

World Journal of *Diabetes*

World J Diabetes 2020 April 15; 11(4): 90-149



**EDITORIAL**

- 90** Hydrocortisone, ascorbic acid and thiamine for sepsis: Is the jury out?

Marik PE, Varon J, Surani SR

- 95** Age of onset of diabetes and all-cause mortality

Ang GY

REVIEW

- 100** Glargine-300: An updated literature review on randomized controlled trials and real-world studies

Ghosh S, Ghosh R

- 115** Novel insight into perirenal adipose tissue: A neglected adipose depot linking cardiovascular and chronic kidney disease

Huang N, Mao EW, Hou NN, Liu YP, Han F, Sun XD

ORIGINAL ARTICLE**Basic Study**

- 126** Lack of Syndecan-1 produces significant alterations in whole-body composition, metabolism and glucose homeostasis in mice

Jaiswal AK, Sadasivam M, Aja S, Hamad ARA

SYSTEMATIC REVIEWS

- 137** Long-term effect of clopidogrel in patients with and without diabetes: A systematic review and meta-analysis of randomized controlled trials

Liang LR, Ma Q, Feng L, Qiu Q, Zheng W, Xie WX

ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Yashdeep Gupta, MD, Assistant Professor, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi 110029, India

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (WJD, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The WJD is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yu-Jie Ma*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Timothy Koch

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

EDITORIAL OFFICE

Ruo-Yu Ma, Director

PUBLICATION DATE

April 15, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Long-term effect of clopidogrel in patients with and without diabetes: A systematic review and meta-analysis of randomized controlled trials

Li-Rong Liang, Qian Ma, Lin Feng, Qi Qiu, Wen Zheng, Wu-Xiang Xie

ORCID number: Li-Rong Liang (0000-0002-9944-3025); Qian Ma (0000-0003-1208-7396); Lin Feng (0000-0002-6134-4937); Qi Qiu (0000-0002-3369-899X); Wen Zheng (0000-0003-4030-0799); Wu-Xiang Xie (0000-0001-7527-1022).

Author contributions: Liang LR and Ma Q contributed equally to this work; Xie WX conceived and designed the study; Xie WX carried out the literature searches; Liang LR and Ma Q extracted the data; Feng L and Xie WX assessed the study quality; Liang LR, Ma Q, and Xie WX performed the statistical analysis. Liang LR and Xie WX wrote the manuscript; Ma Q, Feng L, Qiu Q, and Zheng W revised the manuscript.

Supported by the National Natural Science Foundation of China, No. 81974490; Fundamental Research Funds for the Central Universities of China, No. BMU2017YJ005.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA Checklist (2009), and the manuscript was prepared and revised according to the PRISMA Checklist (2009).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution

Li-Rong Liang, Department of Clinical Epidemiology & Tobacco Dependence Treatment Research, Beijing Institute of Respiratory Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China

Qian Ma, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China

Lin Feng, Wu-Xiang Xie, Peking University Clinical Research Institute, Peking University First Hospital, Beijing 100034, China

Qi Qiu, Institute of Clinical Pharmacology, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China

Wen Zheng, Emergency Critical Care Center, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China

Corresponding author: Wu-Xiang Xie, PhD, Associate Professor, Peking University Clinical Research Institute, Peking University First Hospital, No. 8 Xishiku Street, Xicheng District, Beijing 100034, China. xiewuxiang@hsc.pku.edu.cn

Abstract

BACKGROUND

Previous studies have shown that patients with diabetes mellitus (DM) respond poorly to clopidogrel treatment.

AIM

To systematically evaluate the efficacy of clopidogrel for the treatment of acute coronary syndromes or ischemic stroke in patients with or without DM.

METHODS

PubMed, the Cochrane Central Register of Controlled Trials, and EMBASE were searched from 1980 on 27 June 2019 to identify relevant randomized controlled trials that compared the effect of a combination of clopidogrel and aspirin with aspirin alone. A random-effects meta-analysis was used to estimate the hazard ratio (HR) and its 95% confidence interval (CI). Sensitivity analysis was performed using a fixed-effect model. The I^2 statistic was used to evaluate the heterogeneity of the study data.

RESULTS

Six randomized controlled trials, comprising 43352 participants (13491 with and

NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: October 15, 2019

Peer-review started: October 15, 2019

First decision: November 19, 2019

Revised: January 19, 2020

Accepted: February 17, 2020

Article in press: February 17, 2020

Published online: April 15, 2020

P-Reviewer: Eleazu C, García-Mayor RV, Koch T

S-Editor: Wang YQ

L-Editor: A

E-Editor: Liu MY



29861 without DM) who had received antiplatelet therapy for ≥ 3 mo, were included in the meta-analysis. Compared with aspirin alone, a combination of clopidogrel and aspirin significantly reduced the risk of any cardiovascular event in patients without DM (HR = 0.78, 95%CI: 0.71–0.86, $P < 0.001$; $I^2 = 23\%$, $P = 0.26$). Clopidogrel plus aspirin also significantly reduced cardiovascular risk in patients with DM, although the effect was smaller (HR = 0.89, 95%CI: 0.81–0.99, $P = 0.030$; $I^2 = 0\%$, $P = 0.74$). Nevertheless, there was no significant difference in the efficacy of clopidogrel at reducing the risk of cardiovascular events in patients with DM *vs* those without (P for interaction = 0.062).

CONCLUSION

Thus, the present study shows that the addition of clopidogrel to aspirin significantly lowers cardiovascular risk in patients with or without DM who have experienced ischemic cardiovascular disease. The beneficial effect of the addition of clopidogrel to aspirin for patients with DM was lower than that in patients without DM, although the modifying effect of DM did not reach significance.

Key words: Clopidogrel; Diabetes; Aspirin; Meta-analysis; Randomized controlled trial

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The long-term effects of clopidogrel in patients with and without diabetes mellitus (DM) have not been systematically reviewed. The present meta-analysis firstly investigated the modifying effect of DM on the efficacy of long-term clopidogrel treatment in patients with ischemic cardiovascular disease. Although the analysis showed that the hazard ratio reduction in patients with DM was less than that in those without, this difference was not significant. The efficacy of dual antiplatelet therapy with clopidogrel and aspirin appeared to be slightly lower in patients with DM, emphasizing the need for individualized antiplatelet treatment for patients with DM after myocardial infarction or ischemic stroke.

Citation: Liang LR, Ma Q, Feng L, Qiu Q, Zheng W, Xie WX. Long-term effect of clopidogrel in patients with and without diabetes: A systematic review and meta-analysis of randomized controlled trials. *World J Diabetes* 2020; 11(4): 137-149

URL: <https://www.wjgnet.com/1948-9358/full/v11/i4/137.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v11.i4.137>

INTRODUCTION

Ischemic cardiovascular disease remains the leading cause of mortality globally^[1,2]. Early initiation of dual antiplatelet therapy with a P2Y₁₂ receptor antagonist plus aspirin is recommended for patients with ischemic cardiovascular disease in the current guidelines^[3,4]. Clopidogrel remains the most widely prescribed P2Y₁₂ receptor antagonist and is recommended by the latest guidelines for the management of ischemic stroke and acute coronary syndromes (ACS)^[5,6]. Studies have shown that patients with diabetes mellitus (DM) exhibit a poorer response to clopidogrel than patients without DM^[7,8], leading to a significant difference in the incidence of recurrence of cardiovascular events and mortality associated with DM^[9].

Previous research has shown that hyperglycemia increases platelet reactivity, and the underlying mechanisms include higher platelet receptor expression, intracellular downstream signaling abnormalities, and P2Y₁₂ mutation and expression level^[7,10]. The findings of the OPTIMUS trial, which compared the efficacy of a 150-mg maintenance dose of clopidogrel with 75 mg in 40 patients with both DM and coronary artery disease, showed that the higher maintenance dose of clopidogrel is associated with greater antiplatelet effects^[11]. Hence, it is reasonable to hypothesize that clopidogrel treatment of ischemic vascular disease would be associated with a less substantial reduction in the risk of cardiovascular events in patients with DM than in those without.

Subgroup analyses of data from several randomized controlled trials (RCTs) comparing the efficacy of a combination of clopidogrel and aspirin with aspirin alone have shown that DM reduces the effect of clopidogrel on the incidence of recurrence

of cardiovascular events and all-cause mortality, although the interactions were not significant^[12-14]. A large-scale cohort study also showed that DM was associated with a lower efficacy of clopidogrel for a reduction in 1-year cardiovascular mortality in patients with myocardial infarction^[9]. However, the long-term effects of clopidogrel in patients with and without DM have not been systematically reviewed. Therefore, we hypothesized that the presence of DM modifies the long-term efficacy of clopidogrel for a reduction in cardiovascular risk, and we performed a systematic review and meta-analysis to test this hypothesis.

MATERIALS AND METHODS

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement^[15].

Data sources

The literature search was conducted on 27 June 2019 using the Cochrane Library database for trials, EMBASE, and PubMed. The search strategy was: (1) PubMed (from 1980) 2019/06/27, (clopidogrel[Title/Abstract]) AND aspirin[Title/Abstract], article types: Clinical Trial; (2) EMBASE (from 1980) 2019/06/27, #2 #1 AND 'randomized controlled trial'/de, #1 'clopidogrel':ab,ti AND 'aspirin':ab,ti; and (3) Cochrane Central Register of Controlled Trials (CENTRAL, from 1980) 2019/06/27, keywords: ("clopidogrel" AND "aspirin"); search limits: Trials.

Study selection

The inclusion criteria for RCTs were double-blind design, clopidogrel and aspirin *vs* aspirin for the treatment of ischemic cardiovascular disease, age ≥ 18 years, subgroup analysis according to the presence of diabetes (if not reported, the corresponding author was contacted to obtain the data)^[16], and a duration of treatment ≥ 3 mo^[17]. We also included the CHARISMA trial, because the percentage of patients with documented vascular disease in the trial was high (78%)^[14].

Outcome

The outcomes assessed in the meta-analysis were fatal and non-fatal cardiovascular events. Table 1 summarizes the definitions of the primary outcomes of the included RCTs.

Quality assessment and data extraction

Two researchers (Liang LR and Ma Q) used a specially designed questionnaire to extract data independently. Consensus was reached by discussion. The Cochrane Collaboration's risk-of-bias table was used to assess the quality of the included RCTs independently by two authors (Feng L and Xie WX)^[18]. Figure 1 shows the risk of bias in the RCTs.

Statistical analysis

Review Manager 5.3 (Nordic Cochrane Center, Copenhagen, Denmark) was used to conduct the meta-analysis within random-effect models to estimate the pooled hazard ratio (HR) and its 95% confidence interval (CI). Sensitivity analysis was also performed using fixed-effect models. To evaluate the modifying effect of DM on the efficacy of clopidogrel, we used the Z-test to compare the difference between the two pooled HRs from the subgroup analyses, using the method proposed by Altman and Bland^[19]. We used the I^2 statistic to estimate the heterogeneity of the included RCTs, and the Egger test and funnel plots to estimate the level of publication bias in STATA (version 11; Stata Corp, College Station, TX). All analyses were two-sided, and an alpha value of 0.05 was used as the threshold for statistical significance.

RESULTS

Study characteristics

Figure 2 shows the study selection process, which was conducted according to the PRISMA statement. Two thousand and sixty-four publications were identified in the initial search, from which 598 duplicates were excluded, and a further 1432 articles were removed after reviewing their title and abstract. The full text of the remaining 34 articles was then reviewed independently by two researchers, and 28 of these were excluded because of a treatment duration < 3 mo, a lack of comparison between clopidogrel plus aspirin and aspirin alone, a lack of subgroup analysis according to

Table 1 Definitions of the primary efficacy outcome in each of the included trials

Trial	Definition of primary efficacy outcome
CHANCE 2013	Stroke recurrence (ischemic or hemorrhagic).
CHARISM 2006	The composite of myocardial infarction, stroke, or death from cardiovascular causes.
CREDO 2002	The composite of death, myocardial infarction, and stroke.
CURE 2001	The composite of myocardial infarction, stroke, or death from cardiovascular causes.
POINT 2018	The composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes.
SPS3 2012	Stroke recurrence (ischemic or hemorrhagic).

the presence of DM, a long-term *vs* short-term analysis, a high-dose *vs* low-dose analysis, ACS or ischemic stroke patients were not studied, or duplication (Table 2). Therefore, six RCTs, comprising 43352 participants (13491 with and 29861 without DM), were eligible for the present analysis^[12-14,16,20,21]. Table 3 presents the characteristics of the included RCTs, of which three had recruited patients who had experienced an ischemic stroke or transient ischemic attack, two had recruited ACS patients, and one had recruited patients with cardiovascular disease or multiple risk factors. Table 4 summarizes the antiplatelet treatments and daily doses used in these trials.

Effect of clopidogrel, according to diabetes status

As shown in Figure 3, compared with aspirin alone, the addition of clopidogrel to aspirin significantly reduced the risk of any cardiovascular event in patients without DM (HR = 0.78, 95%CI: 0.71–0.86, $P < 0.001$; $I^2 = 23\%$, $P = 0.26$) and also in patients with DM, although the benefit was less (HR = 0.89, 95%CI: 0.81–0.99, $P = 0.030$; $I^2 = 0\%$, $P = 0.74$). The presence of DM was associated with an 11% higher HR, although the difference in the efficacy of clopidogrel in patients with and without DM did not reach significance (P for interaction = 0.062).

Publication bias

Both funnel plots (Figure 4) and Egger tests ($P = 0.592$ for patients without DM, and $P = 0.296$ for patients with DM) showed no evidence of publication bias.

Sensitivity analysis

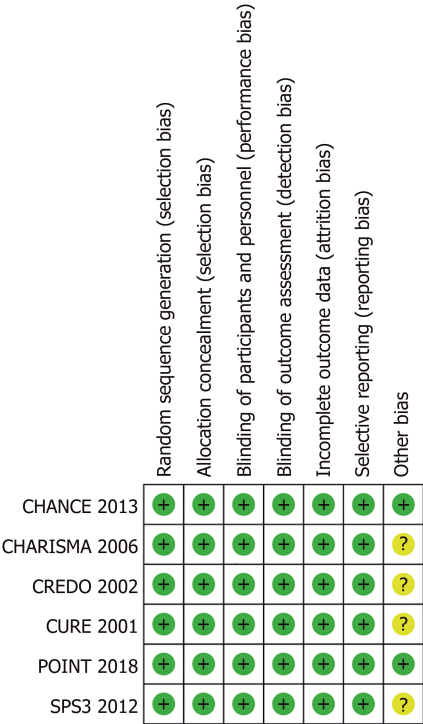
The pooled results of a meta-analysis using fixed-effect models was consistent with the principal findings of random-effect models (Figure 5). Clopidogrel treatment was associated with relative risk reductions of 11% (HR = 0.89, 95%CI: 0.81–0.99, $P = 0.030$) and 21% (HR = 0.79, 95%CI: 0.73–0.85, $P < 0.001$) for any cardiovascular event in patients with and without DM, respectively. However, the modifying effect of DM on the incidence of cardiovascular events was not significant (P for interaction = 0.064).

DISCUSSION

Our systematic review and meta-analysis found that the addition of clopidogrel to aspirin significantly reduced the risk of any cardiovascular event in patients with or without DM. In addition, the results show that the presence of DM is associated with an increase of 11% in the HR, although this difference was not significant. To our knowledge, this is the first meta-analysis to evaluate the efficacy of long-term clopidogrel treatment in patients with ischemic cardiovascular disease, according to the presence or absence of DM.

The latest evidence provided by head-to-head RCTs has led to the current guidelines for the management of ACS stating that clopidogrel is inferior to ticagrelor and prasugrel as a P2Y₁₂ inhibitor for patients with ST-segment elevation myocardial infarction or non-STE ACS^[3,4]. Recently, subgroup analyses of these RCTs have shown that the effects of ticagrelor and prasugrel are not modified by the presence of DM^[22,23]. Evidence from previous trials and the present meta-analysis indicate that it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel for the treatment of ACS patients, and especially those with DM. However, it should be noted that both ticagrelor and prasugrel are associated with higher risks of bleeding than clopidogrel; therefore, clopidogrel can still be used if ticagrelor and prasugrel are not available or are contraindicated^[3,4]. Furthermore, data regarding the clinical efficacy and safety of ticagrelor or prasugrel for the treatment of ischemic stroke are limited. The SOCRATES trial, which compared the efficacy and safety of ticagrelor and aspirin in

A



B

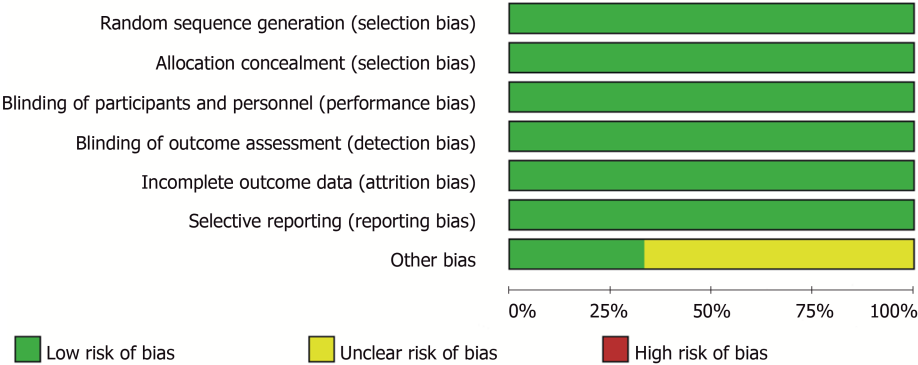


Figure 1 Risk-of-bias of included trials. A: Judgements about each source of bias in each study; B: Review authors' judgements regarding the risk of each source of bias. The data are presented as percentages across all the included studies and are classified as Low, Unclear, or High. We followed the recommended approach for assessing the risk of bias in studies included in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.3.0. This addresses seven specific domains: Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain includes one or more specific entries in a "Risk of bias" table. The tool involves assigning a judgement relating to the risk of bias for that entry. This is achieved by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgement of "Yes" indicates a low risk of bias, "No" indicates a high risk of bias, and 'Unclear' indicates an unclear or unknown risk of bias.

13199 patients who had experienced a mild ischemic stroke or high-risk transient ischemic attack, found that ticagrelor was no more effective than aspirin at lowering cardiovascular risk over 90 days^[24]. Therefore, clopidogrel remains the first choice of P2Y₁₂ inhibitor for the treatment of ischemic stroke^[6]. In the present study, a weaker effect of clopidogrel was identified in patients with DM, which implies that a new antiplatelet agent is needed for ischemic stroke patients with DM.

A prospective cohort study of 58851 patients who had experienced a myocardial infarction confirmed this hypothesis^[9]. Andersson and colleagues reported that clopidogrel treatment was associated with lesser reductions in 1-year all-cause mortality and cardiovascular mortality in patients with DM, compared to those without^[9]. The results of the large-scale cohort study were consistent with the present findings, and we consider that one of the most important reasons why the present meta-analysis did not demonstrate a modifying effect of DM was the relatively small number of RCTs included. Therefore, a second meta-analysis should be performed when data from additional RCTs become available.

Table 2 Characteristics of the excluded trials

Title	Reason for exclusion
A randomised, blinded, trial of clopidogrel <i>vs</i> aspirin in patients at risk of ischaemic events (CAPRIE)	Not clopidogrel + aspirin <i>vs</i> aspirin
Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation	Treatment duration < 3 mo; Not report subgroup results
Addition of clopidogrel to aspirin in 45852 patients with acute myocardial infarction: Randomised placebo-controlled trial	Treatment duration < 3 mo; Not report subgroup results
Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): Randomised, double-blind, placebo-controlled trial	Not clopidogrel + aspirin <i>vs</i> aspirin
Aspirin and extended-release dipyridamole <i>vs</i> clopidogrel for recurrent stroke	Not clopidogrel + aspirin <i>vs</i> aspirin
Aspirin plus clopidogrel therapy increases early venous graft patency after coronary artery bypass surgery	Treatment duration < 3 mo
Aspirin plus clopidogrel <i>vs</i> aspirin alone after coronary artery bypass grafting: The clopidogrel after surgery for coronary artery disease (CASCADE) Trial	Not report subgroup results
Clinical outcomes of patients with diabetic nephropathy randomized to clopidogrel plus aspirin <i>vs</i> aspirin alone	Duplicate trials
Clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE) trial: One year outcomes	Duplicate trials
Dose comparisons of clopidogrel and aspirin in acute coronary syndromes	High dose <i>vs</i> low dose
Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stents	Long-term <i>vs</i> short-term
Efficacy and safety outcomes of ticagrelor compared with clopidogrel in elderly Chinese patients with acute coronary syndrome	Not clopidogrel + aspirin <i>vs</i> aspirin
Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics	Treatment duration < 3 mo
Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study	Duplicate trials
Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): A randomised controlled pilot trial	Not report subgroup results
Prasugrel or double-dose clopidogrel to overcome clopidogrel low-response - The TAILOR randomized trial	Not clopidogrel + aspirin <i>vs</i> aspirin
Prasugrel <i>vs</i> clopidogrel for acute coronary syndromes without revascularization	Not clopidogrel + aspirin <i>vs</i> aspirin
Prasugrel <i>vs</i> clopidogrel in patients with acute coronary syndromes	Not clopidogrel + aspirin <i>vs</i> aspirin
PROCLAIM: Pilot study to examine the effects of clopidogrel on inflammatory markers in patients with metabolic syndrome receiving low-dose aspirin.	Treatment duration < 3 mo
Randomized clinical trial of the antiplatelet effects of aspirin-clopidogrel combination <i>vs</i> aspirin alone after lower limb angioplasty	Treatment duration < 3 mo
Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y ₁₂ antagonist, with clopidogrel in percutaneous coronary intervention	Not clopidogrel + aspirin <i>vs</i> aspirin
Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial	Not report subgroup results
Ticagrelor <i>vs</i> aspirin in acute stroke or transient ischemic attack	Not clopidogrel + aspirin <i>vs</i> aspirin
Ticagrelor <i>vs</i> clopidogrel in patients with acute coronary syndromes	Not clopidogrel + aspirin <i>vs</i> aspirin
Ticagrelor <i>vs</i> clopidogrel after fibrinolytic therapy in patients with ST-elevation myocardial infarction	Not clopidogrel + aspirin <i>vs</i> aspirin
Ticagrelor <i>vs.</i> clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome	Not clopidogrel + aspirin <i>vs</i> aspirin
Twelve or 30 mo of dual antiplatelet therapy after drug-eluting stents	Long-term <i>vs</i> short-term
Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation	Not ACS or ischemic stroke patients

Several potential mechanisms that might explain the variability in the response to clopidogrel have been suggested. Firstly, a pharmacokinetic study showed that variability in intestinal absorption is the principal cause^[25]. Second, polymorphisms in

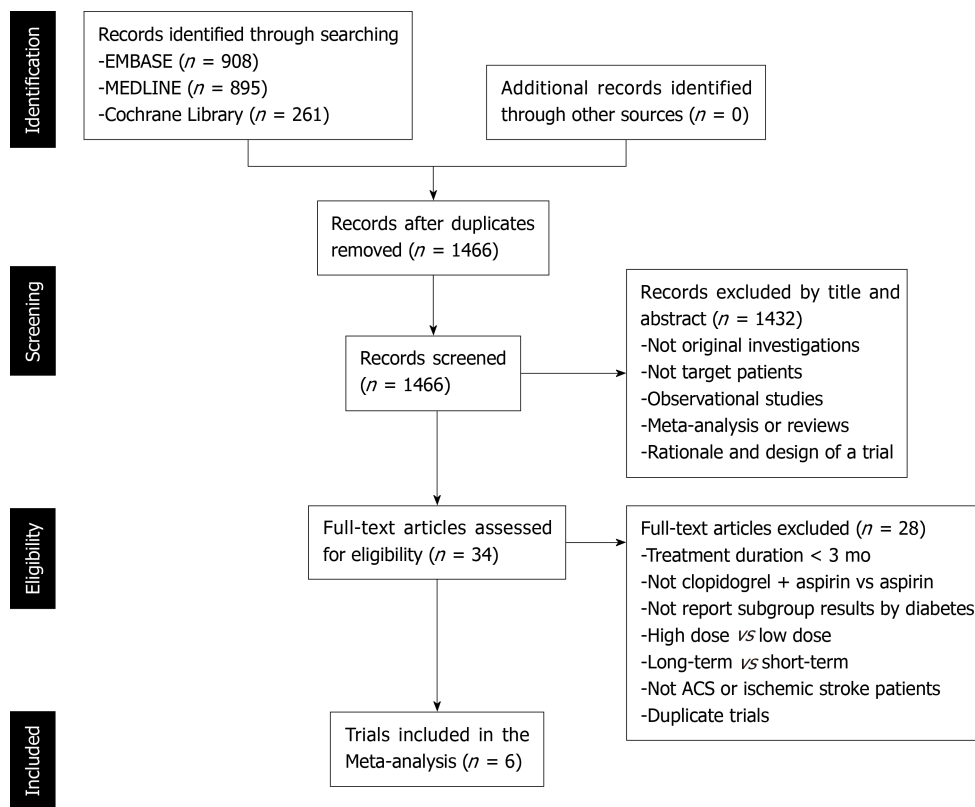


Figure 2 Study selection flow chart.

hepatic cytochrome (CYP) P450 3A, including in CYP3A4 and CYP3A5, may also be important: An inverse correlation has been shown between the percentage platelet aggregation and CYP3A4 activity in clopidogrel users^[26]. In particular, of the multiple polymorphisms of CYP3A4, the IVS10 + 12G>A variant has been shown to regulate clopidogrel responsiveness^[27]. Furthermore, a CYP3A5 polymorphism has been shown to be associated with atherothrombosis after clopidogrel treatment^[28], although there is new evidence that challenges the existence of the association between CYP3A5 genotype and clopidogrel response^[29]. Third, genetic platelet receptor polymorphisms have been implicated. Single-nucleotide polymorphisms of platelet receptors, such as GP IIIa L33P (= P1A1/2) and GP Ia 807 C/T have been suggested to be risk factors for thrombosis^[30]. Fourth, the use of concurrent medication, such as calcium channel blockers, has recently been demonstrated to be a predictor of atherothrombotic events after clopidogrel treatment^[29]. These mechanisms might also explain the effect of DM on the clopidogrel response.

Our study had several strengths: The inclusion of high-quality RCTs, large samples, no significant heterogeneity among the studies, and no evidence of publication bias. However, the study also had some limitations. First, the primary outcomes of the included RCTs were not entirely consistent, and secondary outcome data cannot be collected, because publications describing RCTs only show subgroup data for the primary outcomes. The present study only pooled the results of the primary outcomes of the included trials, which may have caused bias. Second, we estimated the pooled HRs on the basis of trial-level data, whereas pooled HRs derived from individual-level data would be more accurate. Third, although we conducted a thorough literature search to identify relevant RCTs, it is possible that some appropriate RCTs were not included in this study, implying the possibility of selection bias.

In conclusion, the present study found that the addition of clopidogrel to aspirin significantly reduced cardiovascular risk in patients with and without DM who had experienced ischemic cardiovascular disease. The beneficial effect of a combination of clopidogrel and aspirin for patients with DM appeared to be lower than that for patients without DM, although this difference did not reach significance.

Table 3 Baseline characteristics of participants in the included trials

Trial	Country	Centers	Patients	Sample size	Male %	Mean age Y	Diabetes %	Treatment duration M	Lost to follow-up %	Blinding	ITT analysis
CHANCE 2013	China	114	Minor ischemic stroke or high-risk TIA	5170	66	63	21	3	0.7	Double-blind	Yes
CHARISM 2006	Worldwide	768	CVD or multiple risk factors	15603	70	64	42	28	0.5	Double-blind	Yes
CREDO 2002	United States and Canada	99	Those would undergo elective PCI	2116	71	62	26	12	1.1	Double-blind	Yes
CURE 2001	Worldwide	482	ACS without ST-segment elevation	12562	62	64	23	12	0.1	Double-blind	Yes
POINT 2018	Worldwide	269	Acute ischemic stroke or high-risk TIA	4881	55	65	27	3	4.1	Double-blind	Yes
SPS3 2012	Worldwide	82	Recent symptomatic lacunar infarcts	3020	63	63	36	41	2.0	Double-blind	Yes

ITT: Intention-to-treat; TIA: Transient ischemic attack; CVD: Cardiovascular disease; PCI: Percutaneous coronary intervention; ACS: Acute coronary syndromes.

Table 4 Antiplatelet treatments and the daily doses used in the included trials

Trial	Drug (daily doses, mg)	
	Clopidogrel + Aspirin	Aspirin
CHANCE 2013	Clopidogrel (day 1: 300; day 2-90: 75) + Aspirin (day 1: 75-300; day 2-21: 75; day 22-90: placebo)	Aspirin (day 1: 75-300; day 2-90: 75)
CHARISM 2006	Clopidogrel (75) + Aspirin (75-162)	Aspirin (75-162)
CREDO 2002	Clopidogrel (day 1: 300; day 2 to 12 mo: 75) + Aspirin (day 1: 325; day 2 to 12 mo: 81-325)	Clopidogrel (day 2-28: 75) + Aspirin (day 1: 325; day 2 to 12 mo: 81-325)
CURE 2001	Clopidogrel (day 1: 300, and then 75) + Aspirin (75-325)	Aspirin (75-325)
POINT 2018	Clopidogrel (day 1: 600, and then 75) + Aspirin (50-325)	Aspirin (50-325)
SPS3 2012	Clopidogrel (75) + Aspirin (325)	Aspirin (325)

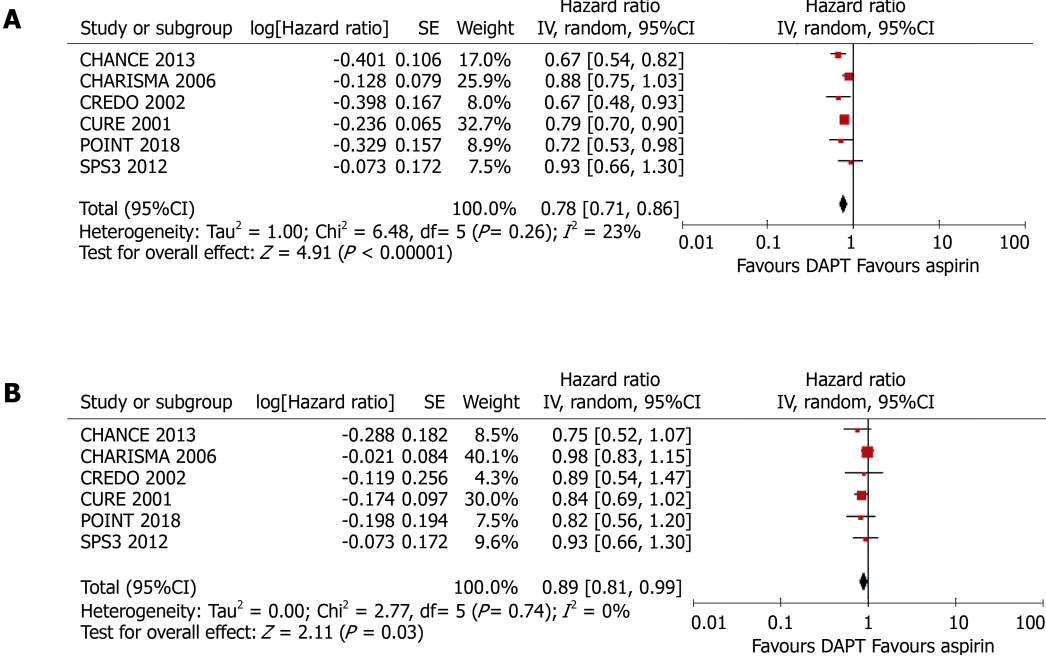


Figure 3 Meta-analyses using random-effect models conducted on the pooled data describing the effect of clopidogrel treatment on the incidence of any cardiovascular event. A: In patients without diabetes mellitus; B: In patients with diabetes mellitus. DAPT: Dual antiplatelet therapy.

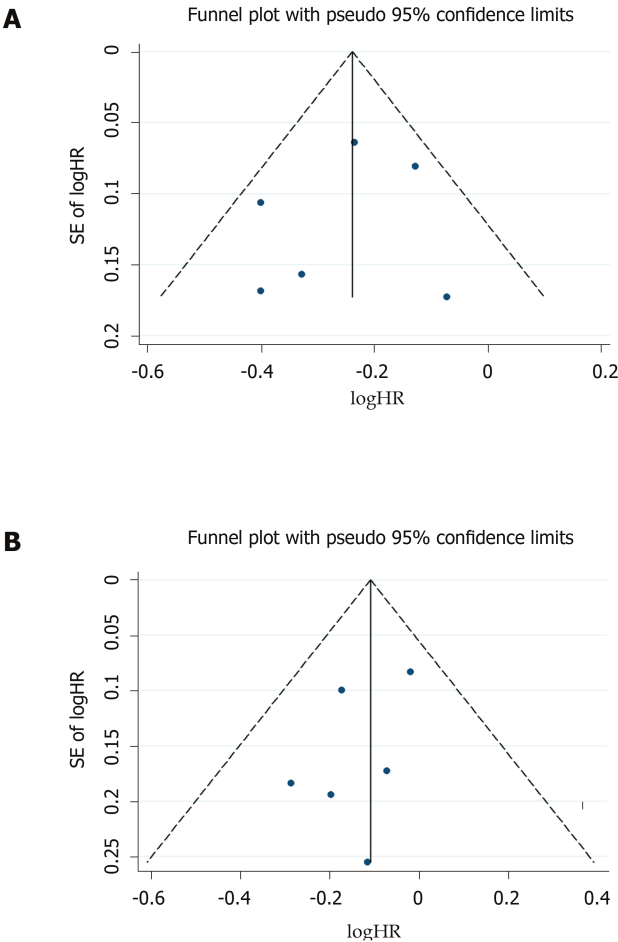


Figure 4 Funnel plot for the included studies, used to evaluate the effect of clopidogrel on the incidence of any cardiovascular event. A: In patients without diabetes mellitus; B: In patients with diabetes mellitus.

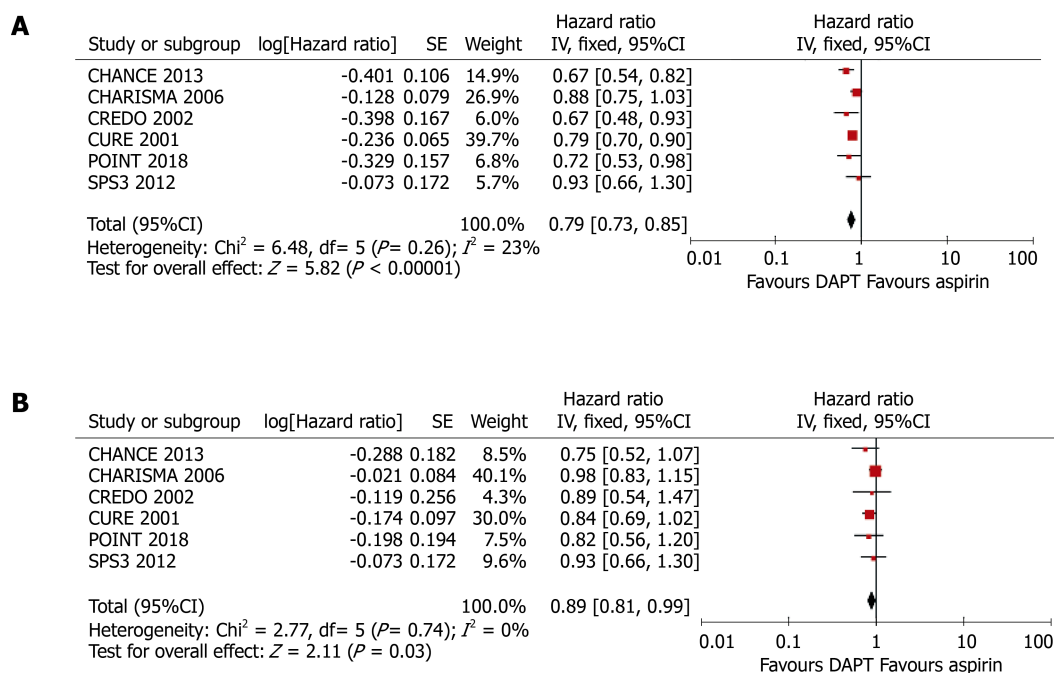


Figure 5 Meta-analyses using fixed-effect models conducted on the pooled data describing the effect of clopidogrel treatment on the incidence of any cardiovascular event. A: In patients without diabetes mellitus; B: In patients with diabetes mellitus. DAPT: Dual antiplatelet therapy.

ARTICLE HIGHLIGHTS

Research background

Clopidogrel remains the most widely prescribed P2Y₁₂ receptor antagonist and is recommended by the latest guidelines for the management of ischemic stroke and acute coronary syndromes. Studies have shown that patients with diabetes mellitus (DM) exhibit a poorer response to clopidogrel than patients without DM, leading to a significant difference in the incidence of recurrence of cardiovascular events and mortality associated with DM. However, the long-term effects of clopidogrel in patients with and without DM have not been systematically reviewed.

Research motivation

We hypothesized that the presence of DM modifies the long-term efficacy of clopidogrel for a reduction in cardiovascular risk. To our knowledge, this is the first meta-analysis to evaluate the efficacy of long-term clopidogrel treatment in patients with ischemic cardiovascular disease, according to the presence or absence of DM.

Research objectives

This study aimed to systematically evaluate the efficacy of clopidogrel for the treatment of acute coronary syndromes or ischemic stroke in patients with or without DM.

Research methods

A systematic review and meta-analysis of randomized controlled trials.

Research results

Six randomized controlled trials, comprising 43,352 participants (13,491 with and 29,861 without DM) who had received antiplatelet therapy for ≥ 3 mo, were included in the meta-analysis. Compared with aspirin alone, a combination of clopidogrel and aspirin significantly reduced the risk of any cardiovascular event in patients without DM (HR = 0.78, 95%CI: 0.71–0.86, $P < 0.001$; $I^2 = 23\%$, $P = 0.26$). Clopidogrel plus aspirin also significantly reduced cardiovascular risk in patients with DM, although the effect was smaller (HR = 0.89, 95%CI: 0.81–0.99, $P = 0.030$; $I^2 = 0\%$, $P = 0.74$). Nevertheless, there was no significant difference in the efficacy of clopidogrel at reducing the risk of cardiovascular events in patients with DM *vs* those without (P for interaction = 0.062).

Research conclusions

The present study found that the addition of clopidogrel to aspirin significantly reduced cardiovascular risk in patients with and without DM who had experienced ischemic cardiovascular disease. The beneficial effect of the addition of clopidogrel to aspirin for patients with DM was lower than that in patients without DM, although the modifying effect of DM did not reach significance. In the present study, a weaker effect of clopidogrel was identified in patients with DM, which implies that a new antiplatelet agent is needed for ischemic stroke patients with DM. We hypothesized that the presence of DM modifies the long-term efficacy of

clopidogrel for a reduction in cardiovascular risk. Cardiologist and neurologist should pay attention to the presence of DM when provide clopidogrel for patients with ischemic cardiovascular disease.

Research perspectives

A systematic review and meta-analysis of randomized controlled trials to summarize the evidence on this topic is important. A new antiplatelet agent is needed for ischemic stroke patients with DM.

ACKNOWLEDGEMENTS

We thank Prof. S. Claiborne Johnston, MD, PhD, from the Dean's Office, Dell Medical School, University of Texas at Austin, Austin, US, for providing the subgroup data according to diabetes status from the POINT trial. We also thank Mark Cleasby, PhD, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

REFERENCES

- 1 **Benjamin EJ**, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation* 2018; **137**: e67-e492 [PMID: [29386200](https://pubmed.ncbi.nlm.nih.gov/29386200/) DOI: [10.1161/CIR.0000000000000558](https://doi.org/10.1161/CIR.0000000000000558)]
- 2 **Lozano R**, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095-2128 [PMID: [23245604](https://pubmed.ncbi.nlm.nih.gov/23245604/) DOI: [10.1016/S0140-6736\(12\)61728-0](https://doi.org/10.1016/S0140-6736(12)61728-0)]
- 3 **Roffi M**, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen S, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37**: 267-315 [PMID: [26320110](https://pubmed.ncbi.nlm.nih.gov/26320110/) DOI: [10.1093/eurheartj/ehv320](https://doi.org/10.1093/eurheartj/ehv320)]
- 4 **Ibanez B**, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; **39**: 119-177 [PMID: [28886621](https://pubmed.ncbi.nlm.nih.gov/28886621/) DOI: [10.1093/eurheartj/ehx393](https://doi.org/10.1093/eurheartj/ehx393)]
- 5 **Valgimigli M**, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery

- (EACTS). *Eur Heart J* 2018; **39**: 213-260 [PMID: [28886622](#) DOI: [10.1093/eurheartj/ehx419](#)]
- 6 **Powers WJ**, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018; **49**: e46-e110 [PMID: [29367334](#) DOI: [10.1161/STR.0000000000000158](#)]
- 7 **Hu L**, Chang L, Zhang Y, Zhai L, Zhang S, Qi Z, Yan H, Yan Y, Luo X, Zhang S, Wang Y, Kunapuli SP, Ye H, Ding Z. Platelets Express Activated P2Y₁₂ Receptor in Patients With Diabetes Mellitus. *Circulation* 2017; **136**: 817-833 [PMID: [28637879](#) DOI: [10.1161/CIRCULATIONAHA.116.026995](#)]
- 8 **Schuetz C**, Steffens D, Witkowski M, Stellbaum C, Bobbert P, Schultheiss HP, Rauch U. The effect of clopidogrel on platelet activity in patients with and without type-2 diabetes mellitus: a comparative study. *Cardiovasc Diabetol* 2015; **14**: 15 [PMID: [25645908](#) DOI: [10.1186/s12933-015-0182-7](#)]
- 9 **Andersson C**, Lyngbæk S, Nguyen CD, Nielsen M, Gislason GH, Køber L, Torp-Pedersen C. Association of clopidogrel treatment with risk of mortality and cardiovascular events following myocardial infarction in patients with and without diabetes. *JAMA* 2012; **308**: 882-889 [PMID: [22948698](#) DOI: [10.1001/2012.jama.10779](#)]
- 10 **Ferreiro JL**, Angiolillo DJ. Diabetes and antiplatelet therapy in acute coronary syndrome. *Circulation* 2011; **123**: 798-813 [PMID: [21343595](#) DOI: [10.1161/CIRCULATIONAHA.109.913376](#)]
- 11 **Angiolillo DJ**, Shoemaker SB, Desai B, Yuan H, Charlton RK, Bernardo E, Zenni MM, Guzman LA, Bass TA, Costa MA. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. *Circulation* 2007; **115**: 708-716 [PMID: [17261652](#) DOI: [10.1161/CIRCULATIONAHA.106.667741](#)]
- 12 **Yusuf S**, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345**: 494-502 [PMID: [11519503](#) DOI: [10.1056/NEJMoa010746](#)]
- 13 **Steinhuyl SR**, Berger PB, Mann JT, Fry ET, DeLago A, Wilmer C, Topol EJ; CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **288**: 2411-2420 [PMID: [12435254](#) DOI: [10.1001/jama.288.19.2411](#)]
- 14 **Bhatt DL**, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhuyl SR, Weber MA, Brennan DM, Fabry-Ribaud L, Booth J, Topol EJ; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; **354**: 1706-1717 [PMID: [16531616](#) DOI: [10.1056/NEJMoa060989](#)]
- 15 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: [19621072](#) DOI: [10.1371/journal.pmed.1000097](#)]
- 16 **Johnston SC**, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY; Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med* 2018; **379**: 215-225 [PMID: [29766750](#) DOI: [10.1056/NEJMoa1800410](#)]
- 17 **Palacio S**, Hart RG, Pearce LA, Benavente OR. Effect of addition of clopidogrel to aspirin on mortality: systematic review of randomized trials. *Stroke* 2012; **43**: 2157-2162 [PMID: [22826359](#) DOI: [10.1161/STROKEAHA.112.656173](#)]
- 18 **Higgins JPT**, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: [www.cochrane-handbook.org](#)
- 19 **Altman DG**, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003; **326**: 219 [PMID: [12543843](#) DOI: [10.1136/bmj.326.7382.219](#)]
- 20 **Wang Y**, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, Jia J, Dong Q, Xu A, Zeng J, Li Y, Wang Z, Xia H, Johnston SC; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013; **369**: 11-19 [PMID: [23803136](#) DOI: [10.1056/NEJMoa1215340](#)]
- 21 **SPS3 Investigators**, Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med* 2012; **367**: 817-825 [PMID: [22931315](#) DOI: [10.1056/NEJMoa1204133](#)]
- 22 **Dalby AJ**, Gottlieb S, Cyr DD, Magnus Ohman E, McGuire DK, Ruzyllo W, Bhatt DL, Wiviott SD, Winters KJ, Fox KAA, Armstrong PW, White HD, Prabhakaran D, Roe MT; TRILOGY ACS Investigators. Dual antiplatelet therapy in patients with diabetes and acute coronary syndromes managed without revascularization. *Am Heart J* 2017; **188**: 156-166 [PMID: [28577671](#) DOI: [10.1016/j.ahj.2017.03.015](#)]
- 23 **Bhatt DL**, Bonaca MP, Bansilal S, Angiolillo DJ, Cohen M, Storey RF, Im K, Murphy SA, Held P, Braunwald E, Sabatine MS, Steg PG. Reduction in Ischemic Events With Ticagrelor in Diabetic Patients With Prior Myocardial Infarction in PEGASUS-TIMI 54. *J Am Coll Cardiol* 2016; **67**: 2732-2740 [PMID: [27046160](#) DOI: [10.1016/j.jacc.2016.03.529](#)]
- 24 **Johnston SC**, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS; SOCRATES Steering Committee and Investigators. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med* 2016; **375**: 35-43 [PMID: [27160892](#) DOI: [10.1056/NEJMoa1603060](#)]
- 25 **Taubert D**, Kastrati A, Harlfinger S, Gorchakova O, Lazar A, von Beckerath N, Schömig A, Schömig E. Pharmacokinetics of clopidogrel after administration of a high loading dose. *Thromb Haemost* 2004; **92**: 311-316 [PMID: [15269827](#) DOI: [10.1160/TH04-02-0105](#)]
- 26 **Lau WC**, Gurbel PA, Watkins PB, Neer CJ, Hopp AS, Carville DG, Guyer KE, Tait AR, Bates ER. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. *Circulation* 2004; **109**: 166-171 [PMID: [14707025](#) DOI: [10.1161/01.CIR.0000112378.09325.F9](#)]
- 27 **Angiolillo DJ**, Fernandez-Ortiz A, Bernardo E, Ramirez C, Cavallari U, Trabetti E, Sabaté M, Hernández R, Moreno R, Escaned J, Alfonso F, Bañuelos C, Costa MA, Bass TA, Pignatti PF, Macaya C.

- Contribution of gene sequence variations of the hepatic cytochrome P450 3A4 enzyme to variability in individual responsiveness to clopidogrel. *Arterioscler Thromb Vasc Biol* 2006; **26**: 1895-1900 [PMID: 16645157 DOI: 10.1161/01.ATV.0000223867.25324.1a]
- 28 **Suh JW**, Koo BK, Zhang SY, Park KW, Cho JY, Jang IJ, Lee DS, Sohn DW, Lee MM, Kim HS. Increased risk of atherothrombotic events associated with cytochrome P450 3A5 polymorphism in patients taking clopidogrel. *CMAJ* 2006; **174**: 1715-1722 [PMID: 16754899 DOI: 10.1503/cmaj.060664]
- 29 **Rodríguez-González F**, Martínez-Quintana E, Saavedra P, Medina-Gil JM, Riaño M, Garay-Sánchez P, Tugores A. CYP2C19 or CYP3A5 Genotyping Does Not Predict Clinical Response to Clopidogrel. *J Clin Pharmacol* 2018; **58**: 1274-1283 [PMID: 29723426 DOI: 10.1002/jcph.1144]
- 30 **Beer JH**, Pederiva S, Pontiggia L. Genetics of platelet receptor single-nucleotide polymorphisms: clinical implications in thrombosis. *Ann Med* 2000; **32** Suppl 1: 10-14 [PMID: 11209974]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

