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

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Abbreviations

ADE:	adverse drug event
BARC:	Bleeding Academic Research Consortium
CI:	confidence interval
COPD:	chronic obstructive pulmonary disease
DAPT:	dual antiplatelet therapy
FDA:	US Food and Drug Administration
GUSTO:	global use of strategies to open occluded arteries
MACCE:	major adverse cardiac and cerebrovascular events
MACE:	major adverse cardiovascular events
OR:	odds ratio
PCI:	percutaneous coronary intervention
PLATO:	platelet inhibition and patient outcomes
PPI:	proton pump inhibitor
RCT:	randomized controlled trial
TIMI:	thrombolysis in myocardial infarction

Abstract

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 (OR) >1 and confidence interval (CI) >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 (more than six 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.

Introduction

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 genotype-guided clopidogrel therapy have demonstrated cost-effectiveness, non-inferiority, 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 (ADEs) account for approximately 6% of all hospital admissions,[12] and gastrointestinal bleeding from antiplatelet agents and other anticoagulants ranks among the most common ADEs.[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. 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 whole blood or PRBCs. "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 *ine*ffectiveness 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 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 1 through 3, and Review Manager (Revman 5.3, Copenhagen: The Nordic Cochrane Center, 2014) was used for the synthesis and data analysis in phase 4.

1) Search for relevant primary studies

In phase 1, we designed a comprehensive search strategy with a medical librarian (ECW) 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 four 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 the supplemental document A.

2) 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:

- Randomized controlled trial (Cohort studies, non-randomized 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 (KN, KF, EM, AK, KD, HO, HB, RY) screened the abstracts. After the pilot appraisal, each abstract was screened independently by two 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, hazard ratio, or relative risk. This process eliminated an additional 1,340 articles, producing a set of 104 articles for data extraction.

3) Quality assessment and data extraction

We used the validated Cochrane assessment tool for RCT[20] (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 supplemental document B 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.

4) 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 odds ratios 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 supplemental document D. 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, 6 unknown).

Our analysis of the 52 articles identified 27 potential risk factors, which we categorized into three groups: clinical factors, comorbidities/medical history, and genetic factors. Potential risk factors with ORs >1 and CIs ranges 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 greater than six 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 odds ratios were identified in a single study: COPD (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 more than six months, and high maintenance dose (150 mg/d instead of the recommended 75 mg/d). (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 since one out of a total of two studies included had a weight of 99.6%.

As with the major bleeding outcome, COPD 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 (PPI) 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. While this risk of ineffectiveness was 2.5 times higher with a mild decrease in renal function compared to 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 supplemental document C. 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 more than 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 metanalysis 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 major and any bleeding. Nearly 30% of patients more than 40 years of age in the US 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 randomized controlled trials 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 six to 12 months post-coronary stent implantation to reduce the risk of thrombotic complications.[26] Some clinicians recommend a duration greater than 12 months to increase the protective effect of the medication. Our results demonstrated that clopidogrel therapy of more than six 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 three to six months of DAPT or 12 months of DAPT with 24 to 48 months, the risk of major bleeding events was significantly lower in the three to six 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 randomized controlled trials 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 to short-term DAPT (three to six 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 while 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). Though a pharmacokinetic interaction could explain this increased risk, alternative hypotheses include either a pharmacodynamic interaction or an overall increase in MACE risk in chronic kidney disease patients, independent of clopidogrel use. Current information on the drug does not recommend any dosage adjustments based on renal 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 randomized control trials. While 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 since most pharmacogenomic guidance and recommendations available at the time of analysis were evaluated through cohort studies. While CYP2C19 mutations have been widely accepted as a risk factor for clopidogrel use in the literature, we only able to include 2 RCTs and potentially excluded many registry-based studies on this genetic risk factor. Nevertheless, using RCTs only 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, since 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.

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 since 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 FDA-approved label for clopidogrel warns that patients with poor metabolism have a risk of ineffectiveness compared to 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.

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 use clopidogrel concomitantly with aspirin or for more than six 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.

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Author Contributions:

KN drafted the initial manuscript. All authors provided critiques to produce the final version and approved the final manuscript. KN and TS designed the research. KN, EW, RY, KF, EM, AK, HO, and KD performed the research and analyzed data. ME and TS reviewed and provided further guidance on data analysis.

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Figure captions

Figure 1: Study procedure based on the PRISMA standard
Figure 2: Forest plots of risk factors for bleeding outcome
Figure 3: Forest plots of risk factors for clinical ineffectiveness

Supplementary information:

1. Supplemental Material
2. Prisma Checklist

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

#	Studies	PMID	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 **supplemental document D**
MB, major bleeding; B, any bleeding; E, clinical effectiveness; SB, selection bias (random sequence generation); PB, performance bias (blinding of participants and personnel); DB, detection bias (blinding of outcome assessment); AB, attrition bias (incomplete outcome data); RB, reporting bias (selective reporting)

L Low risk H High risk U Risk unclear

Table 2: Potential risk factors for major bleeding outcome: studies, participants, odds ratio (OR), and 95% confidence interval (CI)

	Potential risk factors	Control	Total number of studies[#]	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/d)	Clopidogrel 75 mg/d	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 chronic obstructive pulmonary disorder (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 myocardial infarction (MI)	No MI	1[17]	12,434	0.25	0.06, 1.05
	History of coronary artery bypass grafting (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/d)	Non-resistant	1[5]	145	0.51	0.06, 4.70
	Resistance with high maintenance dose (150 mg/d)	Non-resistant	1[5]	94	4.28	0.46, 39.81

LOF, loss of function; [#]superscript numbers refer to chronological number of study in Table 1

Table 3: Potential risk factors for any bleeding outcome: studies, participants, odds ratio (OR), and 95% confidence interval (CI)

	Potential risk factors	Control	Total number of studies[#]	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/d)	Clopidogrel 75 mg/d	6[10,22,28,32, 39,51]	21,420	1.38	1.15, 1.65
	Low clopidogrel	Clopidogrel 75	2[34,44]	1,287	0.83	0.60, 1.14

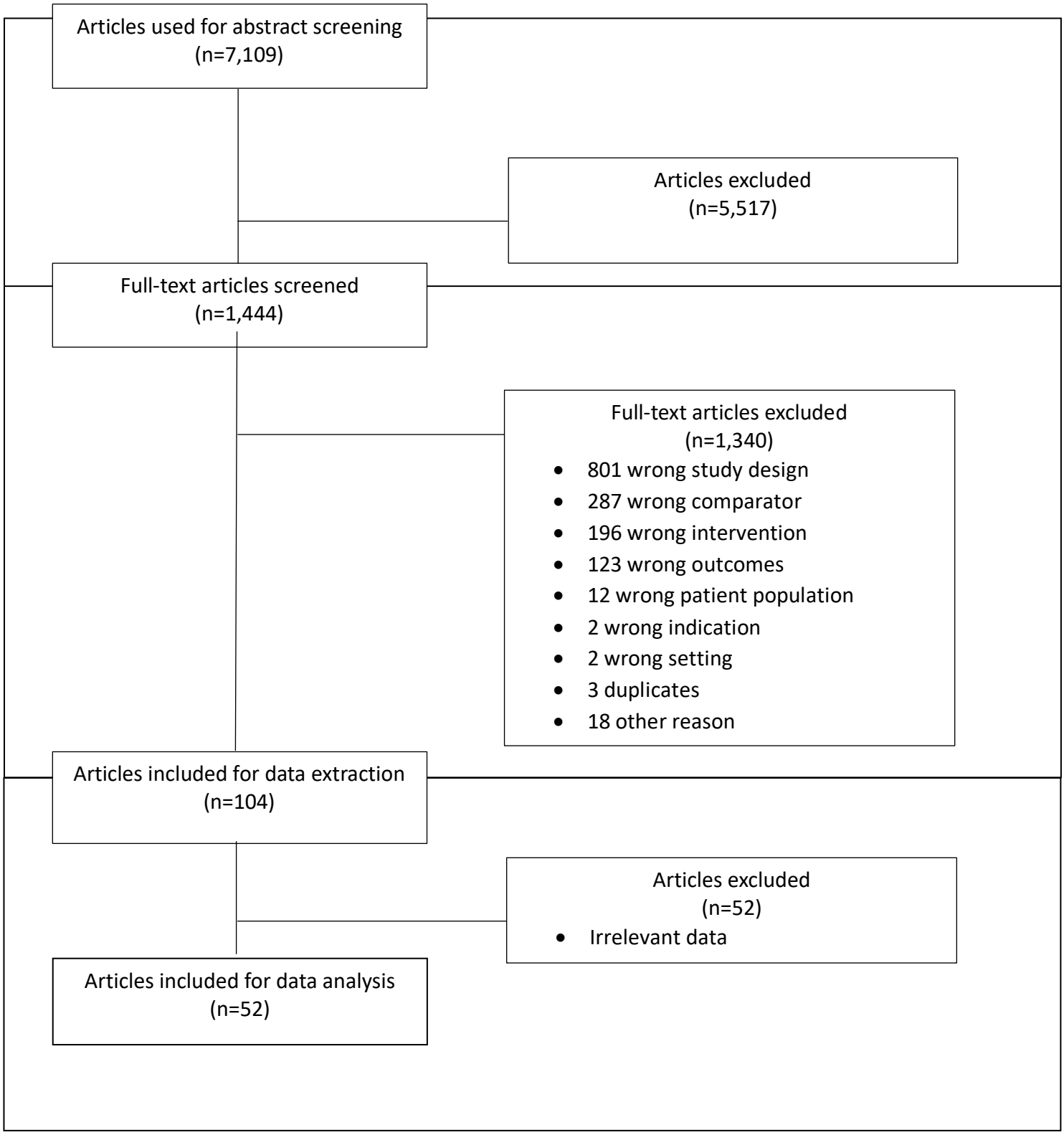
	maintenance dose (clopidogrel 50 mg/d)	mg/d				
	Concomitant with aspirin	Clopidogrel	4[12,14,15,19]	8,866	2.91	2.15, 3.94
	Concomitant with cilostazol	Clopidogrel	8[1,15,22,26, 27,37,48,51]	7,423	1.27	0.87, 1.86
	Concomitant with apixaban 2.5 mg	Clopidogrel	1[2]	683	2.34	1.12, 4.89
	Concomitant with 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 proton pump inhibitors (PPIs)	Clopidogrel	3[9,25,41]	4,098	0.33	0.18, 0.61
Comorbidities/ medical history	History of chronic obstructive pulmonary disorder (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 myocardial infarction (MI)	No MI	1[17]	12,434	0.42	0.21, 0.84
	History of coronary artery bypass grafting (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/d)	Non-resistant	2[4,5]	305	0.51	0.06, 4.70
	Resistance with high maintenance dose (150 mg/d)	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

LOF, loss of function; [#]superscript numbers refer to chronological number of study in Table 1

Table 4: Potential risk factors for clinical ineffectiveness: studies, participants, odds ratio (OR), and 95% confidence interval (CI)

	Potential risk factors	Control	Total number of studies[#]	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/d)	Clopidogrel 75 mg/d	4[10,22,28,51]	19,160	0.62	0.40, 0.96
	Low clopidogrel maintenance dose (clopidogrel 50 mg/d)	Clopidogrel 75 mg/d	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 proton pump inhibitors (PPIs)	Clopidogrel	2[9,41]	3,933	0.99	0.69, 1.41
Comorbidities/ medical history	History of chronic obstructive pulmonary disorder (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 myocardial infarction (MI)	No MI	1[17]	12,252	1.28	1.10, 1.50
	History of coronary artery bypass grafting (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

LOF, loss of function; CCB, calcium channel blocker; [#]superscript numbers refer to chronological number of study in Table 1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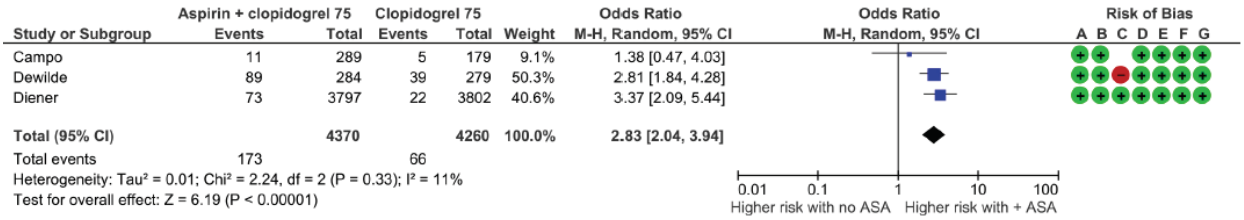
1. Major bleeding

Dual therapy with aspirin



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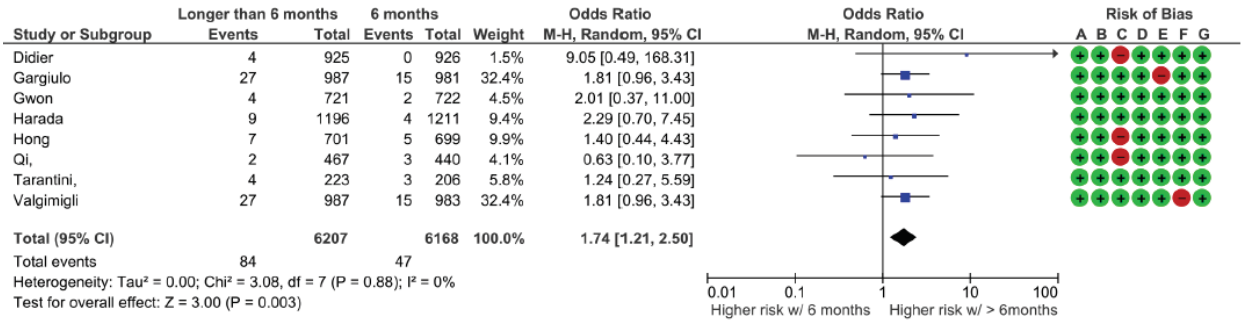
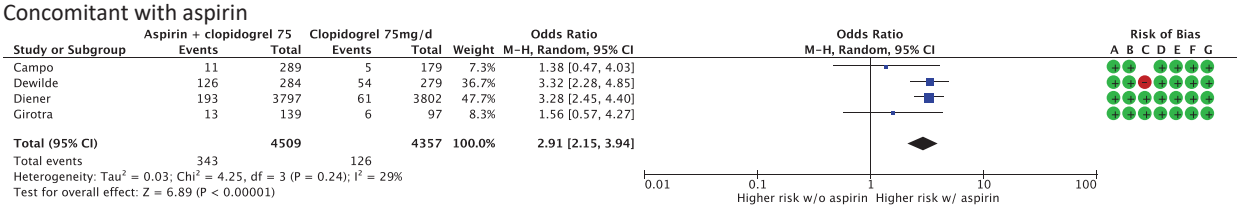
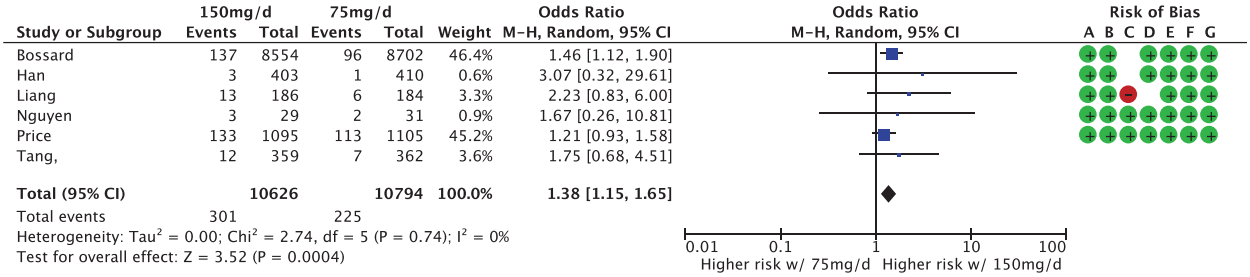


2. Any bleeding

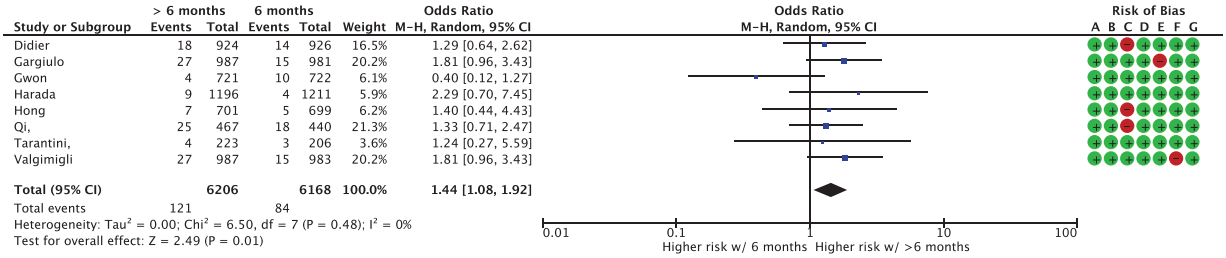
Concomitant with aspirin



High clopidogrel maintenance dose



Long duration of clopidogrel therapy



Risk of bias legend

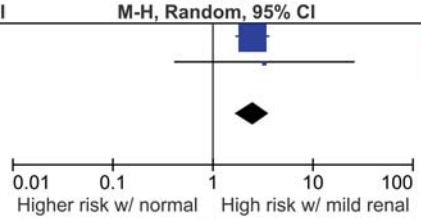
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting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

Forest plots for risk factors of clinical non-effectiveness outcome

Reduced renal function (mild)

Study or Subgroup	Mild renal fxn Events	Total	normal renal fxn Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Best	69	672	44	999	96.6%	2.48 [1.68, 3.67]
Guo,	9	345	1	123	3.4%	3.27 [0.41, 26.06]
Total (95% CI)		**1017**		**1122**	**100.0%**	**2.51 [1.71, 3.68]**
Total events	78		45			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 4.68 (P < 0.00001)



Reduced renal function (moderate to severe)

Study or Subgroup	Mod to severe renal fxn Events	Total	Normal renal fxn Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Best	59	331	44	999	96.1%	4.71 [3.12, 7.12]
Guo,	11	222	1	123	3.9%	6.36 [0.81, 49.86]
Total (95% CI)		**553**		**1122**	**100.0%**	**4.76 [3.18, 7.14]**
Total events	70		45			

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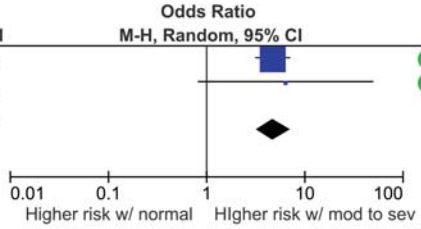
Test for overall effect: Z = 7.56 (P < 0.00001)



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