. 8%, $P < 0.001$), but no difference was found at 1 year.[74] In a retrospective analysis of PLATO, there was no significant difference in the risk of major bleeding between ticagrelor and clopidogrel users as well as between Asians and non-Asians.[75] Therefore, further studies evaluating the bleeding risk of third-generation $P2Y_{12}$ inhibitors in Asian patients may be warranted.

In this meta-analysis, prasugrel was found to increase the risk of fatal bleeding in fixed effects model (RR 2.03, 95% CI 1.10-3.72), mainly because of the findings in the TRITON-TIMI 38 study with more fatal bleeding occurred in patients treated with prasugrel (0.4% vs. 0.1%, HR 4.19, 95% CI 1.58-11.11).[9] However, it was not significant (RR 1.92, 95% CI 0.69-5.56) in random effects model. Intracranial bleeding was the most common site of fatal bleeding in the PLATO study.[7,14] In both the PLATO and TRITON-TIMI 38 studies, more intracranial bleedings were observed for third-generation $P2Y_{12}$ inhibitors, though it was not significant when compared to clopidogrel, which was consistent with the current analysis.

Although there are higher risks of GIB and non-CABG major bleeding with third-generation $P2Y_{12}$ inhibitors than clopidogrel, use of third-generation $P2Y_{12}$ inhibitors were associated with significantly reduction in the mortality risk and major adverse cardiac events as compared with clopidogrel in patients with ACS as shown in previous RCTs and meta-analysis.[7,9,10,76] A meta-analysis including 9 RCTs also showed that the effect of prasugrel in decreasing the risk of major adverse cardiac events outweighed the increased risk of bleeding.[77] Therefore, the bleeding risk and cardiovascular benefits should be carefully balanced when using third-generation $P2Y_{12}$ inhibitors.

This study has several limitations. Firstly, although GIB was the main outcome in our study, the data on GIB was under-reported when compared to reports of all major non-CABG bleeding. Secondly, the bleeding definitions varied in different studies. When we converted other definitions to PLATO, bias could be introduced as the transformation may be inaccurate without the original data of bleeding events. Thirdly, the doses of third-generation $P2Y_{12}$ inhibitors varied among the included studies and the dosage was an important factor of bleeding, which may increase the variance of the studies. As yet, we have performed sensitivity analysis with the lower dose treatment as well as the low risk group. Fourthly, the indications of third-generation $P2Y_{12}$ inhibitors in the included RCTs were not uniform and the bleeding risk may be different in the patients with different indications, which would affect the stability of the results.

In conclusion, third-generation $P2Y_{12}$ inhibitors were associated with a significantly higher risk of GIB when compared with clopidogrel. Subgroup analysis showed that the bleeding risk was significantly increased for upper GIB as well as unspecified GIB. In addition to GIB, third-generation $P2Y_{12}$ inhibitors also increased the risk of non-CABG major bleeding. In low-risk patients (<75 years old or body weight ≥60 kg), third-generation P2Y12 inhibitors still increased the risk of non-CABG major bleeding.

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Author contributions: WKL and CGG designed the research study and wrote the manuscript. CGG and LC collected the data; CGG analyzed the data. EWC, KSC, TI and IW assisted in data interpretation and provided critical review of the manuscript. All authors have approved the final version of the manuscript.

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Table 1 Characteristics of included studies of ticagrelor

Study (year)	Country or area	Indications	ITT subjects‡	Range of age	Intervention, LD (mg, once) /MD (mg, BID)	Clopidogrel, LD (mg, once) /MD (mg, QD)	Exposure duration (median)	Follow-up duration (median)	Bleeding definition
Husted (2006)[36]	Denmark, Hungary and Norway	CAD or artery diseases	201	25-85	-/50-400	-/75	28 d	28 d	Study-defined
DISPERSE-2 (2007)[29]	14 countries	NSTE-ACS	990 (984)	≥18	-/90-180	300/75	4-12 w (56 d)	12 w	Study-defined
PLATO (2009)[7]	43 countries	ACS	18624 (18421)	≥18	180/90	300-600/75	12 m (277 d)	12 m	PLATO, TIMI
Onset/offset (2009)[6]†	USA, UK	Stable CAD	111	≥18	180/90	600/75	6 w	52 d	PLATO
Bonello (2014)[27]	France	NSTE-ACS	60	-	180/90	600/75	-	1 m	TIMI
Hiasa (2014)[35]	Japan, Philippine	PCI or ACS	139	20-80	-/45-90	-/75	28 d	8 w	PLATO
TRIPLETE-RESET (2015)[13]†	Italy	PCI and HTPR	54	18-75	-/90	-/150	30 d	6m	BARC
PHILO (2015)[32]	Japan, South Korea and Taiwan	ACS	801 (767)	-	180/90	600/75	6-12 m (236 vs 244 d)	12 m	PLATO
Li (2015)[37]	China	AMI or coronary artery in-stent restenosis and HTPR	48	20-80	180/90	-/150	-	6 m (138 d¶)	TIMI
Bonello (2015)[26]	France	NSTE-ACS undergoing PCI	106	≥18	180/90	600/75	-	1 m	BARC
Tang (2016)[39]	China	STEMI undergoing PCI	420	>18	180/90	600/75	12 m	6 m	TIMI
Wang (2016)[40]	China	ACS	200	≥65	180/90	300/75	12 m	12 m	PLATO
Zhang (2016)[43]	China	ACS undergoing PCI with *CYP2C19*2* or **3*	181	≥18	180/90	600/75-150	6 m	6 m	PLATO
Xue (2016)[41]	China	NSTE-ACS	75	18-75	90-180/45-90	300/75	5 d	5 d	PLATO
He (2016)[34]*	China	Stable CAD	30	18-75	-/22.5	-/75	7 d	21 d	Study-defined
Gu (2017)[33]	China	NSTE-ACS	74	-	180/90	600/150	-	3 m	TIMI
Yao (2017)[42]	China	AMI undergoing PCI	120	47-72	180/90	600/75	-	6 m	BARC
Choi (2017)[30]	South Korea	In maintenance phase of DAPT after PCI	69	-	-/90§	-/75	28 d	28 d	TIMI
Dehghani (2017)[31]	Canada	STEMI undergoing PCI	144	≥18	180/90	300/75	-	30 d	BARC
EUCLID (2017)[8]	28 countries	Peripheral artery disease	13885	≥50	-/90	-/75	-	30 d	TIMI
NATHAN-NEVER (2017)[28]	Italy	Stable CAD with chronic obstructive pulmonary disease	43	≥18	180/90	600/75	6 m	1 m	BARC

TREAT (2018)[25]	10 countries	STEMI with fibrinolytic therapy	3799 (3788)	≤75	180/90	300-600/75	-	30 d	PLATO, TIMI, BARC
STEEL-PCI (2018)[38]	UK	Stable CAD	180	≥18	180/60-90	600/75	30 d	30 d	PLATO

† Two out of three groups were included; ‡ The number in the brackets is the number of subjects that received at least 1 dose of the assigned study medication; § Switching from clopidogrel; ¶ Mean; * Only the first phase of the crossover study was included.

ITT, intention-to-treat; LD, loading dose; MD, maintenance does; CAD, coronary artery disease; NSTE-ACS, non-ST-elevated acute coronary syndromes, ACS, acute coronary syndromes; PCI, percutaneous coronary intervention; HPR, high platelet reactivity; HTPR, high on-treatment platelet reactivity; STEMI, ST-elevated myocardial infarction; AMI, acute myocardial infarction; DAPT, dual antiplatelet therapy; PLATO, Platelet Inhibition and Patient Outcomes classification; TIMI, Thrombolysis In Myocardial Infarction classification; BARC, Bleeding Academic Research Consortium classification; BID, twice daily; m, months; w, weeks; d, days.

Table 2 Characteristics of included studies of prasugrel

Study (year)	Country or area	Indications	ITT subjects†	Range of age	Intervention, LD (mg, once)/MD (mg, QD)	Clopidogrel, LD (mg, once)/MD (mg, QD)	Exposure duration (median)	Follow-up duration (median)	Bleeding definition
JUMBO-TIMI 26 (2005)[44]	Canada and USA	Elective or urgent PCI	905 (904)	≤75	40-60/7.5-15	300/75	1 m	1 m	TIMI
Jernberg (2006)[45]	Sweden and USA	CAD	101	≤75	40-60/5-15	300/75	1 m	7-14 d after the last dose	Study-defined
TRITON-TIMI 38 (2007)[9]	30 countries	ACS	13,608 (13457)	≥18	60/10	300/75	6-15 (14.5) m	6-15 m	TIMI
PRINCIPLE-TIMI 44 (2007)[46]‡	4 countries	Angina undergo PCI	201	40-75	60/10	600/150	14 d	14 d	TIMI
Wallentin (2008)[47]	Sweden	Stable ACS	110	<75	60/10	600/75	28 d	1 m (29 d)	Study-defined
Ge (2010)[48]	4 countries or areas	ACS	720 (692)	≥18	30-60/5-10	300/75	90 d	90 d	TIMI
TRILOGY-ACS (2012)[15]	52 countries	Unstable angina or NSTEMI without revascularization	9326 (9240)	≥18	30/5-10	300/75	6-30 (14.8) m	6-30 (17.1) m	TIMI
TRIGGER-PCI (2012)[12]	Germany and USA	Stable CAD undergoing PCI with HTPR	423 (420)	18-80	60/10	600/75	-	3 or 6 m	TIMI
Yokoi (2012)[49]	Japan	CAD undergoing elective PCI	84	20-74	10-20/2.5-5	300/75	29 d	14 d after the last dose	Study-defined
Bonello (2013)[50]	France	ACS undergoing PCI	177	<50	60/10	600/75,150	-	1 m	TIMI
TAILOR (2014)[51]	Denmark	ACS scheduled for PCI with HTPR	106	>18	MD 10¶	600/150	1 m	1 m	BARC
Jin (2014)[53]	South Korea	In the maintenance phase of DAPT after PCI	68	18-74	-/5-10	-/75	1 m	1 m	TIMI
PRASFIT-ACS (2014)[54]	Japan	ACS undergoing PCI	1385 (1363)	≥20	20/3.75	300/75	24-48 w (213.5 vs 207.5 d §)	14 d after the last dose	TIMI
PRASFIT-Elective (2014)[52]	Japan	ACS undergoing PCI	751 (742)	≥20	20/3.75	300/75	24-48 w	14 d after the last dose	TIMI
Kimura (2015)[55]	Japan	Elective PCI	422 (421)	20-84	20/2.5-5	300/75	12 w	14 w	TIMI
ETAMI (2015)[56]	Germany	STEMI scheduled for PCI	62	≤70	60/10	600/75	-	1 m	TIMI
PRAISE (2016)[57]	South Korea	NSTEMI scheduled for PCI	76	20-80	20/5	300/75	30 d	30 d	TIMI
Elderly ACS 2 (2018)[58]	Italy	ACS undergoing PCI	1455 (1443)	>74	60/5	300-600/75	-	12 (12.1) m	BARC

† The number in the brackets is the number of subjects that received at least 1 dose of the assigned study medication; ‡ Only the first phase of the crossover study was included; ¶ 600 clopidogrel was administered as the loading does; § Mean

ITT, intention-to-treat; LD, loading dose; MD, maintenance does; CAD, coronary artery disease; NSTE-ACS, non-ST-elevated acute coronary syndromes, ACS, acute coronary syndromes; PCI, percutaneous coronary intervention; HTPR, high on-treatment platelet reactivity; STEMI, ST-elevated myocardial infarction; AMI, acute myocardial infarction; DAPT, dual antiplatelet therapy; NSTEMI, non-ST-elevated myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction classification; BARC, Bleeding Academic Research Consortium classification; QD, once daily; m, months; w, weeks; d, days.

Table 3 Primary and Secondary Outcomes

	Analyses	No. of studies	Patients	RR (95% CI)†	I^2, %	*P*-value for heterogeneity*	*P*-value for Begg's test	*P*-value for Egger's test
All GIB	Combined	12	58,678	1.28 (1.13-1.46)	0	0.513	0.493	0.188
	Ticagrelor	7	34,127	1.15 (0.94-1.39)	0	0.796	-	-
	Prasugrel	5	24,551	1.40 (1.10-1.77)	19	0.290	-	-
Duration ≥1 month	Combined	11	58,477	1.28 (1.13-1.46)	0	0.437	0.484	0.335
	Ticagrelor	6	33,926	1.15 (0.94-1.40)	0	0.702	-	-
	Prasugrel	5	24,551	1.40 (1.10-1.77)	19	0.287	-	-
Asian subgroup	Combined	4	1,371	1.06 (0.40-2.78)	0	0.742	-	-
	Ticagrelor	3	724	0.55 (0.09-3.46)	0	0.754	-	-
Standard dosage‡	Combined	5	32,838	1.27 (1.05-1.54)	0	0.733	-	-
	Ticagrelor	3	18,961	1.24 (0.95-1.62)	0	0.507	-	-
	Prasugrel	2	13,877	1.30 (0.99-1.72)	0	0.434	-	-
Upper GIB	Combined	7	56,814	1.32 (1.05-1.67)	0	0.457	-	-
	Ticagrelor	2	32,263	1.39 (0.83-2.33)	54	0.141	-	-
	Prasugrel	5	24,551	1.23 (0.89-1.70)	0	0.541	-	-
Lower GIB	Combined	6	56,072	1.25 (0.95-1.65)	0	0.588	-	-
	Ticagrelor	2	32,263	1.00 (0.64-1.55)	0	0.643	-	-
	Prasugrel	4	23,809	1.45 (1.02-2.07)	0	0.609	-	-
Unspecified GIB	Combined	7	56,814	1.25 (1.01-1.53)	0	0.465	-	-
	Ticagrelor	2	32,263	1.09 (0.80-1.48)	0	0.986	-	-
	Prasugrel	5	24,551	1.36 (0.98-1.87)	6	0.374	-	-
Major GIB	Combined	6	15,943	1.28 (0.98-1.67)	0	0.833	-	-
	Ticagrelor	4	1,744	1.16 (0.40-3.35)	0	0.834	-	-
	Prasugrel	2	14,199	1.19 (0.65-2.15)	18	0.269	-	-
Duration ≥1 month	Combined	5	15,742	1.28 (0.98-1.68)	0	0.742	-	-
	Ticagrelor	3	1,543	1.24 (0.40-3.82)	0	0.686	-	-
	Prasugrel	2	14,199	1.28 (0.65-2.15)	18	0.269	-	-
Asian subgroup	Ticagrelor	2	559	0.71 (0.07-6.74)	0	0.515	-	-
All-cause major bleeding	Combined	41	69,727	1.18 (1.08-1.28)	0	0.981	0.243	0.116
	Ticagrelor	23	40,062	1.15 (1.03-1.28)	0	0.999	-	-
	Prasugrel	18	29,665	1.23 (1.08-1.40)	0	0.497	-	-
Duration ≥1 month	Combined	20	63,087	1.19 (1.09-1.29)	0	0.537	0.270	0.120
	Ticagrelor	12	35,309	1.16 (1.04-1.29)	0	0.966	-	-
	Prasugrel	8	27,087	1.08 (0.83-1.40)	47	0.066	-	-
Asian subgroup	Combined	18	5,569	1.08 (0.84-1.39)	0	0.571	0.211	0.054
	Ticagrelor	11	2,125	1.36 (0.95-1.96)	0	0.995	-	-
	Prasugrel	7	4,555	0.67 (0.37-1.22)	40	0.123	-	-
Standard dosage	Combined	21	38,971	1.23 (1.11-1.37)	0	0.999	0.398	0.980
	Ticagrelor	15	24,544	1.18 (1.03-1.35)	0	0.938	-	-
	Prasugrel	6	14,427	1.32 (1.12-1.56)	0	0.996	-	-
Low-risk patients§	Combined	17	24,497	1.26 (1.02-1.55)	0	0.944	0.249	0.781
	Ticagrelor	5	4,067	0.89 (0.52-1.51)	0	0.783	-	-
	Prasugrel	12	20,430	1.34 (1.07-1.68)	0	0.954	-	-
TIMI major bleeding	Combined	20	64,483	1.17 (1.04-1.32)	0	0.824	0.604	0.008
	Ticagrelor	8	36,724	1.16 (1.00-1.35)	0	0.900	-	-
	Prasugrel	12	27,759	1.19 (0.99-1.45)	0	0.490	-	-
Excluding studies with high risk of bias	Combined	23	62,632	1.19 (1.09-1.29)	0	0.650	0.509	0.247
	Ticagrelor	11	34,936	1.16 (1.03-1.29)	0	0.960	-	-
	Prasugrel	12	27,696	1.13 (0.90-1.43)	25	0.198	-	-
Life-threatening bleeding	Combined	13	64,695	1.06 (0.94-1.20)	10	0.341	0.143	0.159
	Ticagrelor	5	37,455	1.01 (0.91-1.13)	0	0.822	-	-
	Prasugrel	6	27,240	1.10 (0.80-1.51)	27	0.209	-	-

Fatal bleeding	Combined	8	62,538	1.19 (0.65-2.16)	47	0.067	-	-
	Ticagrelor	4	37,035	0.77 (0.49-1.22)	0	0.460	-	-
	Prasugrel	4	25,503	1.92 (0.67-2.16)	48	0.121	-	-
Intracranial bleeding	Combined	6	59,168	1.08 (0.81-1.44)	0	0.475	-	-
	Ticagrelor	4	36,471	1.19 (0.83-1.72)	2	0.382	-	-
	Prasugrel	2	22,697	0.92 (0.57-1.47)	0	0.393	-	-

† Random effects model; ‡ Ticagrelor, loading dose of 180mg once and maintenance does of 90mg twice per day; Prasugrel, loading dose of 60mg once and maintenance does of 10mg once per day; § Patients that less than 75 years old or body weight ≥60 kg as defined in TRITON-TIMI 38 study; * *P* value <0.1 indicates significant heterogeneity.

RR, relative risk; CI, confidence interval; GIB, gastrointestinal bleeding; TIMI, Thrombolysis In Myocardial Infarction classification.

Figure Legends

Figure 1 Flow chart of study selection.

Figure 2 Forest plot for gastrointestinal bleeding risk of third-generation P2Y12 inhibitors vs clopidogrel.

Figure 3 Forest plot for all-cause major bleeding risk of third-generation P2Y12 inhibitors vs clopidogrel.

Figure 1

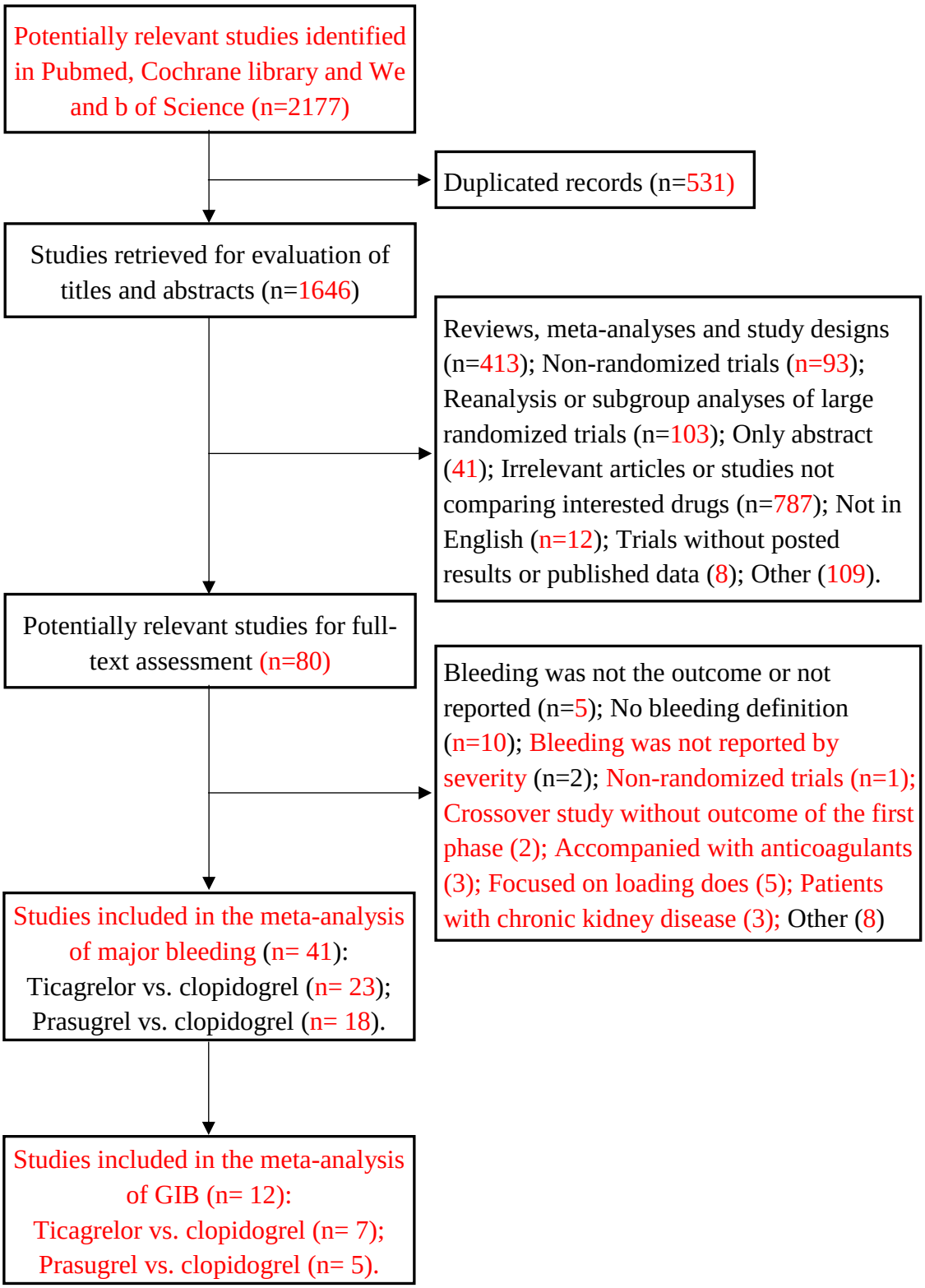

Potentially relevant studies identified in Pubmed, Cochrane library and We and b of Science (n=2177)
Duplicated records (n=531)
Studies retrieved for evaluation of titles and abstracts (n=1646)
Reviews, meta-analyses and study designs (n=413); Non-randomized trials (n=93); Reanalysis or subgroup analyses of large randomized trials (n=103); Only abstract (41); Irrelevant articles or studies not comparing interested drugs (n=787); Not in English (n=12); Trials without posted results or published data (8); Other (109).
Potentially relevant studies for full-text assessment (n=80)
Bleeding was not the outcome or not reported (n=5); No bleeding definition (n=10); Bleeding was not reported by severity (n=2); Non-randomized trials (n=1); Crossover study without outcome of the first phase (2); Accompanied with anticoagulants (3); Focused on loading does (5); Patients with chronic kidney disease (3); Other (8)
Studies included in the meta-analysis of major bleeding (n= 41):
Ticagrelor vs. clopidogrel (n= 23);
Prasugrel vs. clopidogrel (n= 18).
Studies included in the meta-analysis of GIB (n= 12):
Ticagrelor vs. clopidogrel (n= 7);
Prasugrel vs. clopidogrel (n= 5).

Figure 2

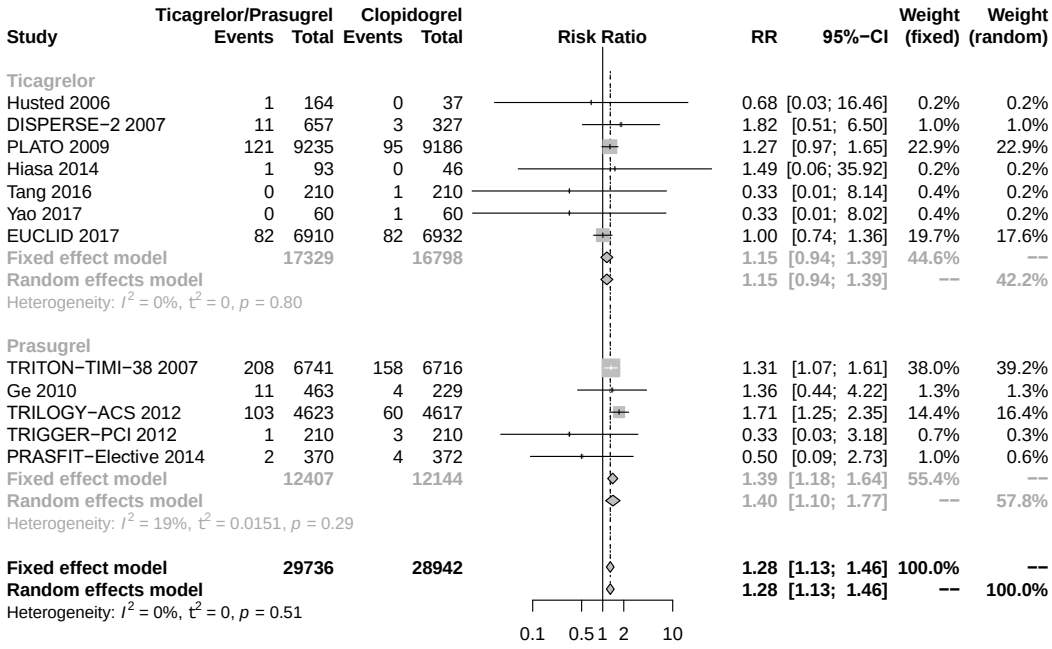
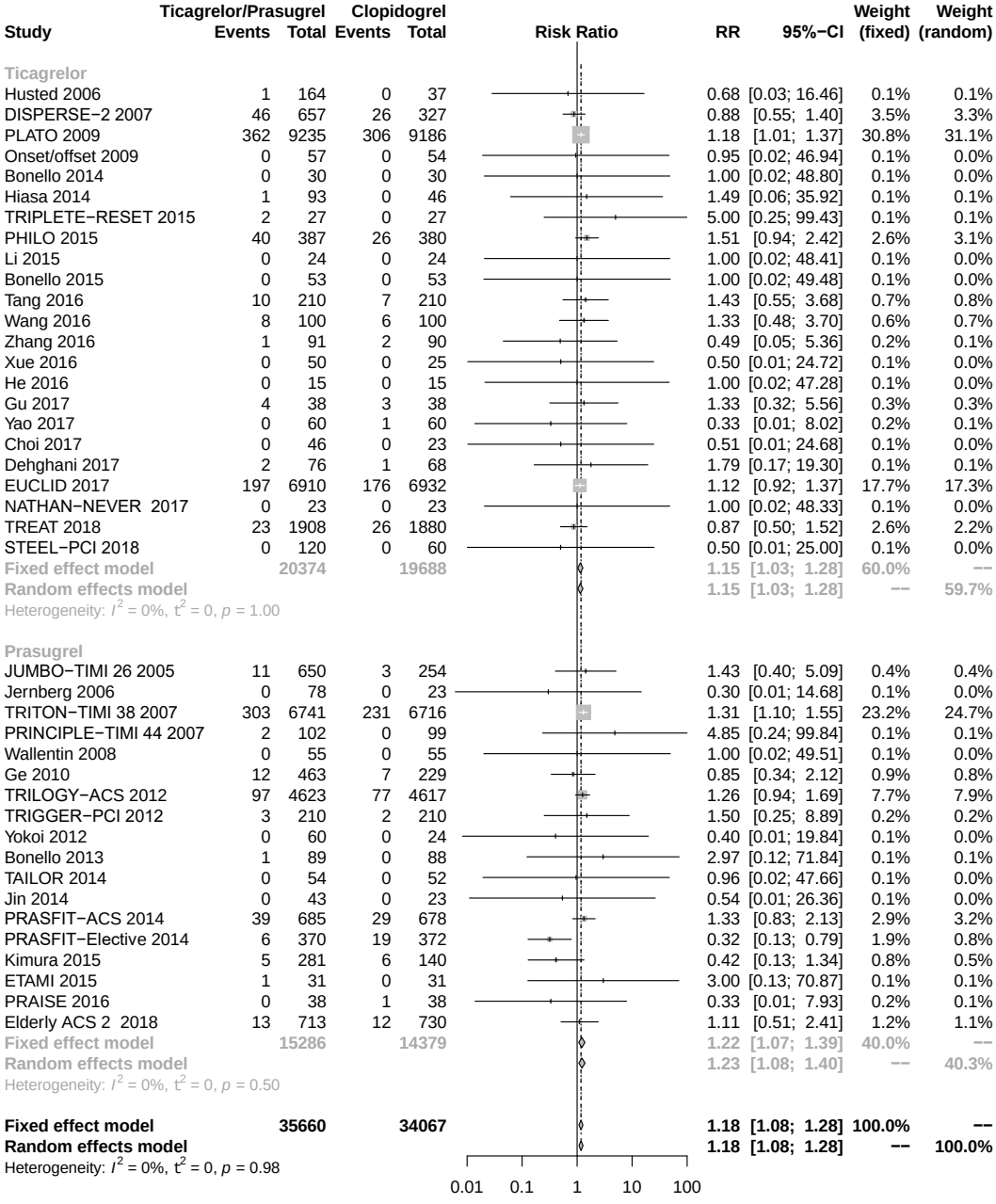

Study
Ticagrelor/Prasugrel Events Total
Clopidogrel Events Total
Risk Ratio
RR 95%−CI
Weight (fixed)
Weight (random)
Ticagrelor
Husted 2006 1 164 0 37 0.68 [0.03; 16.46] 0.2% 0.2%
DISPERSE−2 2007 11 657 3 327 1.82 [0.51; 6.50] 1.0% 1.0%
PLATO 2009 121 9235 95 9186 1.27 [0.97; 1.65] 22.9% 22.9%
Hiasa 2014 1 93 0 46 1.49 [0.06; 35.92] 0.2% 0.2%
Tang 2016 0 210 1 210 0.33 [0.01; 8.14] 0.4% 0.2%
Yao 2017 0 60 1 60 0.33 [0.01; 8.02] 0.4% 0.2%
EUCLID 2017 82 6910 82 6932 1.00 [0.74; 1.36] 19.7% 17.6%
Fixed effect model 17329 16798 1.15 [0.94; 1.39] 44.6% −−
Random effects model 1.15 [0.94; 1.39] −− 42.2%
Heterogeneity: I^2 = 0%, t^2 = 0, p = 0.80
Prasugrel
TRITON−TIMI−38 2007 208 6741 158 6716 1.31 [1.07; 1.61] 38.0% 39.2%
Ge 2010 11 463 4 229 1.36 [0.44; 4.22] 1.3% 1.3%
TRILOGY−ACS 2012 103 4623 60 4617 1.71 [1.25; 2.35] 14.4% 16.4%
TRIGGER−PCI 2012 1 210 3 210 0.33 [0.03; 3.18] 0.7% 0.3%
PRASFIT−Elective 2014 2 370 4 372 0.50 [0.09; 2.73] 1.0% 0.6%
Fixed effect model 12407 12144 1.39 [1.18; 1.64] 55.4% −−
Random effects model 1.40 [1.10; 1.77] −− 57.8%
Heterogeneity: I^2 = 19%, t^2 = 0.0151, p = 0.29
Fixed effect model 29736 28942 1.28 [1.13; 1.46] 100.0% −−
Random effects model 1.28 [1.13; 1.46] −− 100.0%
Heterogeneity: I^2 = 0%, t^2 = 0, p = 0.51
0.1 0.5 1 2 10

Figure 3


Study
Ticagrelor/Prasugrel Events Total
Clopidogrel Events Total
Risk Ratio
RR 95%−CI
Weight (fixed) Weight (random)
Ticagrelor
Husted 2006 1 164 0 37 0.68 [0.03; 16.46] 0.1% 0.1%
DISPERSE−2 2007 46 657 26 327 0.88 [0.55; 1.40] 3.5% 3.3%
PLATO 2009 362 9235 306 9186 1.18 [1.01; 1.37] 30.8% 31.1%
Onset/offset 2009 0 57 0 54 0.95 [0.02; 46.94] 0.1% 0.0%
Bonello 2014 0 30 0 30 1.00 [0.02; 48.80] 0.1% 0.0%
Hiasa 2014 1 93 0 46 1.49 [0.06; 35.92] 0.1% 0.1%
TRIPLETE−RESET 2015 2 27 0 27 5.00 [0.25; 99.43] 0.1% 0.1%
PHILO 2015 40 387 26 380 1.51 [0.94; 2.42] 2.6% 3.1%
Li 2015 0 24 0 24 1.00 [0.02; 48.41] 0.1% 0.0%
Bonello 2015 0 53 0 53 1.00 [0.02; 49.48] 0.1% 0.0%
Tang 2016 10 210 7 210 1.43 [0.55; 3.68] 0.7% 0.8%
Wang 2016 8 100 6 100 1.33 [0.48; 3.70] 0.6% 0.7%
Zhang 2016 1 91 2 90 0.49 [0.05; 5.36] 0.2% 0.1%
Xue 2016 0 50 0 25 0.50 [0.01; 24.72] 0.1% 0.0%
He 2016 0 15 0 15 1.00 [0.02; 47.28] 0.1% 0.0%
Gu 2017 4 38 3 38 1.33 [0.32; 5.56] 0.3% 0.3%
Yao 2017 0 60 1 60 0.33 [0.01; 8.02] 0.2% 0.1%
Choi 2017 0 46 0 23 0.51 [0.01; 24.68] 0.1% 0.0%
Dehghani 2017 2 76 1 68 1.79 [0.17; 19.30] 0.1% 0.1%
EUCLID 2017 197 6910 176 6932 1.12 [0.92; 1.37] 17.7% 17.3%
NATHAN−NEVER 2017 0 23 0 23 1.00 [0.02; 48.33] 0.1% 0.0%
TREAT 2018 23 1908 26 1880 0.87 [0.50; 1.52] 2.6% 2.2%
STEEL−PCI 2018 0 120 0 60 0.50 [0.01; 25.00] 0.1% 0.0%
Fixed effect model 20374 19688 1.15 [1.03; 1.28] 60.0% --
Random effects model 1.15 [1.03; 1.28] -- 59.7%
Heterogeneity: I^2 = 0%, t^2 = 0, p = 1.00
Prasugrel
JUMBO−TIMI 26 2005 11 650 3 254 1.43 [0.40; 5.09] 0.4% 0.4%
Jernberg 2006 0 78 0 23 0.30 [0.01; 14.68] 0.1% 0.0%
TRITON−TIMI 38 2007 303 6741 231 6716 1.31 [1.10; 1.55] 23.2% 24.7%
PRINCIPLE−TIMI 44 2007 2 102 0 99 4.85 [0.24; 99.84] 0.1% 0.1%
Wallentin 2008 0 55 0 55 1.00 [0.02; 49.51] 0.1% 0.0%
Ge 2010 12 463 7 229 0.85 [0.34; 2.12] 0.9% 0.8%
TRILOGY−ACS 2012 97 4623 77 4617 1.26 [0.94; 1.69] 7.7% 7.9%
TRIGGER−PCI 2012 3 210 2 210 1.50 [0.25; 8.89] 0.2% 0.2%
Yokoi 2012 0 60 0 24 0.40 [0.01; 19.84] 0.1% 0.0%
Bonello 2013 1 89 0 88 2.97 [0.12; 71.84] 0.1% 0.1%
TAILOR 2014 0 54 0 52 0.96 [0.02; 47.66] 0.1% 0.0%
Jin 2014 0 43 0 23 0.54 [0.01; 26.36] 0.1% 0.0%
PRASFIT−ACS 2014 39 685 29 678 1.33 [0.83; 2.13] 2.9% 3.2%
PRASFIT−Elective 2014 6 370 19 372 0.32 [0.13; 0.79] 1.9% 0.8%
Kimura 2015 5 281 6 140 0.42 [0.13; 1.34] 0.8% 0.5%
ETAMI 2015 1 31 0 31 3.00 [0.13; 70.87] 0.1% 0.1%
PRAISE 2016 0 38 1 38 0.33 [0.01; 7.93] 0.2% 0.1%
Elderly ACS 2 2018 13 713 12 730 1.11 [0.51; 2.41] 1.2% 1.1%
Fixed effect model 15286 14379 1.22 [1.07; 1.39] 40.0% --
Random effects model 1.23 [1.08; 1.40] -- 40.3%
Heterogeneity: I^2 = 0%, t^2 = 0, p = 0.50
Fixed effect model 35660 34067 1.18 [1.08; 1.28] 100.0% --
Random effects model 1.18 [1.08; 1.28] -- 100.0%
Heterogeneity: I^2 = 0%, t^2 = 0, p = 0.98
0.01 0.1 1 10 100

Supplementary Table 1 Studies excluded after full-text review with rationale

Study	Reason for exclusion
Park DW, Lee PH, Jang S, et al. Effect of Low-Dose Versus Standard-Dose Ticagrelor and Clopidogrel on Platelet Inhibition in Acute Coronary Syndromes. *J Am Coll Cardiol.* 2018;71(14):1594-1595.	Results of bleeding were not reported
Comparison of Low-Dose, Standard-Dose Ticagrelor and Clopidogrel for Inhibition of Platelet Reactivity in Patients With Acute Coronary Syndromes (OPTIMA); URL: https://clinicaltrials.gov/ct2/show/NCT02319941	Results of bleeding were not reported
Rudolph TK, Fuchs A, Klinke A, et al. Prasugrel as opposed to clopidogrel improves endothelial nitric oxide bioavailability and reduces platelet-leukocyte interaction in patients with unstable angina pectoris: A randomized controlled trial. Int J Cardiol. 2017;248:7-13.	Bleeding was not one of the outcomes
Zafar MU, Baber U, Smith DA, et al. Antithrombotic potency of ticagrelor versus clopidogrel in type-2 diabetic patients with cardiovascular disease. Thromb Haemost. 2017;117(10):1981-1988.	Bleeding was not one of the outcomes
Yang A, Pon Q, Lavoie A, et al. Long-term pharmacodynamic effects of Ticagrelor versus Clopidogrel in fibrinolytic-treated STEMI patients undergoing early PCI. J Thromb Thrombolysis. 2018;45(2):225-233.	Bleeding was not one of the outcomes
Brugaletta S, Gomez-Lara J, Caballero J, et al. Ticagrelor versus clopidogrel for recovery of vascular function immediately after successful chronic coronary total occlusion recanalization: A randomized clinical trial. Am Heart J. 2018.	No bleeding definition
Dasbiswas A, Rao MS, Babu PR, et al. A comparative evaluation of prasugrel and clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. J Assoc Physicians India. 2013;61(2):114-116, 126.	No bleeding definition
Erlinge D, Gurbel PA, James S, et al. Prasugrel 5 mg in the very elderly attenuates platelet inhibition but maintains noninferiority to prasugrel 10 mg in nonelderly patients: the GENERATIONS trial, a pharmacodynamic and pharmacokinetic study in stable coronary artery disease patients. J Am Coll Cardiol. 2013;62(7):577-583.	No bleeding definition
Lu Y, Yao R, Li Y, Li L, Zhao L, Zhang Y. Clinical effect of ticagrelor administered in acute coronary syndrome patients following percutaneous coronary intervention. Exp Ther Med. 2016;11(6):2177-2184.	No bleeding definition

Ottani F, Femia EA, Cattaneo M, Caravita L, Attanasio C, Galvani M. Switching from clopidogrel to prasugrel to protect early invasive treatment in acute coronary syndromes: Results of the switch over trial. Int J Cardiol. 2018;255:8-14.	No bleeding definition
Payne CD, Li YG, Small DS, et al. Increased active metabolite formation explains the greater platelet inhibition with prasugrel compared to high-dose clopidogrel. J Cardiovasc Pharmacol. 2007;50(5):555-562.	No bleeding definition
Price MJ, Clavijo L, Angiolillo DJ, et al. A randomised trial of the pharmacodynamic and pharmacokinetic effects of ticagrelor compared with clopidogrel in Hispanic patients with stable coronary artery disease. J Thromb Thrombolysis. 2014;39(1):8-14.	No bleeding definition
Wang S, Yang X, Li Z, Zhang B, Cheng Y. Safety and efficacy of ticagrelor with emergency percutaneous coronary intervention in senile patients with ST-segment elevation myocardial infarction and dementia. Int J Clin Exp Med. 2016;9(6):11831-11837.	No bleeding definition
Wu HB, Tian HP, Wang XC, et al. Clinical efficacy of ticagrelor in patients undergoing emergency intervention for acute myocardial infarction and its impact on platelet aggregation rate. Am J Transl Res. 2018;10(7):2175-2183.	No bleeding definition
Xiong R, Liu W, Chen L, Kang T, Ning S, Li J. A randomized controlled trial to assess the efficacy and safety of doubling dose clopidogrel versus ticagrelor for the treatment of acute coronary syndrome in patients with CYP2C19*2 homozygotes. Int J Clin Exp Med. 2015;8(8):13310-13316.	No bleeding definition
Alexopoulos D, Perperis A, Koniari I, et al. Ticagrelor versus high dose clopidogrel in ST-segment elevation myocardial infarction patients with high platelet reactivity post fibrinolysis. J Thromb Thrombolysis. 2015;40(3):261-267.	Bleeding was not reported by severity
Modi NV, Anand IS. Comparative study of efficacy and safety of clopidogrel versus prasugrel in patient with acute coronary syndrome. International Journal of Pharmaceutical Research. 2012;4(4):37-42.	Bleeding was not reported by severity
Xu Q, Sun Y, Zhang Y, et al. Effect of a 180 mg ticagrelor loading dose on myocardial necrosis in patients undergoing elective percutaneous coronary intervention: a preliminary study. Cardiol J. 2017;24(1):15-24.	Non-randomized study
Therapy With High Clopidogrel Dose or Prasugrel Standard Dose Reduces the Platelet Reactivity in Patients With Genotype Variation RESET GENE Trial (RESET GENE); URL: https://clinicaltrials.gov/ct2/show/NCT01465828	Crossover study without outcome of the first phase

The Effect on Blood Cells, Known as Platelets, Using Prasugrel vs Clopidogrel in Patients With the Heart Problem Acute Coronary Syndrome (ACS); URL: https://clinicaltrials.gov/ct2/show/NCT00385944	Crossover study without outcome of the first phase
Ohman EM, Roe MT, Steg PG, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. Lancet. 2017;389(10081):1799-1808.	Accompanied with anticoagulants
Schulz S, Richardt G, Laugwitz KL, et al. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. Eur Heart J. 2014;35(34):2285-2294.	Accompanied with anticoagulants
Liu Y, Liu H, Hao Y, et al. Short-term efficacy and safety of three different antiplatelet regimens in diabetic patients treated with primary percutaneous coronary intervention: a randomised study. Kardiol Pol. 2017;75(9):850-858.	Accompanied with anticoagulants
Diodati JG, Saucedo JF, French JK, et al. Effect on platelet reactivity from a prasugrel loading dose after a clopidogrel loading dose compared with a prasugrel loading dose alone: Transferring From Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome Patients (TRIPLET): a randomized controlled trial. Circ Cardiovasc Interv. 2013;6(5):567-574.	Only loading dose of treatment drugs
Angiolillo DJ, Franchi F, Waksman R, et al. Effects of Ticagrelor Versus Clopidogrel in Troponin-Negative Patients With Low-Risk ACS Undergoing Ad Hoc PCI. J Am Coll Cardiol. 2016;67(6):603-613.	Only loading dose of treatment drugs
Hochholzer W, Amann M, Titov A, et al. Randomized Comparison of Different Thienopyridine Loading Strategies in Patients Undergoing Elective Coronary Intervention: The ExcelsiorLOAD Trial. JACC Cardiovasc Interv. 2016;9(3):219-227.	Only loading dose of treatment drugs
Hochholzer W, Kleiner P, Younas I, et al. Randomized Comparison of Oral P2Y12-Receptor Inhibitor Loading Strategies for Transitioning From Cangrelor: The ExcelsiorLOAD2 Trial. JACC Cardiovasc Interv. 2017;10(2):121-129.	Only loading dose of treatment drugs
Prasugrel With Lower Dose - Loading Dose (PRELOAD-LD); URL: https://clinicaltrials.gov/ct2/show/NCT02070159	Only loading dose of treatment drugs
Jeong KH, Cho JH, Woo JS, et al. Platelet reactivity after receiving clopidogrel compared with ticagrelor in patients with kidney failure treated with hemodialysis: a randomized	Patients with kidney failure

crossover study. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2015;65(6):916-924.	
Wang HY, Qi J, Li Y, et al. Pharmacodynamics and pharmacokinetics of ticagrelor vs. clopidogrel in patients with acute coronary syndromes and chronic kidney disease. Br J Clin Pharmacol. 2018;84(1):88-96.	Patients with chronic kidney disease
Prasugrel Versus High Dose Clopidogrel in Clopidogrel Resistant Patients Undergoing Chronic Hemodialysis; URL: https://clinicaltrials.gov/ct2/show/NCT01155765	Patients with chronic hemodialysis
Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J. 2017;38(41):3070-3078.	P2Y12 inhibitors switched to clopidogrel
Pourdjabbar A, Hibbert B, Chong AY, et al. A randomised study for optimising crossover from ticagrelor to clopidogrel in patients with acute coronary syndrome. The CAPITAL OPTI-CROSS Study. Thromb Haemost. 2017;117(2):303-310	Not comparing ticagrelor with clopidogrel
Wakabayashi S, Ariyoshi N, Kitahara H, Fujii K, Fujimoto Y, Kobayashi Y. Efficacy of 2.5-mg Prasugrel in Elderly or Low-Body-Weight Patients. Circ J. 2018;82(9):2326-2331.	Not comparing prasugrel with clopidogrel
Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet. 2017.	Guided by platelet function testing
Antiplatelet Therapy Guided by Thrombelastography in Patients With Acute Coronary Syndromes (TEGCOR Study); URL: https://clinicaltrials.gov/ct2/show/NCT01612884	Treatment determined by clopidogrel response
Lee MS, Shlofmitz E, Haag E, et al. Optimal Same-Day Platelet Inhibition in Patients Receiving Drug-Eluting Stents With or Without Previous Maintenance Thienopyridine Therapy: from the Evaluation of Platelet Inhibition in Patients Having A VerifyNow Assay (EPIPHANY) Trial. Am J Cardiol. 2017;119(7):991-995.	Not fully randomized, and treatment changed according to platelet function testing
Cubero Gomez JM, Acosta Martinez J, Mendias Benitez C, et al. VERifyNow in DIabetes high-on-treatment platelet reactivity: a pharmacodynamic study on switching from clopidogrel to prasugrel. Acta Cardiol. 2015;70(6):728-734.	Full text was not obtained
Pharmacogenomics of Anti-platelet Intervention-2 (PAPI-2) Study (PAPI-2); URL: https://clinicaltrials.gov/ct2/show/NCT01452152	Terminated, only 9 patients included

Supplementary Table 2 Potential bias of included studies

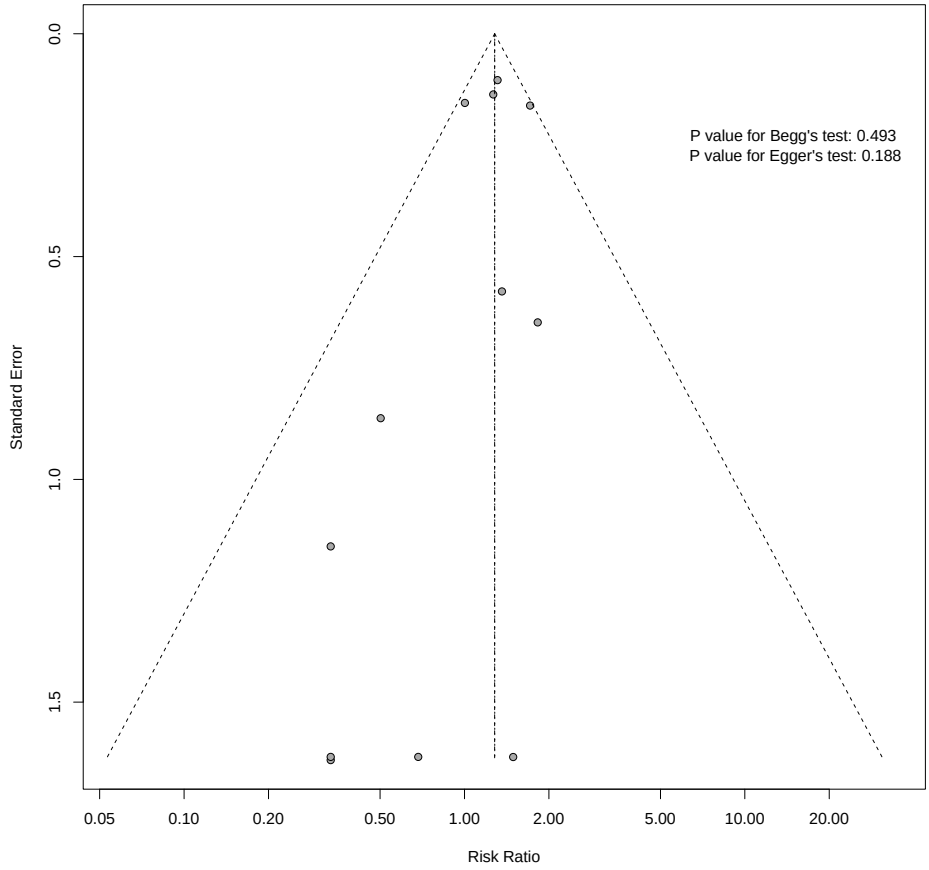
	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Selection bias	Notes
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	
Husted (2006)	L	U	L	L	L	L	L	
DISPERSE-2 (2007)	U	U	L	L	L	L	L	
PLATO (2009)	U	U	L	L	L	L	L	
Onset/offset (2009)	L	U	L	L	L	L	L	
Bonello (2014)	U	U	H	H	L	L	U	Open-label, no exposure duration
Hiasa (2014)	L	U	L	L	L	L	L	
TRIPLETE-RESET (2015)	U	U	H	L	L	L	L	Open-label with blinded analysis
PHILO (2015)	L	U	L	L	L	L	L	
Li (2015)	U	U	H	L	L	L	H	Single-blind, no exposure duration, clinical follow-up was obtained by telephone interviews
Bonello (2015)	L	U	H	H	H	L	U	Not ITT, open-label, no exposure duration
Tang (2016)	U	L	U	U	H	L	L	Not ITT
Wang H (2016)	U	U	L	L	L	L	L	
Zhang (2016)	U	U	H	H	L	L	L	Open-label
Xue (2016)	U	U	L	L	L	L	L	
He (2016)	L	U	H	L	U	L	L	Single-blind

Gu (2017)	U	U	U	U	L	L	U	No exposure duration
Yao (2017)	L	U	U	U	L	L	U	No exposure duration
Choi (2017)	U	U	H	H	H	L	L	Not ITT, Open-label
Dehghani (2017)	U	U	H	L	L	L	U	Open-label, no exposure duration
EUCLID (2017)	L	U	L	L	L	L	U	No exposure duration
NATHAN-NEVER (2017)	U	L	H	H	L	L	U	Open-label, COPD
TREAT (2018)	L	L	H	L	L	L	U	Open-label with blinded outcome assessment, no exposure duration
STEEL-PCI (2018)	U	U	H	H	L	L	L	Open-label
JUMBO-TIMI 26 (2005)	U	U	L	L	L	L	L	
Jernberg (2006)	U	U	H	H	L	L	L	Partially blind
TRITON-TIMI 38 (2007)	U	U	L	L	L	L	L	
PRINCIPLE-TIMI 44 (2007)	U	L	L	L	L	L	L	
Wallentin (2008)	L	L	L	L	L	L	L	
Ge (2010)	U	L	L	L	L	L	L	
TRILOGY-ACS (2012)	L	U	L	L	L	L	L	
TRIGGER-PCI (2012)	U	U	L	L	L	L	U	No exposure duration
Yokoi (2012)	U	U	U	L	L	L	L	
Bonello (2013)	U	U	H	L	L	L	U	Open-label with blinded end points, no exposure duration
TAILOR (2014)	L	L	H	H	L	L	L	Open-label

Jin (2014)	U	U	H	H	L	L	L	Open-label
PRASFIT-ACS (2014)	L	U	U	L	L	L	L	
PRASFIT-Elective (2014)	U	U	L	L	L	L	L	
Kimura (2015)	U	U	L	L	L	L	L	
ETAMI (2015)	U	U	L	L	L	L	U	
PRAISE (2016)	L	L	H	H	L	L	L	Open-label
Elderly ACS 2 (2018)	L	L	H	L	L	L	U	Open-label with blinded end points, no exposure duration

H, high risk of bias; L, low risk of bias; U, unclear.

Supplementary Figure 1 Funnel plot for the analysis of all GIB.



Supplementary Figure 2 Funnel plot for the analysis of all-cause major bleeding.