ARTICLE

Risk Factors for Bleeding and Clinical Ineffectiveness Associated With Clopidogrel Therapy: A Comprehensive Meta-Analysis

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Although clopidogrel is a frequently used antiplatelet medication to treat and prevent atherothrombotic disease, clinicians must balance its clinical effectiveness with the potential side effect of bleeding. However, many previous studies have evaluated beneficial and adverse factors separately. The objective of our study was to perform a comprehensive meta-analysis of studies of clopidogrel's clinical effectiveness and/or risk of bleeding in order to identify and assess all reported risk factors, thus helping clinicians to balance patient safety with drug efficacy. We analyzed randomized controlled trials (RCTs) of maintenance use in four stages: search for relevant primary articles; abstract and full article screening; quality assessment and data extraction; and synthesis and data analysis. Screening of 7,109 articles yielded 52 RCTs that met the inclusion criteria. Twenty-seven risk factors were identified. "Definite risk factors" were defined as those with aggregated odds ratios (ORs) > 1 and confidence intervals (CIs) > 1 if analyzed in more than one study. Definite risk factors for major bleeding were concomitant aspirin use (OR 2.83, 95% CI 2.04–3.94) and long duration of clopidogrel therapy (> 6 months) (OR 1.74, 95% CI 1.21–2.50). Dual antiplatelet therapy, extended clopidogrel therapy, and high maintenance dose (150 mg/day) of clopidogrel were definite risk factors for any bleeding. Reduced renal function, both mild and severe, was the only definite risk factor for clinical ineffectiveness. These findings can help clinicians predict the risks and effectiveness of clopidogrel use for their patients and be used in clinical decision support tools.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Use of clopidogrel, an important therapeutic option to treat and prevent atherothrombotic disease, must balance desired clinical effectiveness with risks of bleeding. Prior studies have primarily assessed beneficial and adverse factors separately.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ By analyzing a large number of randomized controlled trials, we sought to identify a comprehensive list of risk factors and determine those most significant for patient care.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Our meta-analysis produced a comprehensive list of factors affecting risks and effects of clopidogrel use.

We identified three key risk factors: the risk of bleeding is significantly higher when patients used clopidogrel concomitantly with aspirin or for > 6 months, and patients with renal dysfunction have higher risk of clinical failure.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Clinicians can use these risk factors to evaluate potential benefits and risks of clopidogrel therapy for individual patients. In addition, clinical decision support tools can be developed using these risk factors to help improve patient safety and clinical effectiveness.

Antiplatelet therapy using clopidogrel is an important and widely used therapeutic option in the armamentarium to treat and prevent atherothrombotic disease. Maintenance therapy with clopidogrel has been found to reduce the risk of myocardial infarction, stroke, and cardiovascular death in patients with peripheral artery disease or coronary artery disease.[1] A medical expenditure survey by the Agency for Healthcare Research and Quality showed that clopidogrel was, with almost 20 million prescriptions in 2017, the 19th most commonly prescribed drug in the United States.[2]

Genetic testing is beginning to be used to assess the clinical effectiveness of clopidogrel. Clinical studies of

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genotype-guided clopidogrel therapy have demonstrated cost-effectiveness, noninferiority, and improved safety compared to other oral P2Y$_{12}$ antagonists.[3–5] Previously, some healthcare systems implemented genetic testing of *CYP2C19*[6,7] to predict the clinical effectiveness of clopidogrel in their patients.[7,8] However, genetic variation is only one contributor to therapeutic outcomes. To help predict clinical effectiveness and prevent unnecessary adverse events, healthcare systems and clinical providers need to be aware of the range of risk factors that can impact patient outcomes.

Clopidogrel maintenance therapy is considered clinically effective when its use results in the avoidance of such outcomes as cardiac death, myocardial infarction, stroke, and acute ischemic events.[1] However, increased risk of bleeding is a major potential side effect; indeed, major bleeding has been reported in up to 8.8% of subjects in clinical trials.[8,9] Thus, clinicians must balance the protective effects of antiplatelet therapy for their patients with its risks.[10,11] Adverse drug events account for ~ 6% of all hospital admissions,[12] and gastrointestinal bleeding from antiplatelet agents and other anticoagulants ranks among the most common adverse drug events.[13]

Clinical trials and prior meta-analyses have contributed to the body of knowledge on the subject, but have most often evaluated individual risk factors for clinical ineffectiveness and adverse events separately, rather than in combination.[14,15] There is a lack of a comprehensive review that uniformly assess both inefficacy and adverse events from randomized controlled trials (RCTs). Therefore, the objective of our study was to perform a comprehensive meta-analysis of studies of clopidogrel's clinical effectiveness and/or risk of bleeding in order to identify and assess all reported risk factors. The results of this study can help clinicians quantitatively and objectively assess and balance patient safety with drug efficacy.

METHODS

We designed the study to assess two primary outcomes of maintenance clopidogrel therapy: bleeding and clinical effectiveness. The first outcome—bleeding as a side effect—was broken down into two categories: major bleeding or any bleeding (major, minor, or uncategorized). "Major bleeding" was defined as fatal bleeding; any intracranial bleeding; signs of hemorrhage associated with a drop in hemoglobin ≥ 3 g/dL; bleeding resulting in hypovolemic shock or severe hypotension that requires pressor or surgery; or bleeding requiring transfusion of two to three units of whole blood or packed red blood cells. "Any bleeding" was defined as major bleeding as described above or any other type of bleeding that did not meet those criteria. We derived the bleeding outcomes from various reporting criteria used in each study. These criteria included the Thrombolysis in Myocardial Infarction (TIMI), Global Use of Strategies to Open Occluded Arteries (GUSTO), Bleeding Academic Research Consortium (BARC), and Platelet Inhibition and Patient Outcomes (PLATO) criteria.[16–19] For the other outcome assessed, we defined clinical ineffectiveness by relevant thrombosis outcomes such as cardiac death,

myocardial infarction, stent thrombosis, stroke, revascularization, rehospitalization for an acute ischemic event, and coronary artery bypass surgery. This definition was similar to that of the Major Adverse Cardiovascular Events (MACE) and Major Adverse Cardiac and Cerebrovascular Events (MACCE).

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard to guidance our study. Our review of the literature proceeded in four phases: (1) search for relevant primary studies; (2) screening of abstracts and full articles; (3) quality assessment and data extraction; and (4) synthesis and data analysis. For each phase, we processed a subset of samples first to standardize the evaluation process and improve interrater reliability. **Figure 1** outlines the process. The Covidence systematic review software (Covidence, Veritas Health Innovation, Melbourne, Australia; www.covidence.org) was used to manage the review process in phases I through III, and Review Manager (Revman 5.3, Copenhagen: The Nordic Cochrane Center, 2014) was used for the synthesis and data analysis in phase IV.

Search for relevant primary studies
In phase I, we designed a comprehensive search strategy with a medical librarian (E.C.W.) to identify articles related to risk factors of clopidogrel in the two categories: bleeding and clinical ineffectiveness. We searched on August 30, 2018, and reran the searches on June 5, 2020, in 4 databases (MEDLINE, EMBASE, Cochrane, and Ovid) from inception to June 2020 for primary studies in English with the following search terms: clopidogrel (with all generic and brand names), bleeding and hematoma (and synonyms), no clinical response (including clot and thrombosis), and risk factors. We intended to capture all potential patient contexts for clopidogrel therapy, such as specific ethnicities or therapeutic procedures (such as dental procedures). The complete search strategy can be found in **Supplementary Document SA**.

Abstract and full article screening
Our initial search yielded 9,520 articles, with 2,565 articles removed due to duplication or lack of an abstract. We screened abstracts of the remaining 7,109 articles using the following inclusion criteria:

- RCT (cohort studies, nonrandomized studies, case reports, letters, reviews, commentaries, and editorials were excluded).
- Human studies (animal and *in vitro* studies were excluded).
- English language.
- Addressed outcomes of interests (risk factors, bleeding risk, or clinical response).
- Evaluated maintenance clopidogrel therapy (studies that only evaluated loading dose therapy were excluded).

Eight investigators (K.N., K.F., E.M., A.K., K.D., H.O., H.B., and R.Y.) screened the abstracts. After the pilot appraisal, each abstract was screened independently by two
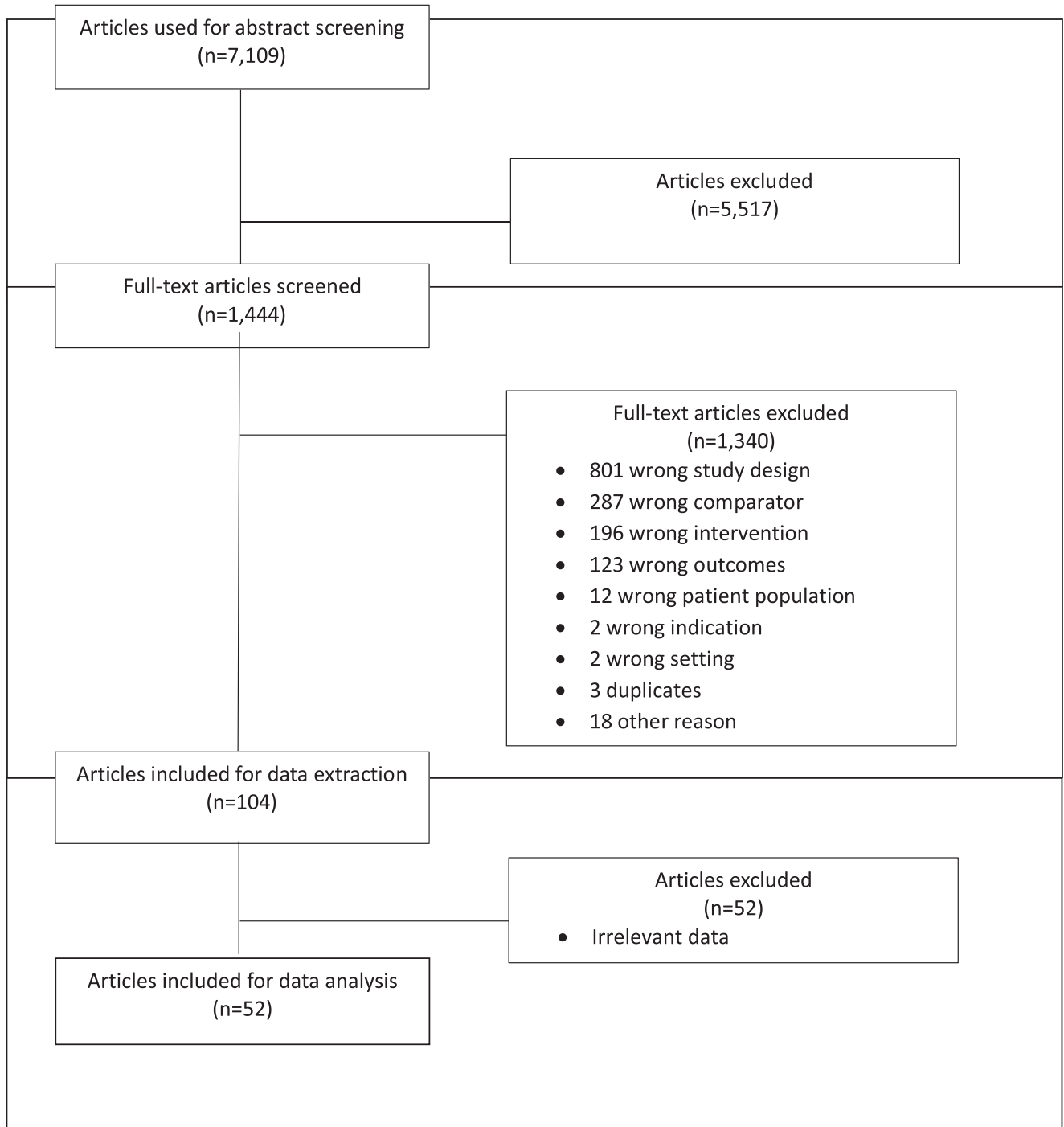
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┌─────────────────────────────────┐
│  Articles used for abstract     │
│         screening               │
│         (n=7,109)               │
└─────────────────────────────────┘
                              ┌─────────────────────────────┐
                              │   Articles excluded         │
                              │      (n=5,517)              │
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│  Full-text articles screened    │
│         (n=1,444)               │
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                              │   Full-text articles excluded           │
                              │         (n=1,340)                       │
                              │   • 801 wrong study design              │
                              │   • 287 wrong comparator                │
                              │   • 196 wrong intervention              │
                              │   • 123 wrong outcomes                  │
                              │   • 12 wrong patient population         │
                              │   • 2 wrong indication                  │
                              │   • 2 wrong setting                     │
                              │   • 3 duplicates                        │
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│  Articles included for data     │
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│  Articles included for data     │
│         analysis                │
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Figure 1 Study procedure based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard.

investigators. Discrepancies and conflicts were resolved by a third investigator. This screening process yielded 1,444 articles for full article screening.

The eight investigators performed full article screening in a fashion similar to the abstract screening. Articles that related one or more risk factors of clopidogrel to one or more clinical outcomes of interest were included. We required the relationship between a risk factor and outcome of interest to be quantified with statistical measures, such as the odds

ratio (OR), hazard ratio, or relative risk (RR). This process eliminated an additional 1,340 articles, producing a set of 104 articles for data extraction.

Quality assessment and data extraction
We used the validated Cochrane assessment tool for RCTs[20] to assess the studies' quality. Articles were assessed for five types of bias: selection bias, performance bias, detection bias, attrition bias, and reporting bias. We extracted study

type, patient population, duration of intended comparison, outcomes, intervention studies and control, statistical methods, and risk factor estimate (see **Supplementary Document SB** for definitions of each term) from each article. A pilot phase included a training set of 10 studies assessed by all reviewers to ensure calibration. The remaining articles were evaluated for bias assessment and data extraction by two independent reviewers. Any discrepancies were discussed and resolved at weekly meetings. Of the 104 articles, 52 (with irrelevant data) failed to meet one or more inclusion criteria for data extraction. The remaining 52 articles were included in the synthesis and data analysis phase.

Synthesis and data analysis

Extracted data from the 52 included studies were grouped and analyzed based on similarity in outcomes (bleeding or ineffectiveness) and potential risk factors. We used a random effects model[21,22] to analyze our data due to study heterogeneity. Data were analyzed to provide aggregated ORs for each potential risk factor.

RESULTS

Table 1 reports the outcomes measured and bias assessment of each of the 52 articles included in this meta-analysis. References for these articles are included in **Supplementary Document SB**. Bleeding outcomes were reported in 46 articles, with 33 of those reporting major bleeding. Effectiveness was reported in 35 articles. Most articles (34/52) showed a low risk of bias. Performance bias (bias as a result of failure to blind participants and/or personnel) was the most common form of bias observed (16 articles: 13 high and 6 unknown).

Our analysis of the 52 articles identified 27 potential risk factors, which we categorized into 3 groups: clinical factors, comorbidities/medical history, and genetic factors. Potential risk factors with ORs > 1 and confidence intervals (CIs) range did not cross 1 were considered "definite risk factors" if they were reported in more than one study, but were considered only "probable risk factors" if the results were reported in only a single study. Similarly, factors with ORs < 1 and CIs range did not cross 1 were considered "definite protective factors" if the protective effect was reported in more than one study or "probable protective factors" if the results were reported in only one study.

Major bleeding outcome

A total of 16 risk factors were analyzed for the major bleeding outcome (**Table 2**). Two definite risk factors significantly increased the risk of major bleeding: concomitant aspirin use (OR 2.83, 95% CI 2.04–3.94) and duration of clopidogrel maintenance therapy > 6 months (OR 1.74, 95% CI 1.21–2.50; see **Figure 2** for calculation of overall OR and CI from the relevant articles). Two probable risk factors with statistically significant ORs were identified in a single study: chronic obstructive pulmonary disease; OR 155, 95% CI 1.17–2.06) and diabetes (OR 1.64, 95% CI 1.12–2.39). Similarly, concomitant statin use (OR 0.66, 95% CI 0.52–0.85) was found to be a probable protective factor.

Any bleeding outcome

We analyzed 25 factors for any bleeding outcome (**Table 3**). Among these, four risk factors were associated with an increased risk of any bleeding. However, only three were considered definite risk factors: dual therapy with aspirin, clopidogrel therapy for > 6 months, and high maintenance dose (150 mg/day instead of the recommended 75 mg/day; (see **Figure 2** for calculation of overall OR and CI from the relevant articles). The use of a 600 mg loading dose of clopidogrel was considered a probable risk factor because one out of a total of two studies included had a weight of 99.6%.

As with the major bleeding outcome, chronic obstructive pulmonary disease and diabetes were also identified as probable risk factors for any bleeding (OR 1.53, 95% CI 1.23–1.91 and OR 1.96, 95% CI 1.45–2.66, respectively). Of note, a single study's findings indicated that concomitant statin use was both a probable protective factor for major bleeding and a probable risk factor for any major or minor bleeding. Finally, concomitant proton pump inhibitor use was a definite protective factor for any bleeding (OR 0.33, 95% CI 0.18–0.61) as these drugs are known to reduce the formation of clopidogrel's active metabolite.

Clinical ineffectiveness outcome

We identified 20 factors that can affect the clinical effectiveness of clopidogrel (**Table 4**). A decrease in renal function, both mild and severe, was found to definitively increase the risk of clinical ineffectiveness. Although this risk of ineffectiveness was 2.5 times higher with a mild decrease in renal function compared with normal renal function (OR 2.51, 95% CI 1.71–3.76), the risk nearly doubled if patients had moderate to severe renal function impairment (OR 4.76, 95% CI 3.18–7.14; see **Figure 3** for calculation of overall OR and CI from the relevant articles). The definition of mild, moderate, and severe renal function impairment is included in **Supplementary Document SC**. Finally, triple therapy (aspirin, anticoagulant, and clopidogrel), calcium channel blocker use, history of diabetes, myocardial infarction, coronary artery bypass grafting, and smoking were all identified as probable risk factors for ineffectiveness.

DISCUSSION

Our meta-analysis provides a comprehensive list of all potential risk factors for both safety and effectiveness of clopidogrel maintenance therapy. This study expanded upon the current literature in important ways. First, our careful screening of > 7,000 abstracts yielded 52 high-quality RCTs for inclusion—a larger body of literature than included in any prior study. Second, only RCTs were included in our meta-analysis as retrospective investigations were excluded, thus limiting our findings to results from only the highest-quality type of research. Finally, our study examined both bleeding and ineffectiveness, thus providing a more comprehensive assessment than in prior studies. As a result, we identified several important risk factors for either outcome—three of which were the most salient.

First, our data conclusively demonstrated that dual therapy of aspirin and clopidogrel is a risk factor for both

Table 1 Included studies with outcomes measured and bias assessment of each

No.	Studies	PMID	MB	Outcomes		Bias assessment SB	PB	DB	AB	RB
1	Ahn *et al.*	21153029	MB	B		H	H	H	L	L
2	Alexander *et al.*	18760147		B		L	L	L	L	L
3	Andell *et al.*	26452988	MB	B	E	L	L	L	L	L
4	Aradi *et al.*	21902692		B		L	L	L	L	L
5	Ari *et al.*	21239075	MB	B		H	L	L	L	L
6	Aronow *et al.*	19185647	MB	B		L	L	L	L	L
7	Bertrand *et al.*	10931801	MB	B	E	L	L	L	L	L
8	Best *et al.*	18371477		B	E	L	U	U	L	L
9	Bhatt *et al.*	20925534	MB	B	E	L	L	L	L	L
10	Bossard *et al.*	29101117	MB	B	E	L	U	L	L	L
11	Brilakis *et al.*	24016496	MB	B	E	L	L	L	L	L
12	Campo *et al.*	20951320	MB	B		L	U	L	L	L
13	Cornel *et al.*	24952863	MB	B	E	L	L	U	L	L
14	Dewilde *et al.*	23415013	MB	B	E	L	H	L	L	L
15	Didier *et al.*	28641840	MB	B	E	L	H	L	L	L
16	Diener *et al.*	15276392	MB	B	E	L	L	L	L	L
17	Eisen *et al.*	29030140	MB	B	E	L	L	L	H	L
18	Gargiulo *et al.*	28198091	MB	B	E	L	L	L	H	L
19	Girotra *et al.*	24074486		B		L	L	L	L	L
20	Guo *et al.*	27533756		B	E	L	L	L	L	L
21	Gwon *et al.*	22179532	MB	B	E	L	L	L	L	L
22	Han *et al.*	19332203	MB	B	E	L	U	L	L	L
23	Harada *et al.*	28783201	MB	B	E	L	L	L	L	L
24	Hong *et al.*	27212028	MB	B	E	L	H	L	L	L
25	Hsu *et al.*	21144850		B		L	L	L	L	L
26	Lee *et al.* (2011)	21392640	MB	B	E	L	L	L	L	L
27	Lee *et al.* (2008)	18355656			E	L	H	L	L	L
28	Liang *et al.*	24913197	MB	B	E	L	H	U	L	L
29	Ma *et al.*	29773949	MB	B		L	L	L	U	L
30	Mega *et al.*	20801494			E	L	L	L	U	L
31	Mehta *et al.*	20817281	MB	B		L	L	L	L	L
32	Nguyen *et al.*	19689661		B		L	L	L	L	L
33	Ntalas *et al.*	27081185		B		L	U	U	L	L
34	Ohkubo *et al.*	23274578		B	E	L	H	U	U	L
35	Ojeifo *et al.*	24239201			E	H	L	L	L	L
36	Park J.B. *et al.*	23328268			E	L	H	L	L	L
37	Park K.W. *et al.*	24050860	MB	B		L	L	L	L	L
38	Pourdjabbar *et al.*	27761582	MB	B	E	L	H	U	L	L
39	Price *et al.*	21406646	MB	B		L	L	L	L	L
40	Qi *et al.*	28318138	MB	B	E	L	H	L	L	L
41	Ren *et al.*	21518592		B	E	L	U	U	L	L
42	Saw *et al.*	17659194	MB		E	L	L	L	U	L
43	Tarantini *et al.*	26803236	MB	B	E	L	L	L	L	L
44	Uchiyama *et al.*	23018233		B	E	L	L	L	L	L
45	Valgimigli *et al.*	22438530	MB	B	E	L	L	L	L	H
46	Wiviott *et al.*	18757948	MB	B	E	L	L	L	L	L
47	Zhu *et al.*	25678901			E	H	L	H	L	L
48	Chen *et al.*	30467686		B	E	L	H	H	L	L
49	Chi *et al.*	29943350		B		L	H	L	L	L
50	Pan *et al.*	30742211		B		L	L	L	L	L
51	Tang *et al.*	29420189	MB	B	E	L	H	L	L	L
52	Wu *et al.*	29520080	MB	B		L	L	L	L	L

References are included in **Supplementary Document SD**.

AB, attrition bias (incomplete outcome data); B, any bleeding; DB, detection bias (blinding of outcome assessment); E, clinical effectiveness; H, high; L, low; MB, major bleeding; PB, performance bias (blinding of participants and personnel); RB, reporting bias (selective reporting); SB, selection bias (random sequence generation).
☐ Low risk; ▪ High risk; ▪ Risk unclear.

Table 2 Potential risk factors for major bleeding outcome: studies, participants, OR, and 95% CI

	Potential risk factors	Control	Total number of studies[a]	Participants	OR	95% CI
Clinical factors	300 mg loading dose of clopidogrel	No loading dose	2[6,7]	2,496	1.46	0.95–2.33
	600 mg loading dose of clopidogrel	No loading dose	2[31,38]	17,320	1.35	0.97–1.88
	Long duration of clopidogrel therapy, > 6 months	6 months of clopidogrel	8[15,18,21,23,24,40,43,45]	12,375	1.74	1.21–2.50
	High clopidogrel maintenance dose, clopidogrel 150 mg/day	Clopidogrel 75 mg/day	5[10,22,28,39,51]	21,347	1.20	0.73–1.96
	Concomitant with aspirin	Clopidogrel	3[12,14,16]	8,630	2.83	2.04–3.94
	Concomitant with cilostazol	Clopidogrel	6[1,15,22,27,37,51]	6,805	1.42	0.81–2.49
	Concomitant with statins	Clopidogrel	1[42]	15,574	0.66	0.52–0.85
Comorbidities/ medical history	History of COPD	No COPD	1[3]	9,288	1.55	1.17–2.06
	History of diabetes (DM)	No DM	1[46]	6,795	1.64	1.12–2.39
	History of MI	No MI	1[17]	12,434	0.25	0.06–1.05
	History of CABG	No CABG	1[11]	9,288	0.74	0.54–1.00
	Smoker	Nonsmoker	1[13]	3,513	1.07	0.54–2.11
	High body weight (> 65 kg)	≤ 65 kg	1[29]	1,733	0.21	0.03–1.49
Genetic	CYP2C19 LOF carrier	LOF noncarrier	2[9,52]	3,742	1.14	0.73–1.80
	Resistance to clopidogrel, 75 mg/day	Non-resistant	1[5]	145	0.51	0.06–4.70
	Resistance with high maintenance dose, 150 mg/day	Non-resistant	1[5]	94	4.28	0.46–39.81

CABG, coronary artery bypass graft; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; LOF, loss of function; MI, myocardial infarction; OR, odds ratio.
[a]Superscript numbers refer to chronological numbers of studies in **Table 1**.

major and any bleeding. Nearly 30% of patients more than 40 years of age in the United States take aspirin regularly.[23] Current percutaneous coronary intervention (PCI) guidelines recommend dual antiplatelet therapy (DAPT), commonly aspirin with clopidogrel, as the cornerstone of treatment after the placement of drug-eluting stents.[24,25] The results from Columbo *et al.*'s meta-analysis of retrospective observations found that DAPT did not increase the risk of bleeding that required further intervention (RR 1.51, 95% CI 0.92–2.49).[14] However, DAPT did increase the risk of bleeding that required a blood transfusion (RR 1.33, 95% CI 1.15–1.55). Requirement for a blood transfusion met the criteria for major bleeding in our definition. Our meta-analysis included only RCTs and included clopidogrel monotherapy as a potential control group. In contrast, Columbo *et al.*'s study included observational studies and used placebo as their control group. Nonetheless, the results from both studies align closely and suggest that adding aspirin to clopidogrel is a risk factor for major bleeding.
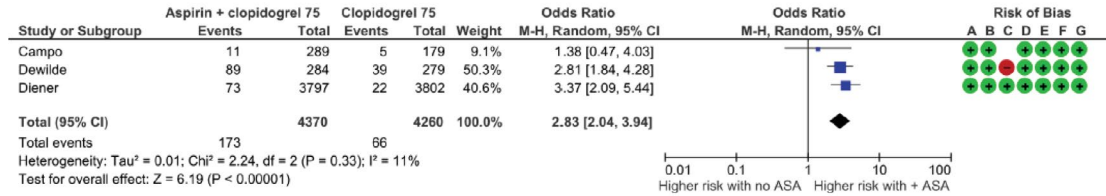
In addition, our findings showed that extended duration of clopidogrel therapy is a definite risk factor for patient safety and clinical efficacy. Clopidogrel maintenance therapy is recommended for the first 6 to 12 months post-coronary stent implantation to reduce the risk of thrombotic complications.[26] Some clinicians recommend a duration > 12 months to increase the protective effect of the medication. Our results demonstrated that clopidogrel therapy of > 6 months significantly increases the risk of both major bleeding (OR 1.74, 95% CI 1.21–5.50) and any bleeding (OR 1.44, 95% CI 1.08–1.92). Further, the risk of ineffectiveness does not decrease (OR 0.91, 95% CI 0.80–1.05). These bleeding risk results were also confirmed in

a meta-analysis by Barbarawi *et al.*[27] In their meta-analysis comparing either 3 to 6 months of DAPT or 12 months of DAPT with 24 to 48 months, the risk of major bleeding events was significantly lower in the 6 to 6 month group (OR 0.32, 95% CI 0.17–0.54) and 12-month group (OR 0.43, 95% CI 0.27–0.63). In another pooled analysis of RCTs by Giustino *et al*. with a focus on patients post-PCI, the results were conflicting for the effectiveness outcome.[28] Their analysis of 9,577 patients indicated that long-term DAPT (12 months) compared with short-term DAPT (3–6 months) had a significantly lower incidence of MACE (HR 0.56, 95% CI 0.35–0.89). Overall, the complexity of the PCI procedure and the patient population are important variables to take into account for the duration of clopidogrel maintenance therapy.
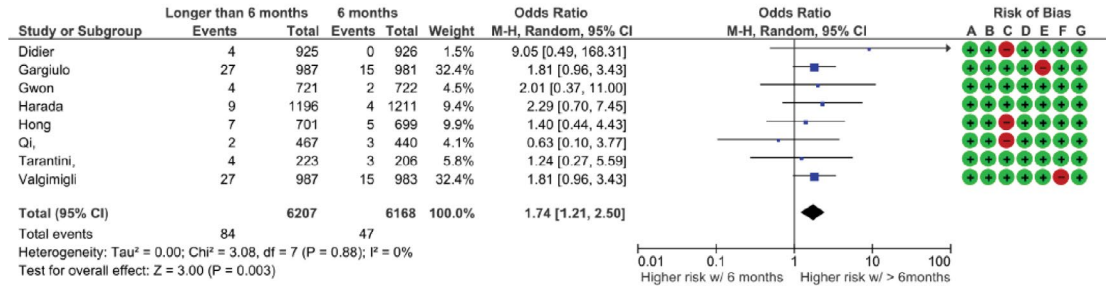
Of the 18 potential risk factors for clinical ineffectiveness identified in our study, only reduced renal function was found to be a definite risk factor—a third major finding. Even though clopidogrel is extensively metabolized by the liver, product information reports that renal function may alter effectiveness because up to 50% of the elimination process is renal.[29] Our study found that although reduced renal function does not increase the risk of bleeding, it significantly affects the drug's effectiveness. The risk of ineffectiveness was found to be four times higher with moderate to severely reduced renal function (OR 4.76, 95% CI 3.18–7.14). Although a pharmacokinetic interaction could explain this increased risk, alternative hypotheses include either a pharmacodynamic interaction or an overall increase in MACE risk in patients with chronic kidney disease, independent of clopidogrel use. Current information on the drug does not recommend any dosage adjustments based on renal
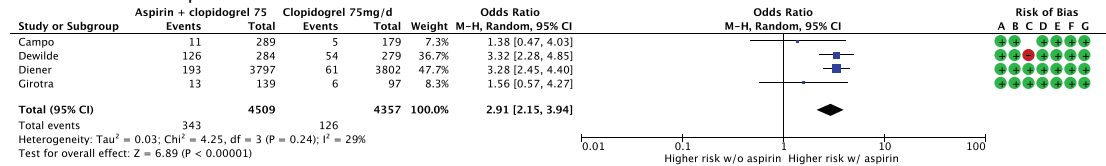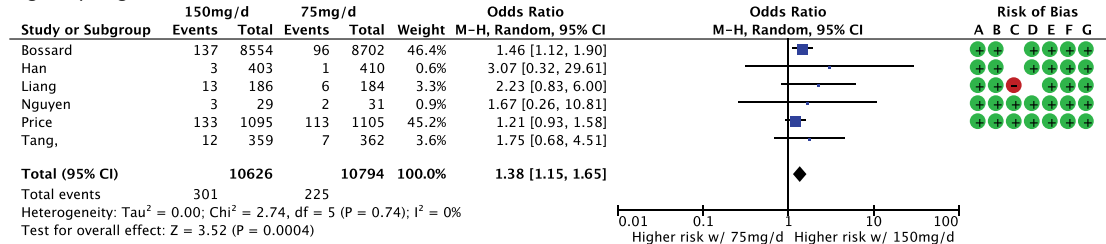
1. Major bleeding

Dual therapy with aspirin

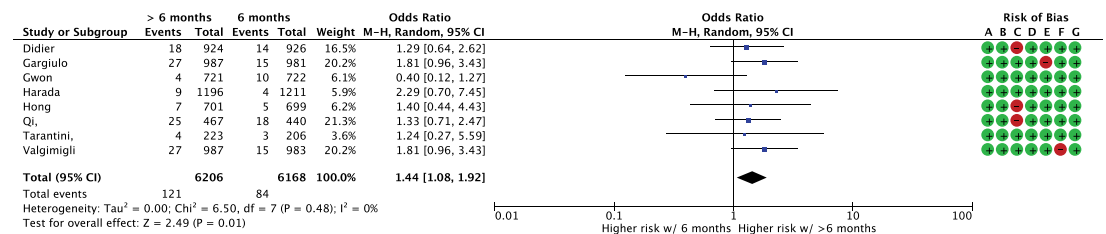| Study or Subgroup	Aspirin + clopidogrel 75 Events	Total	Clopidogrel 75 Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Campo	11	289	5	179	9.1%	1.38 [0.47, 4.03]
Dewilde	89	284	39	279	50.3%	2.81 [1.84, 4.28]
Diener	73	3797	22	3802	40.6%	3.37 [2.09, 5.44]
Total (95% CI)		**4370**		**4260**	**100.0%**	**2.83 [2.04, 3.94]**
Total events	173		66			

Heterogeneity: Tau² = 0.01; Chi² = 2.24, df = 2 (P = 0.33); I² = 11%
Test for overall effect: Z = 6.19 (P < 0.00001)

Duration of therapy

Study or Subgroup	Longer than 6 months Events	Total	6 months Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Didier	4	925	0	926	1.5%	9.05 [0.49, 168.31]
Gargiulo	27	987	15	981	32.4%	1.81 [0.96, 3.43]
Gwon	4	721	2	722	4.5%	2.01 [0.37, 11.00]
Harada	9	1196	4	1211	9.4%	2.29 [0.70, 7.45]
Hong	7	701	5	699	9.9%	1.40 [0.44, 4.43]
Qi,	2	467	3	440	4.1%	0.63 [0.10, 3.77]
Tarantini,	4	223	3	206	5.8%	1.24 [0.27, 5.59]
Valgimigli	27	987	15	983	32.4%	1.81 [0.96, 3.43]
Total (95% CI)		**6207**		**6168**	**100.0%**	**1.74 [1.21, 2.50]**
Total events	84		47			

Heterogeneity: Tau² = 0.00; Chi² = 3.08, df = 7 (P = 0.88); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)

2. Any bleeding

Concomitant with aspirin

Study or Subgroup	Aspirin + clopidogrel 75 Events	Total	Clopidogrel 75mg/d Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Campo	11	289	5	179	7.3%	1.38 [0.47, 4.03]
Dewilde	126	284	54	279	36.7%	3.32 [2.28, 4.85]
Diener	193	3797	61	3802	47.7%	3.28 [2.45, 4.40]
Girotra	13	139	6	97	8.3%	1.56 [0.57, 4.27]
Total (95% CI)		**4509**		**4357**	**100.0%**	**2.91 [2.15, 3.94]**
Total events	343		126			

Heterogeneity: Tau² = 0.03; Chi² = 4.25, df = 3 (P = 0.24); I² = 29%
Test for overall effect: Z = 6.89 (P < 0.00001)

High clopidogrel maintenance dose

Study or Subgroup	150mg/d Events	Total	75mg/d Events	Total	Weight	Odds Ratio M–H, Random, 95% CI
Bossard	137	8554	96	8702	46.4%	1.46 [1.12, 1.90]
Han	3	403	1	410	0.6%	3.07 [0.32, 29.61]
Liang	13	186	6	184	3.3%	2.23 [0.83, 6.00]
Nguyen	3	29	2	31	0.9%	1.67 [0.26, 10.81]
Price	133	1095	113	1105	45.2%	1.21 [0.93, 1.58]
Tang,	12	359	7	362	3.6%	1.75 [0.68, 4.51]
Total (95% CI)		**10626**		**10794**	**100.0%**	**1.38 [1.15, 1.65]**
Total events	301		225			

Heterogeneity: Tau² = 0.00; Chi² = 2.74, df = 5 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.52 (P = 0.0004)

Long duration of clopidogrel therapy

Study or Subgroup	> 6 months Events	Total	6 months Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Didier	18	924	14	926	16.5%	1.29 [0.64, 2.62]
Gargiulo	27	987	15	981	20.2%	1.81 [0.96, 3.43]
Gwon	4	721	10	722	6.1%	0.40 [0.12, 1.27]
Harada	9	1196	4	1211	5.9%	2.29 [0.70, 7.45]
Hong	7	701	5	699	6.2%	1.40 [0.44, 4.43]
Qi,	25	467	18	440	21.3%	1.33 [0.71, 2.47]
Tarantini,	4	223	3	206	3.6%	1.24 [0.27, 5.59]
Valgimigli	27	987	15	983	20.2%	1.81 [0.96, 3.43]
Total (95% CI)		**6206**		**6168**	**100.0%**	**1.44 [1.08, 1.92]**
Total events	121		84			

Heterogeneity: Tau² = 0.00; Chi² = 6.50, df = 7 (P = 0.48); I² = 0%
Test for overall effect: Z = 2.49 (P = 0.01)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 2 Forest plots of risk factors for bleeding outcome. ASA, aspirin; CI, confidence interval.

Table 3 Potential risk factors for any bleeding outcome: studies, participants, OR, and 95% CI

	Potential risk factors	Control	Total number of studies[a]	Participants	OR	95% CI
Clinical factors	300 mg loading dose of clopidogrel	No loading dose	2[6,7]	2,496	1.13	0.82–1.56
	600 mg loading dose of clopidogrel	No loading dose	2[31,38]	17,320	1.24	1.09–1.42
	Long duration of clopidogrel therapy, > 6 months	6 months of clopidogrel	8[15,18,21, 23,24,40,43,45]	12,374	1.44	1.08–1.92
	High clopidogrel maintenance dose, clopidogrel 150 mg/day	Clopidogrel 75 mg/day	6[10,22,28,32, 39,51]	21,420	1.38	1.15–1.65
	Low clopidogrel maintenance dose, clopidogrel 50 mg/day	Clopidogrel 75 mg/day	2[34,44]	1,287	0.83	0.60–1.14
	Concomitant with aspirin	Clopidogrel	4[12,14,15,19]	8,866	2.91	2.15–3.94
	Concomitant with cilostazol	Clopidogrel	8[1,15,22,26, 27,37,48,51]	7,423	1.27	0.87–1.86
	Concomitant with apixaban 2.5 mg	Clopidogrel	1[2]	683	2.34	1.12–4.89
	Concomitant with apixaban 10 mg	Clopidogrel	1[2]	694	3.15	1.58–6.28
	Concomitant with rivaroxaban	Warfarin	1[49]	514	0.60	0.49–0.74
	Concomitant with statins	Clopidogrel	1[13]	15,574	2.28	1.78–2.92
	Concomitant with PPIs	Clopidogrel	3[9,25,41]	4,098	0.33	0.18–0.61
Comorbidities/ medical history	History of COPD	No COPD	1[3]	9,288	1.53	1.23–1.91
	History of diabetes (DM)	No DM	1[46]	6,795	1.96	1.45–2.66
	History of MI	No MI	1[17]	12,434	0.42	0.21–0.84
	History of CABG	No CABG	1[11]	9,288	0.74	0.54–1.00
	Smoker	Nonsmoker	1[13]	3,513	1.07	0.54–2.11
	Reduced renal function, mild	Normal renal function	2[8,20]	2,139	1.06	0.42–2.67
	Reduced renal function, moderate to severe	Normal renal function	2[8,20]	1,675	1.26	0.61–2.59
	High body weight, > 65 kg	≤65 kg	1[29]	1,733	0.49	0.19–1.27
Genetic	CYP2C19 LOF carrier	LOF noncarrier	2[9,52]	3,742	0.65	0.33–1.30
	ABCB1 3435 CT/TT	CC	1[50]	1414	1.21	0.52–2.82
	Resistance to clopidogrel, 75 mg/day	Non-resistant	2[4,5]	305	0.51	0.06–4.70
	Resistance with high maintenance dose, 150 mg/day	Non-resistant	2[4,5]	20,699	3.92	0.62–24.56
	Different generic components, clopidogrel besylate	Clopidogrel bisulfate	1[33]	1,557	0.81	0.52–1.27

CABG, coronary artery bypass graft; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; LOF, loss of function; MI, myocardial infarction; OR, odds ratio; PPI, proton pump inhibitor.
[a]Superscript numbers refer to the chronological numbers of studies in **Table 1**.

impairment.[30] In addition, our results were pooled from only two studies (3,814 patients total). Nevertheless, our study suggests that both clopidogrel dose and cardiovascular risk should be closely monitored to improve clinical effectiveness in patients with reduced renal function. Our results, furthermore, highlight the need for further investigation of renal function as a risk factor.

Limitations
Our study had some limitations. First, we only included RCTs. Although RCTs are the gold standard for clinical trials, we might have overlooked other potential risk factors detected through observational or registry-based studies in more general study populations. For example, we potentially excluded many cohort studies that evaluate the dual antiplatelet therapy, as discussed in Columbo's meta-analysis.[14] Genetic studies are also a prime example of this limitation because most pharmacogenomic guidance and recommendations available at the time of analysis were evaluated through cohort studies. Although CYP2C19 mutations have been widely accepted as a risk factor for clopidogrel use in the literature, we were

only able to include two RCTs and potentially excluded many registry-based studies on this genetic risk factor. Nevertheless, using only RCTs' data allowed us to assess the risk of bias as well as analyze outcomes uniformly for many other potential risk factors. Second, heterogeneity of patient populations and outcomes in this study may limit the ability to discern the significance of the clinical ineffectiveness outcome. For example, mortality is an extreme outcome for clinical ineffectiveness of clopidogrel use. However, we were not able to separate all-cause mortality from cardiovascular-related death due to the nature of the data collected. Third, we were not able to distinguish the effects of clopidogrel monotherapy from DAPT in many included studies when aspirin was used in both the control and comparison groups. Fourth, because we sought to understand the risks and benefits of maintenance clopidogrel therapy at the recommended 75 mg daily, we assumed that the recommended dosage was used if a study did not report medication dose. However, it could be that a study that does not report dose should be considered deficient and should have been excluded from the analysis altogether.

**Table 4 Potential risk factors for clinical ineffectiveness: studies, participants, OR, and 95% CI**

	Potential risk factors	Control	Total number of studies[a]	Participants	OR	95% CI
Clinical factors	300 mg loading dose of clopidogrel	No loading dose	1[7]	683	0.77	0.20, 2.88
	600 mg loading dose of clopidogrel	No loading dose	1[38]	57	1.74	0.37, 8.07
	Long duration of clopidogrel therapy, > 6 months	6 months of clopidogrel	8[15,18,21, 23,24,40,43.45]	12,376	0.91	0.80, 1.05
	High clopidogrel maintenance dose, clopidogrel 150 mg/day	Clopidogrel 75 mg/day	4[10,22,28,51]	19,160	0.62	0.40, 0.96
	Low clopidogrel maintenance dose, clopidogrel 50 mg/day	Clopidogrel 75 mg/day	2[34,44]	1,310	0.48	0.14, 1.65
	Triple therapy with anticoagulant	DAPT	1[14]	581	2.07	1.17, 3.67
	Dual therapy with CCB	Clopidogrel	1[35]	6,795	1.40	1.15, 1.70
	Clopidogrel + aspirin	Clopidogrel	1[16]	7,599	0.93	0.82, 1.05
	Concomitant with cilostazol	Clopidogrel	7[22,26,27,37, 47,48,51]	7,099	0.67	0.42, 1.07
	Concomitant with statins	Clopidogrel	2[35,42]	22,369	0.78	0.55, 1.11
	Concomitant with PPIs	Clopidogrel	2[9,41]	3,933	0.99	0.69, 1.41
Comorbidities/ medical history	History of COPD	No COPD	1[3]	9,288	0.90	0.75, 1.07
	History of diabetes (DM)	No DM	1[46]	6,795	1.97	1.70, 2.29
	History of MI	No MI	1[17]	12,252	1.28	1.10, 1.50
	History of CABG	No CABG	1[11]	9,288	2.07	1.70, 2.50
	Smoker	Nonsmoker	1[13]	3,525	1.37	1.04, 1.80
	Reduced renal function, mild	Normal renal function	2[8,20]	2,139	2.51	1.71, 3.68
	Reduced renal function, moderate to severe	Normal renal function	2[8,20]	1,675	4.76	3.18, 7.14
Genetics	CYP2C19 LOF carrier	LOF noncarrier	2[9,52]	3742	1.21	0.98, 1.50
	ABCB1 3435 CT/TT	CC	2[30,50]	2,885	1.30	0.94, 1.79

CABG, coronary artery bypass graft; CCB, calcium channel blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; LOF, loss of function; MI, myocardial infarction; OR, odds ratio; PPI, proton pump inhibitor.
[a]Superscript numbers refer to chronological numbers of studies in **Table 1**.

Forest plots for risk factors of clinical non-effectiveness outcome

Reduced renal function (mild)
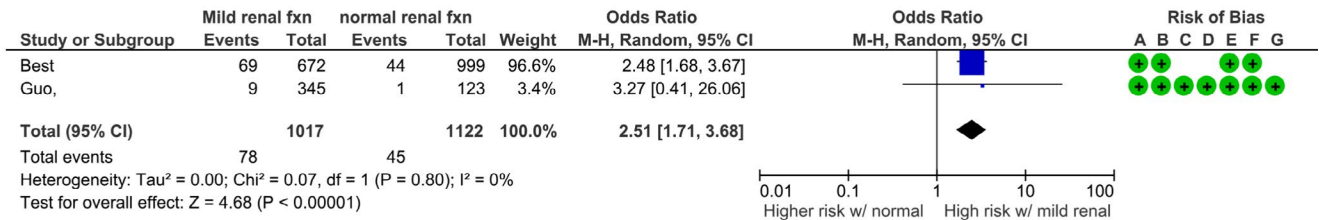
Reduced renal function (moderate to severe)
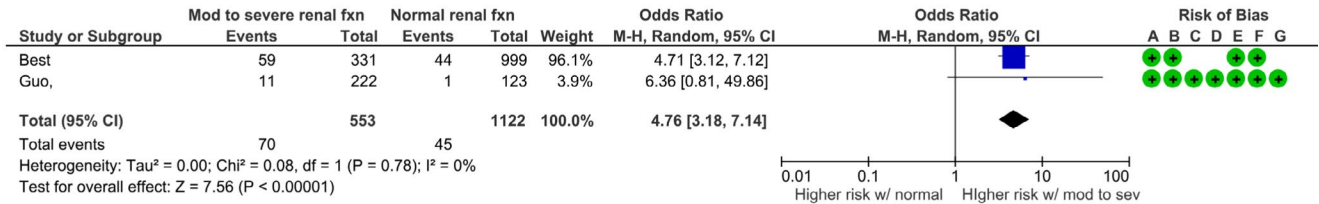
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 3 Forest plots of risk factors for clinical ineffectiveness. CI, confidence interval.

Future directions

The list of risk factors our study developed can serve as the necessary first step to develop a computational model for the cost-effectiveness of clopidogrel use. A novel analysis method that combines data from our review with patient-level data from electronic health records can help estimate the benefit, harm, and cost of clopidogrel use in a specific subpopulation. The clinical decision support developed from such a methodology could aid prescribers in selecting and dosing clopidogrel optimally. Genetic analysis also provides opportunities for future research because clopidogrel must be metabolized by CYP450 enzymes to form the active metabolite that inhibits platelet aggregation. Genetic variations in CYP2C19 are known to affect the effectiveness of clopidogrel.[31–33] The US Food and Drug Administration (FDA)-approved label for clopidogrel warns that patients with poor metabolism have a risk of ineffectiveness compared with patients with normal CYP2C19 function.[29] However, due to the nature of pharmacogenomic research, most of these studies are conducted as prospective cohort studies or retrospective analyses, rather than RCTs. As a result, we identified only a limited number of RCTs with CYP2C19 genotyping in our meta-analysis. To more completely understand the effects of genotype on the safety and efficacy of clopidogrel, future analyses will need to include prospective cohort data in addition to RCTs for genetic factors.

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