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SYSTEMATIC REVIEW AND META-ANALYSIS

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A Meta-Analysis of Randomized Controlled Trials on Antiplatelet Agents Versus Placebo/Control for Treating Peripheral Artery Disease

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Abstract: Effect of aspirin (antiplatelet agents) in patients with peripheral artery disease (PAD) was still controversial. Varying studies reported varying results. Therefore, we did this meta-analysis to investigate if aspirin could reduce cardiovascular events in patients with PAD.

A comprehensive literature search (PubMed, CCTR, Embase, Web of Science, CNKI, CBM-disc, and relevant websites) was conducted from 1990 to September 2014. The key search terms (''aspirin,'' ''PAD,'' ''peripheral arterial occlusive diseases,'' and ''claudication'') produced 9 high-quality randomized controlled trials (RCTs) of aspirin versus placebo/control. Mantel–Haenszel random-effects model was used to analysis of the 9 RCTs. The primary outcome was the cardiovascular events.

Nine RCTs, composed of 9526 patients (4786 aspirin-treated and 4740 placebo or control-treated patients), were meta-analyzed. The results indicated that compared to placebo/control, aspirin could not significantly reduce the cardiovascular events (OR = 0.81, 95% CI = 0.56–1.15). Moreover, aspirin could not produce better effect on prevention of nonfatal myocardial infarction (OR = 0.98, 95% CI = 0.52–1.84), nonfatal stroke (OR = 0.89, 95% CI = 0.69–1.14), cardiovascular death (OR = 0.97, 95% CI = 0.68–1.38), any death (OR = 1.05, 95% CI = 0.85–1.30), and major bleeding (OR = 1.16, 95% CI = 0.82–1.65) than placebo/control. But aspirin, as monotherapy therapy, did significantly reduce the risk of nonfatal stroke (OR = 0.42, 95% CI = 0.21–0.84).

Aspirin, as monotherapy or combination therapy, did not result in a significant decrease in the cardiovascular events. But aspirin, as monotherapy therapy, did significantly reduce the risk of nonfatal stroke. Our conclusion might help clinicians in clinical treating PAD. Future studies are needed to draw firm conclusions about the clinical benefit and risks of aspirin and other antiplatelet agents.

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Abbreviations: ABI = ankle-brachial index, CI = confidence interval, CLI = critical limb ischemia, IC = intermittent claudication, IMS = Information Management System, MI = myocardial infarction, OR = odds ratio, PAD = peripheral artery disease, RCTs = randomized controlled trials.

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INTRODUCTION

Peripheral artery disease (PAD) refers to chronic narrowing or atherosclerosis of the lower extremities.[1] Symptoms of PAD includes intermittent claudication (IC), critical limb ischemia (CLI) and acute limb ischemia. PAD and coronary artery disease have a similar atherosclerotic process and share similar risk factors: gender, smoking, age, high cholesterol, diabetes, hypertension, and renal insufficiency.[2] PAD is powerful indicator of systemic atheroma. Patients with this disease have an increased risk of myocardial infarction (MI), stroke, and are 6 times more likely to die from cardiovascular disease within 10 years than patients without PAD.[3] On the basis of an ankle-brachial index (ABI) < 0.90, there were an average of 5 million adults (>40 years) who were classified as having PAD in 2000.[4] Previous studies reported that patients with PAD have a 15-year survival rate of ~22% compared with 78% in patients without such disease.[5,6]

Generally, the goals of treatment for patients with PAD include cardiovascular protection, preservation of walking and functional status, relief of symptoms, and prevention of amputation. Among the existed treatment methods, antiplatelet agents have an important role in preventing cardiovascular events, which are widely used to prevent the recurrence of cardiovascular events. These agents act on the platelet activation process while GIIb/IIa inhibitors impede platelet aggregation by blocking activated fibrinogen receptors.[7] Some studies reported that antiplatelet agents could reduce future secondary cardiovascular events in patients with PAD.[8–10] Aspirin, as antiplatelet agent, can block thromboxane synthesis by acetylation of platelet cyclooxygenase. Nowadays, aspirin are widely used for primary and secondary prevention of cardiovascular and cerebrovascular events in patients with PAD.[11,12] However, this phenomenon might be caused by an incorrectly assumption that the antiplatelet agents studied in PAD was aspirin. Actually, in the population with PAD the results were driven mainly by nonaspirin antiplatelet agents.[13] Moreover, clinical guidelines have recommended patients with risk factors for coronary heart disease to take aspirin for cardiovascular prevention,[14] although the effect of aspirin on patients with PAD is still controversial.[15,16] Meanwhile, researchers reported that the use of aspirin was associated with bleeding adverse events.[17]

To assess the benefit of aspirin in treating PAD, previous systematic reviews have done much work.[18,19] But one thing should be noticed, many included studies in these reviews were performed more than thirty years ago. Nowadays, the diagnosis and treatment of PAD have changed. Therefore, the applicability of the conclusions to current patients might be limited. Furthermore, recently, several randomized controlled trials (RCTs) on aspirin for PAD treatment have been published.[20,21] Therefore, there is an urgent need for additional systematic review to assess the effect of aspirin on treating PAD. In this

meta-analysis, in order to make the conclusion more robust, we only included the studies from 1990 to 2014.

METHODS

This study is a meta-analysis, so the ethical statement is not required.

Study Selection

The first step of the meta-analysis was a selective literature search for potential studies. Scientific and medical databases, including 4 international databases (PubMed, Web of Science, CCTR, Embase), 2 Chinese databases (CNKI and CBM-disc), and relevant websites from 1990 to September 2014, were searched for potential RCTs on aspirin in the treatment of patients with PAD. The key search terms were aspirin, PAD, peripheral arterial diseases, peripheral arterial occlusive diseases and claudication, as well as the different combinations of these key words. No language was imposed to mitigate potential bias. Meanwhile, to avoid overlooking potential studies, the conference summaries and reference documents listed in the studies were also researched.

Inclusion Criteria

Among the studies identified in the initial search, only those meeting the following criteria were used for subsequent analysis: studies about aspirin treatment versus placebo or control group; patients over 18 years of age with PAD; informed consent provided; outcomes included cardiovascular death, or nonfatal myocardial infarction (MI), or nonfatal stroke, or all-cause mortality, or major bleeding. Meanwhile, studies with no events in any of the study groups were excluded; studies with nonrandom allocation, case reports, and reviews were also excluded.

Outcome Definition

The effect of aspirin on the prevention of composite cardiovascular end points was chosen as the primary outcome. Each component of the primary end point (cardiovascular death, or nonfatal MI, or nonfatal stroke) and all-cause mortality were chosen as the secondary outcome. The occurrence of major bleeding as defined by each study was chosen as the safety outcome. The treatment endpoint was preferentially viewed as the study endpoint.

Bias Risk Measures

Two primary authors of this study served as reviewers to independently assess the quality of each potential study according to the Cochrane Collaboration criteria. Bias risk was determined by the following points: randomization quality, allocation concealment, outcome blinding assessment, similarity in baseline clinical characteristics and incomplete data reported. Studies with 3 or more bias risks were not included in this meta-analysis.

Data Extraction

Two reviewers independently completed the following works: verified all potentially suitable studies by the aforementioned criteria; assessed the quality of the identified studies; completed a standardized data extraction form. Any disagreements were resolved by discussion. Data retrieved from the studies included the first author, year of publication, country of origin, participant characteristics, the number of patients, therapy period, intervention methods and outcomes. For data that could not be directly extracted from the studies, good faith efforts were applied to obtain the data by dispatching e-mails to the author, researching other studies citing the study in question, and researching associated conference summaries.

Statistical Analysis

RevMan5.0 software (Cochrane Information Management System [IMS]) and STATA software 8.0 (Stata Corporation, College Station, TX) were used to perform statistical analyses. This analysis was conducted according to the recommendations of Sacks et al.[22] Dichotomous data were chosen for clinical reasons. In order to make the interpretation of results easier for clinicians,[23] the odds ratio (OR) reduction of aspirin therapy was used as an efficacy measure in lieu of the continuous symptom score. Therefore, in this meta-analysis, we used the summary OR and 95% confidence intervals (CI) as the effect parameters. The Mantel–Haenszel random-effects model was used here, as it was assumed that the included studies probably had varying true treatment effects.[24] If needed, sensitivity and subgroup analysis were conducted. We assessed heterogeneity using the Chi-square based Q test and I squared index (I^2) for each analysis.[25,26] Both Egger test and inverted funnel plots were used to assess the potential publication bias. All tests were 2-sided with statistical significance set to a $P < 0.05$ unless otherwise stated.

RESULTS

Literature Search

The initial Internet search yielded 257 potentially relevant studies. In order to obtain the studies that met our inclusion criteria, we did the following steps: 103 studies were excluded because their titles did not meet the aforementioned inclusion criteria; 124 studies from the rest of studies were excluded by reviewing the abstracts; a total of 21 studies from the rest of

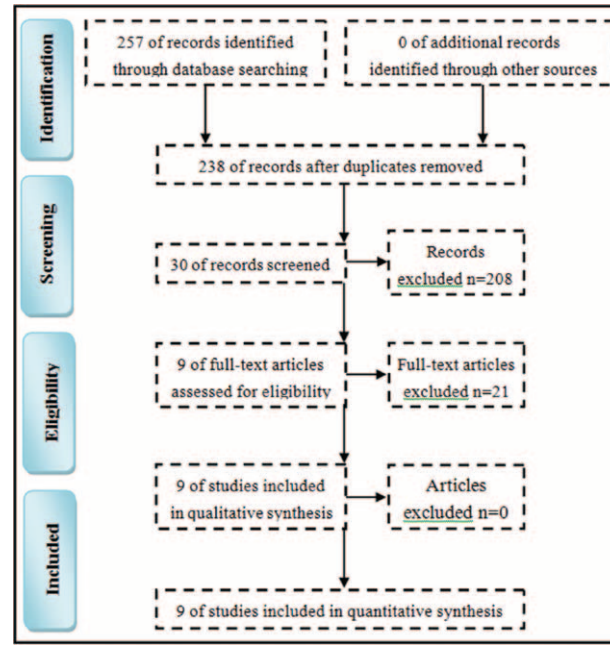

FIGURE 1. Workflow of literature search.

TABLE 1. Demographic and Clinical Characteristics of Included Studies

Refs.	Patient	Number	Mean Age	M/F	Experiment	Control	Follow-Up	Country
Chen et al[31]	PAD	38	51–91 years	21/17	100 mg aspirin	100 mg cilostazol	8–30 months	China
Fu et al[32]	PAD, ABI < 0.9	126	59 years	105/21	100 mg aspirin	1. Molecular heparin 2. Placebo	Not available	China
Katakami et al[21]	Diabetes with PAD	297	63 years	155/142	81–100 mg aspirin	100–200 mg cilostazol	2 years	Japan/Korea/China/ Philippines
Belch et al[13]	Diabetes with PAD, ABI ≤ 0.99	1276	60 years	561/715	1. 100 mg aspirin	1. Placebo	6.7 years	United Kingdom
					2. 100 mg aspirin + antioxidant	2. Antioxidant		
Catalano et al[27]	Outpatients with stage I–II PAD	366	66 years	282/84	1. 100 mg aspirin	1. Placebo	21 months	Italy
					2. 100 mg aspirin + antioxidant	2. Antioxidant		
CAPRIE Steering Committee[10]	Symptomatic PAD	6452	64 years	4678/1774	325 mg aspirin	75 mg clopidogrel	1.91 years	Canada
Study group on pharmacological treatment after PTA[28]	PAD	223	66 years	143/80	50 mg aspirin + 400 mg dipyridamole	Placebo	30 days	Sweden
McCollum et al[30]	PAD	549	67 years	412/137	600 mg aspirin + 300 mg dipyridamole	Placebo	35 months	United Kingdom
Heiss et al[29]	PAD	199	62 years	133/66	1. 990 mg aspirin + 225 mg dipyridamole	Placebo	6 months	Germany
					2. 300 mg aspirin			

ABI = ankle-brachial index, F = female, M = male, PAD = peripheral artery disease.

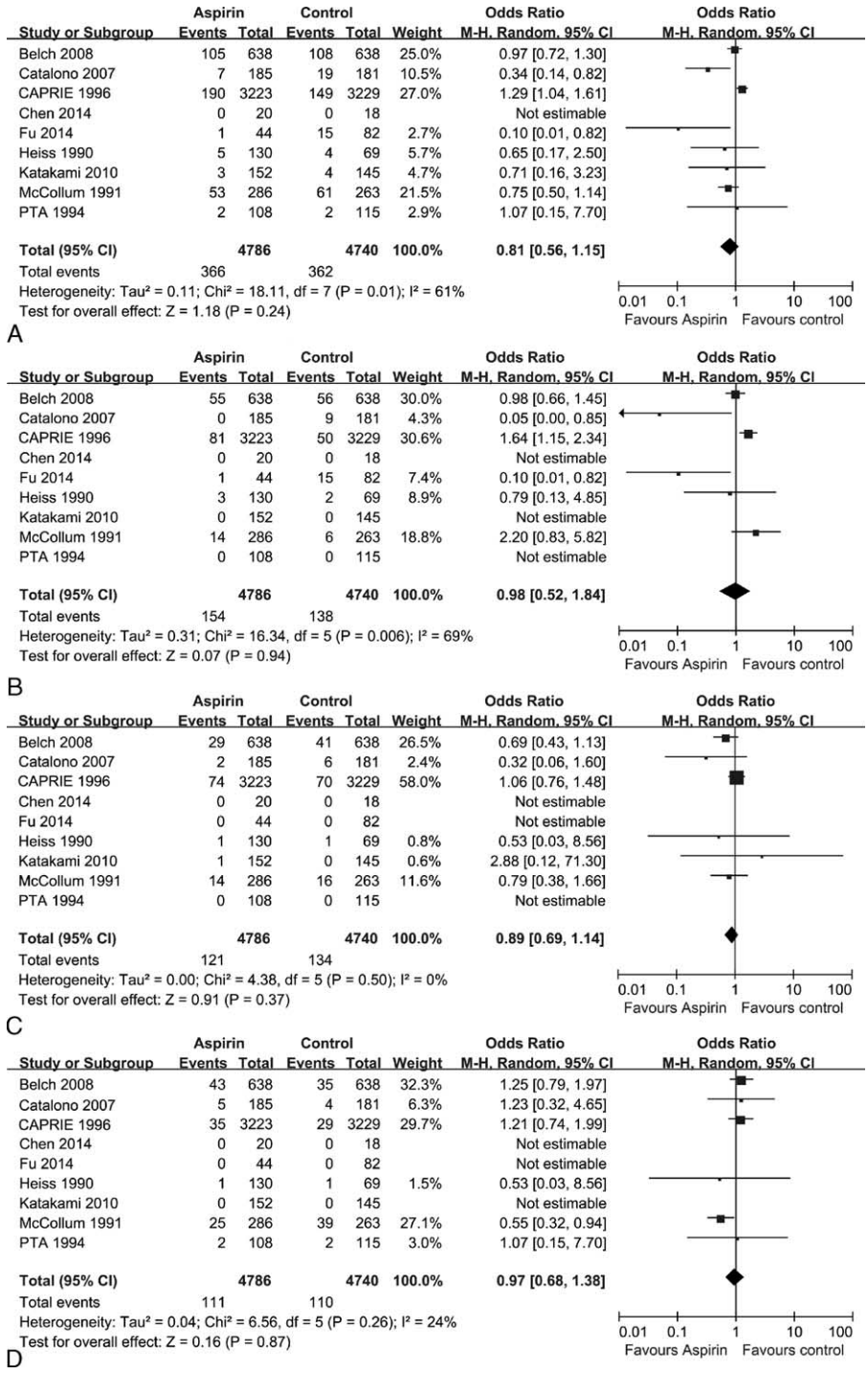

FIGURE 2. Meta-analysis of any aspirin on composite cardiovascular end points (A), nonfatal myocardial infarction (B), nonfatal stroke (C), and cardiovascular death (D).

studies were excluded after 2 reviewers independently read the full texts. Finally, 9 RCTs met all inclusion criteria.[10,13,21,27–32] Detailed procedures were described in Figure 1. These studies contained 9526 patients with PAD in the aggregate, including 4786 aspirin-treated and 4740 placebo- or control-treated patients. The references listed in these studies were also researched for possibly overlooked studies. All steps were independently performed by 2 reviewers, and any disagreements were resolved by consensus.

Main Characteristics

Overall, 9 RCTs were included in our analysis. The mean follow-up time ranged from 1 month to 6.7 years. Some of the

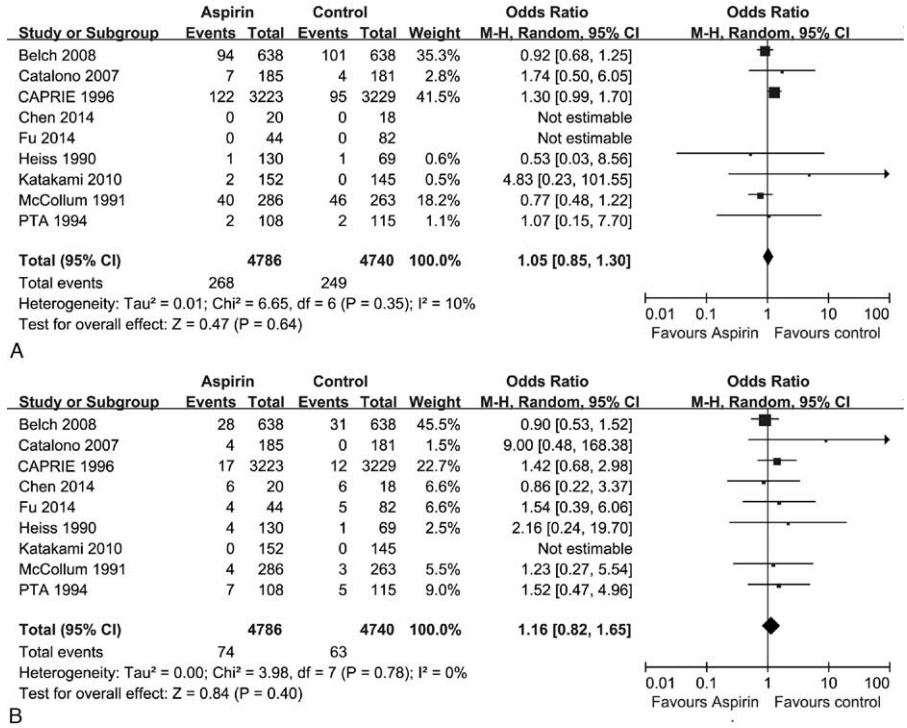

FIGURE 3. Meta-analysis of any aspirin on all-cause mortality (A) and major bleeding (B).

included patients had diabetes. The dose of aspirin ranged from 75 to 990 mg daily. The combination of aspirin plus antioxidant or dipyridamole was used to treat PAD in 5 RCTs, and the aspirin was used as monotherapy strategy for PAD in 7 RCTs (6 RCTs about aspirin vs. placebo, 1 RCT about aspirin vs. cilostazol). Three RCTs had multiple arms (aspirin monotherapy, aspirin plus antioxidant or dipyridamole, antioxidant and placebo). The detailed characteristics of the included RCTs were described in Table 1.

Cardiovascular End Points

Data on composite cardiovascular end points were available for 9 RCTs (Figure 2A). Overall, 366 (out of 4786, 7.6%) and 362 (out of 4740, 7.6%) patients experienced cardiovascular events, respectively. The pooled OR was 0.81 (95% CI = 0.56–1.15, z = 1.18, $P = 0.24$), indicating a 19% reduction in cardiovascular event rates in aspirin group, but not statistically significant. Heterogeneity was existed ($I^2 = 61\%$, $P = 0.01$). Additionally, the inverted funnel plots of these RCTs appeared to be approximately symmetrical. As the total number of RCTs was too small to show clear asymmetry, Egger test was performed and the result showed this outcome was not influenced by publication bias.

Nonfatal Myocardial Infarction

Data on this outcome were available for 9 RCTs (Figure 2B). Overall, 154 (out of 4786, 4.1%) and 138 (out of 4740, 2.9%) patients experienced nonfatal MI, respectively. The pooled OR was 0.98 (95% CI = 0.52–1.84, z = 0.07, $P = 0.94$), indicating a comparable nonfatal MI occurrence rates between aspirin group and placebo/control group. Heterogeneity was existed ($I^2 = 69\%$, $P = 0.006$).

Nonfatal Stroke

Data on this outcome were available for 9 RCTs (Figure 2C). Overall, 121 (out of 4786, 2.5%) and 134 (out of 4740, 2.8%) patients had nonfatal stroke, respectively. The pooled OR was 0.89 (95% CI = 0.69–1.14, z = 0.91, $P = 0.37$), indicating an 11% reduction in nonfatal stroke occurrence rates in aspirin group, but not statistically significant. Heterogeneity was not existed ($I^2 = 0\%$, $P = 0.50$).

Cardiovascular Death

Data on this outcome were available for 9 RCTs (Figure 2D). Overall, 111 (out of 4786, 2.3%) and 110 (out of 4740, 2.3%) patients experienced cardiovascular death, respectively. The pooled OR was 0.97 (95% CI = 0.68–1.38, z = 0.16, $P = 0.87$), indicating a comparable cardiovascular death occurrence rates between aspirin group and placebo/control group. Heterogeneity was not existed ($I^2 = 24\%$, $P = 0.26$).

All-Cause Mortality

Data on this outcome were available for 9 RCTs (Figure 3A). Overall, 268 (out of 4786, 5.6%) and 249 (out of 4740, 5.3%) patients experienced this events, respectively. The pooled OR was 1.05 (95% CI = 0.85–1.30, z = 0.47, $P = 0.64$), indicating a comparable occurrence rates of this events between aspirin group and placebo/control group. Heterogeneity was not existed ($I^2 = 10\%$, $P = 0.35$).

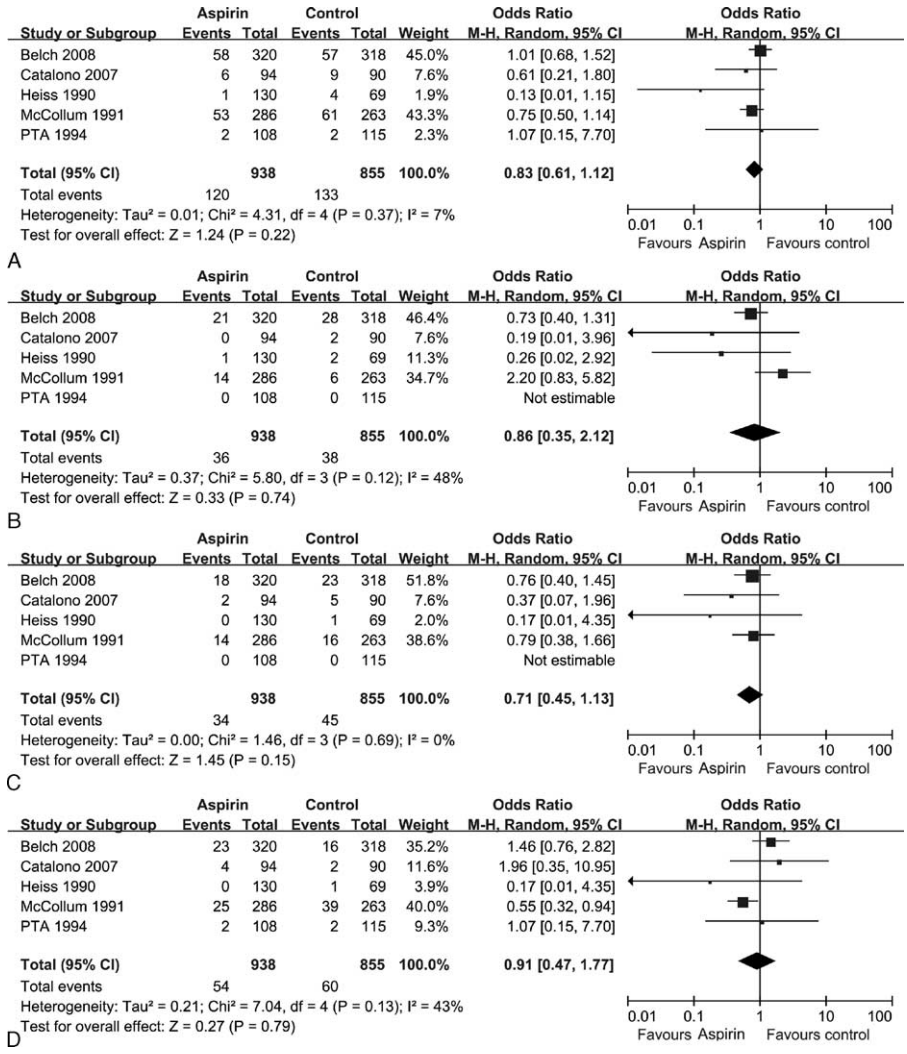

FIGURE 4. Effect of aspirin combination versus placebo on composite cardiovascular end points (A), nonfatal myocardial infarction (B), nonfatal stroke (C), and cardiovascular death (D).

Major Bleeding

Data on this outcome were available for 9 RCTs (Figure 3B). Overall, 74 (out of 4786, 1.5%) and 63 (out of 4740, 1.3%) patients experienced major bleeding, respectively. The pooled OR was 1.16 (95% CI = 0.82–1.65, z = 0.84, $P = 0.40$), indicating a nonstatistically significant increase (11%) in major bleeding occurrence rates in aspirin group. Heterogeneity was not existed ($I^2 = 0\%$, $P = 0.78$).

Aspirin Combination

Five RCTs studied the combination of aspirin with antioxidant or dipyridamole versus placebo for PAD treatment (Figure 4). The results showed that the 2 treatment methods had no significantly different effects on reducing composite cardiovascular end points (OR = 0.83, 95% CI = 0.61–1.12) (Figure 4A), nonfatal MI events (OR = 0.86, 95% CI = 0.35–2.12) (Figure 4B), nonfatal stroke events (OR = 0.71, 95% CI = 0.45–1.13) (Figure 4C) and cardiovascular death events (OR = 0.91, 95% CI = 0.47–1.77) (Figure 4D). Heterogeneity was not existed ($P > 0.10$).

Aspirin Monotherapy

Aspirin Versus Placebo

Four RCTs studied the aspirin monotherapy versus placebo for PAD treatment (Figure 5). The results showed that the 2 treatment methods had no significantly different effects on reducing composite cardiovascular end points (OR = 0.37, 95% CI = 0.11–1.25) (Figure 5A), nonfatal MI events (OR = 0.47, 95% CI = 0.13–1.74) (Figure 5B) and cardiovascular death events (OR = 1.13, 95% CI = 0.60–2.14) (Figure 5D); the pooled OR of nonfatal stroke events was 0.42 (95% CI = 0.21–0.84), indicating a significant reduction in aspirin group (z = 2.45, $P = 0.01$) (Figure 5C).

Aspirin Versus Control

Six RCTs studied the aspirin monotherapy versus control for PAD (Figure 6). The results showed that the 2 treatment methods had no significantly different effects on reducing composite cardiovascular end points (OR = 0.79, 95% CI = 0.44–1.41)

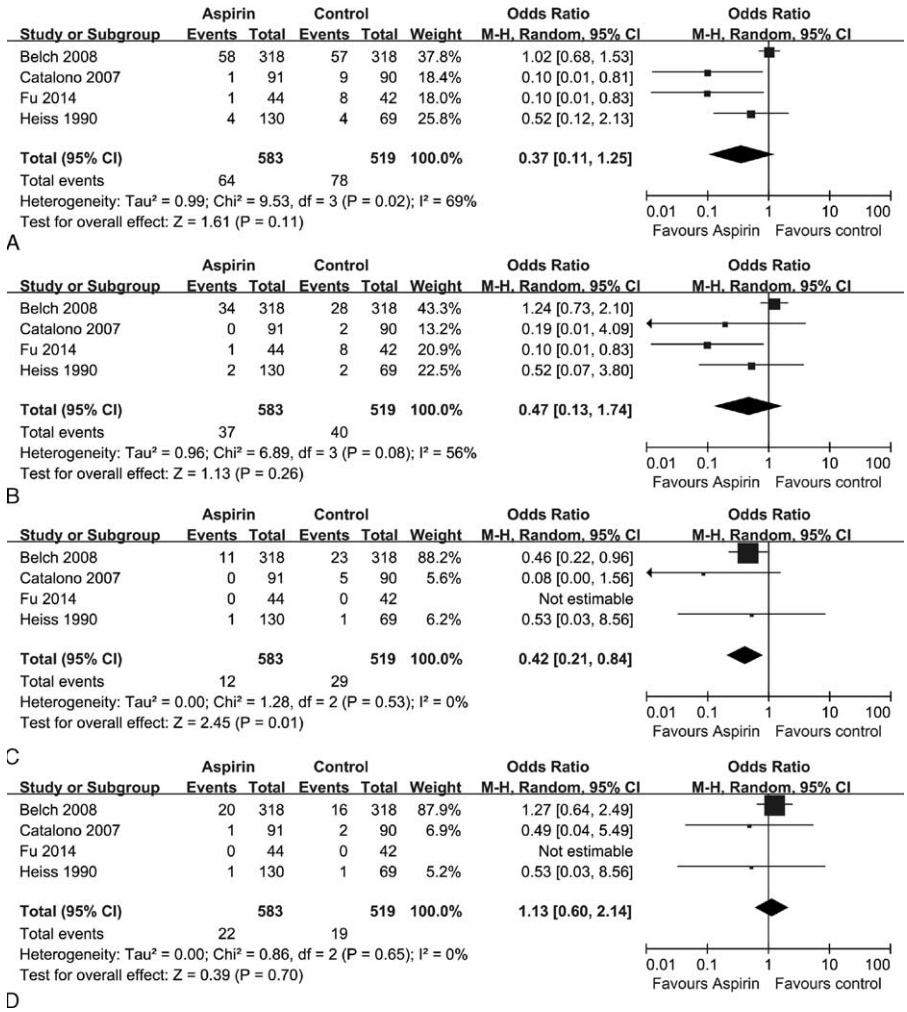

FIGURE 5. Effect of aspirin monotherapy versus placebo on composite cardiovascular end points (A), nonfatal myocardial infarction (B), nonfatal stroke (C), and cardiovascular death (D).

(Figure 6A), nonfatal MI events (OR = 0.86, 95% CI = 0.37–1.98) (Figure 6B), nonfatal stroke events (OR = 0.97, 95% CI = 0.72–1.31) (Figure 6C) and cardiovascular death events (OR = 1.13, 95% CI = 0.77–1.67) (Figure 6D).

DISCUSSION

This meta-analysis was based on 9 RCTs composed of 9526 patients randomly assigned to either aspirin treatment group or placebo/control treatment group. We found no evidence of benefit from aspirin treatment on the significantly decrease the primary end point of cardiovascular events. The pooled OR was 0.81 (95% CI = 0.56–1.15) for cardiovascular event rates, 0.98 (95% CI = 0.52–1.84) for nonfatal MI occurrence rates, 0.89 (95% CI = 0.69–1.14) for nonfatal stroke occurrence rates, 0.97 (95% CI = 0.68–1.38) for cardiovascular death occurrence rates, 1.05 (95% CI = 0.85–1.30) all-cause mortality occurrence rates and 1.16 (95% CI = 0.82–1.65) for major bleeding occurrence rates. Subgroup analysis showed that the effects of aspirin plus antioxidant or dipyridamole versus placebo were not significantly different; the effects of aspirin monotherapy versus placebo were not significantly different on cardiovascular events, nonfatal MI events and cardiovascular death events, but there was a significant reduction in aspirin group on nonfatal stroke events; the effects of aspirin versus control (antioxidant, clopidogrel, low molecular heparin) were not significantly different. These results might aid clinicians to make optimal treating strategy for patients with PAD. However, this conclusion should be interpreted with caution owing to the limited number of RCTs.

Many studies reported that antiplatelet agents were effective in preventing the recurrence of cardiovascular events. But, in this work, we found that aspirin could not significantly reduce the cardiovascular events compared to placebo/control. Some previous studies suggested that 100 mg daily favored the efficacy of aspirin,[27,31,32] but the results of another study did not support the use of 100 mg daily aspirin or in primary prevention of cardiovascular events in patients with PAD. Campbell and colleagues[33] reported that low dose was at least as effective as high dose of aspirin in treating symptomatic coronary heart disease and had less harm, which made the low dose to be a recommendation for secondary prevention of cardiovascular

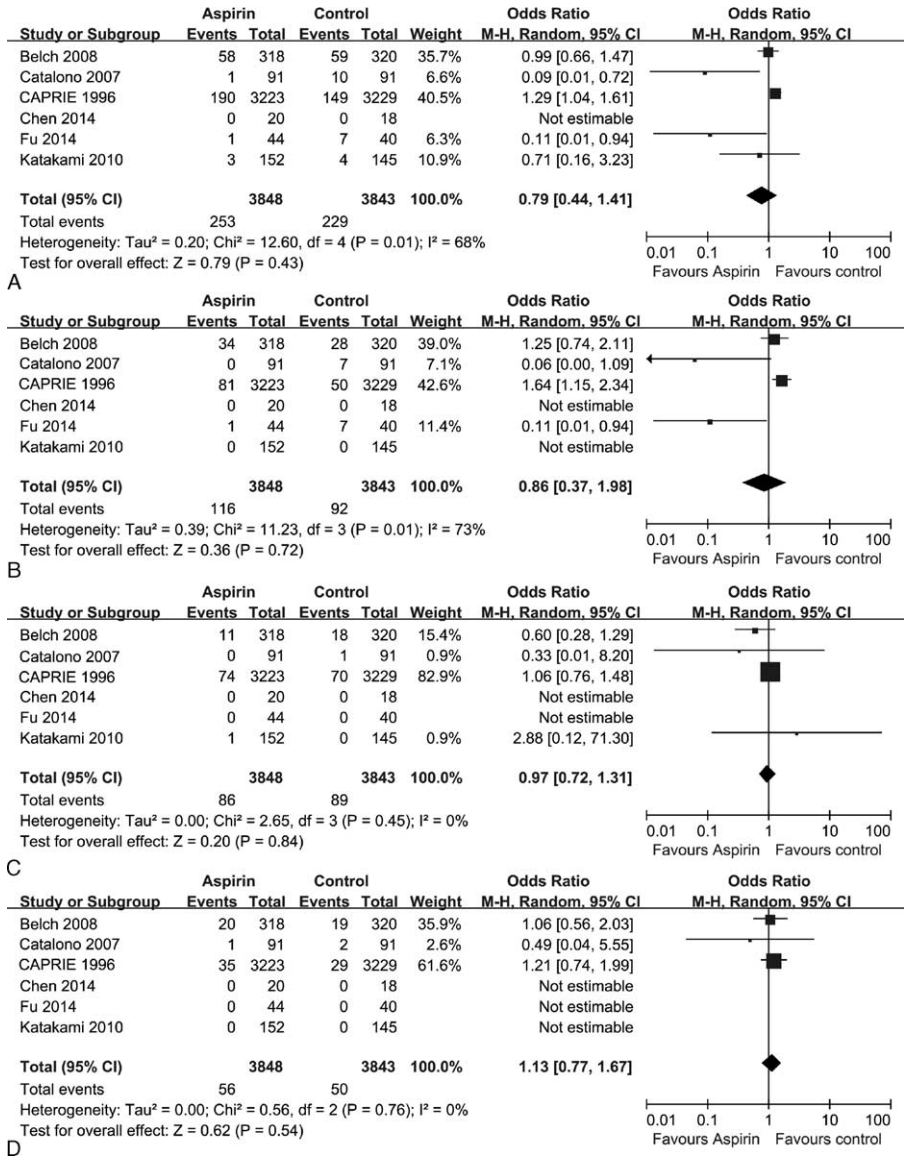

FIGURE 6. Effect of aspirin monotherapy versus control on composite cardiovascular end points (A), nonfatal myocardial infarction (B), nonfatal stroke (C), and cardiovascular death (D).

disease. But 1 study reported that 50 mg daily (low dose) did not favor the efficacy of aspirin,[28] whereas Heiss et al[29] found that the combination use of 225 mg dipyridamole with 990 mg daily (high dose) aspirin could yield better efficacy in PAD. Additionally, other clinical settings supports that varying antiplatelet medications have varying efficacy in distinct patient populations. For example, the combination of warfarin with aspirin could prevent cardiovascular events among patients with coronary heart disease,[34] but this method was not efficacious for patients with PAD.[35] Therefore, future studies were needed to find out how the aspirin used was the best choice for patients with PAD.

This meta-analysis had several limitations. First, the dose of aspirin was different across studies. Second, a relatively small number of studies included. Third, the patient phenotype was varying in the included studies. However, these limitations were the general problems for meta-studies to solve. Fourth, the follow-up time was also different in the included studies, with a range from 1 month to 6.7 years. The short-term and long-term outcomes of aspirin compared to placebo should be further investigated by future studies. Fifth, definitions of major bleeding varied across the trials, which made it difficult to determine accurate measure of bleeding and approximate risk. Sixth, the genetic background was not considered. For example, many studies suggested that the PlA2 polymorphism was a genetic determinant of ischemic stroke in high-risk hypertensive population.[36,37] Santulli et al[38] reported that of the 7 mammalian G-protein-coupled receptor kinases (GRKs), GRK2 seems to be the most relevant isoform at the cardiovascular level.

Notwithstanding these limitations, this study found that aspirin might not be more effective than placebo/control on reducing cardiovascular events. But aspirin, as monotherapy

therapy, did significantly reduce the risk of nonfatal stroke. Limited by the included studies, this conclusion should be interpreted with caution. Meanwhile, further lager prospective RCTs of aspirin and other antiplatelet agents for PAD are needed to draw firm conclusions about clinical benefit and risks. Also, researchers should use novel strategies to treat vascular disorders, such as used micro-RNA-based approaches to preserve endothelial function and prevent thrombosis.[39]

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