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The safety and efficacy of oral anticoagulants with dual versus single antiplatelet therapy in patients after percutaneous coronary intervention

A meta-analysis

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Abstract

Background: A growing number of patients require oral anticoagulant (OAC) after undergoing percutaneous coronary intervention (PCI) with stent implantation due to the development of atrial fibrillation, but the optimal antithrombotic regimen remains controversial in these patients.

Methods: We systematically searched PUBMED, EMBASE, and CENTRAL from inception until September 2016 for randomized controlled trials or cohort studies that evaluated the comparative effects of TT versus DT. Relative risks (RRs) with 95% confidence intervals (95% CIs) were pooled by a random-effects model or a fixed-effects model.

Results: Twelve studies with a total of 30,823 patients were included in this analysis, including 6134 in the TT group and 24,689 in the DT group. No significant differences were found between the TT group and the DT group regarding major adverse cardiovascular events (MACE) (RR = 0.82, 95% CI: 0.58–1.17; I^2 = 87.3%), stroke (RR = 1.08, 95% CI: 0.56–2.07; I^2 = 65.5%), all-cause mortality (RR = 0.90, 95% CI: 0.54–1.51; I^2 = 79.1%), or stent thrombosis (RR = 0.71, 95% CI: 0.41–1.24; I^2 = 12.7%), and lower rates were observed for myocardial infarction (RR = 0.59, 95% CI: 0.50–0.70; I^2 = 31.1%) and major bleeding with TT (RR = 0.86, 95% CI: 0.74–0.99; I^2 = 24.3%). Meanwhile, we also found that compared with TT, OAC with clopidogrel treatment shows equal efficacy and safety outcomes.

Conclusion: In patients on OAC undergoing PCI with stent implantation, compared with DT, TT shows equal effectiveness in terms of MACE, stroke, all-cause mortality, and stent thrombosis and lower risks of myocardial infarction and major bleeding. However, similar efficacy and safety outcomes were observed between the TT group and the OAC along with clopidogrel group.

Abbreviations: ACS = acute coronary syndrome, CI = confidence interval, DAPT = dual antiplatelet therapy, DT = dual therapy, MACE = major adverse cardiovascular events, MI = myocardial infarction, PCI = percutaneous coronary intervention, RR = relative risk, TT = triple therapy.

Keywords: atrial fibrillation, dual therapy, percutaneous coronary intervention, triple therapy

1. Introduction

In patients with atrial fibrillation, mechanical heart valves, and other venous thromboembolisms, long-term oral anticoagulation (OAC) is essential for the prevention of systemic thromboembolic events.[1] Dual antiplatelet therapy (DAPT) is the basic treatment for patients with myocardial infarction (MI) or acute coronary syndrome (ACS).[2] In fact, 20% to 30% of patients with atrial fibrillation also have ischemic heart disease and require percutaneous coronary intervention (PCI) with stent implantation.[3] Triple therapy (TT; warfarin, aspirin, and clopidogrel) was recommended as the optimal antithrombotic regimen in patients on OAC undergoing PCI with stent implantation. Although TT is more effective in reducing cardiovascular events and stroke, an increasing risk of major bleeding is evident compared with DAPT.[4–7] Therefore, the optimal antithrombotic therapy for these patients remains controversial. Currently, some specialists recommend that dual therapy (DT; OAC with single antiplatelet) can replace TT for similar efficacy outcomes and without the additional risk of bleeding. Therefore, some studies[8–11] and several meta-analyses[6,12,13] have been performed to evaluate the safety and efficacy of TT compared with DT, but the results are inconsistent. A previous meta-analysis showed data selection and methodological biases and 2 new

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studies have since been published.[14,15] Therefore, we performed an updated systematic review and meta-analysis to generate the largest analysis comparing the benefits and risks between TT and DT in patients on OAC undergoing coronary stenting.

2. Methods

2.1. Search strategy

Our review and meta-analysis strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] A systematic search was performed on PubMed, Embase, and CENTRAL (the Cochrane Central Register of Controlled Trials) with no language limitations and the included studies should be published as original literature in peer-reviewed scientific journals. In addition, the references from relevant articles were manually searched for potential studies using combinations of various keywords for the search strategy, including "triple therapy," "dual therapy," "oral anticoagulation with antiplatelet therapy," "percutaneous coronary intervention," "stent," and "atrial fibrillation." Ultimately, 12 studies were included, and our search was updated in September 2016. All analyses were based on previous published studies. Therefore, no ethical approval or patient consent is required.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: OAC with DAPT versus single antiplatelet therapy; direct comparisons between TT and DT; outcomes of interest are reported (see below); and randomized controlled trials (RCTs) or cohort studies with follow-ups ≥6 months. The exclusion criteria were as follows: nonhuman studies; no report of any main outcomes; and duplicate studies or reviews.

2.3. Data extraction and quality assessment

Data extraction was carried out by 2 reviewers independently, and a special standardized form was used to record the following data: study name, publication date, country of study, study design, baseline demographics, and follow-up. The authors of the articles were contacted if the original data were not included in the publication. Controversy was resolved by consensus. The efficacy endpoints included major adverse cardiovascular events (MACE), ischemic stroke, MI, all-cause mortality, and stent thrombosis. Major bleeding was used as a safety endpoint. We used the outcome definitions from the original articles because the meanings of each outcome were slightly different in all included studies. The quality of the included studies was evaluated by 2 reviewers using the Cochrane risk-of-bias tool and the Newcastle–Ottawa assessment tool.[17] Studies were considered low-quality if 2 or more quality assessment items were identified as high or unclear risk of bias.

2.4. Statistical analysis

The pooled effects of the interventions were calculated using relative risk (RR) with 95% confidence intervals (95% CIs). The heterogeneity across the trials was assessed with the Q test and the I^2 statistic, with $P < .1$ and/or $I^2 > 50\%$, indicating statistically significant heterogeneity. When heterogeneity was present, the randomized-effects model was used. Otherwise, the Mantel–Haenszel fixed-effects model was used. In cases of statistical heterogeneity, sensitivity analyses were carried out by eliminating 1 study at a time to evaluate the influence of each study on the results and the robustness of the results.[18] A subgroup analysis was performed according to the follow-up periods: short-term follow-up (<1 year) and long-term follow-up (≥1 year). The publication bias was tested by a funnel plot and Egger test (P for significant asymmetry <.1). All data analyses were conducted using Stata 12.0 (Stata Corporation LP, College Station, TX).

3. Results

3.1. Eligible studies and patient characteristics

As shown in Fig. 1, a total of 107 potentially eligible studies were identified, but 7 were duplicates and 67 were excluded after screening the titles and abstracts. Further screening of the full-texts of the remaining 33 articles resulted in the exclusion of 21 studies. Finally, 12 studies were included.[8–11,14,15,19–24] The characteristics of the included studies are summarized in Table 1. Twelve studies (2 RCTs and 10 prospective or retrospective cohort studies) including a total of 30,823 patients were included in our analysis. Of them, 6134 patients were in the TT group and 24,689 patients were in the DT group. The mean follow-up times were between 6 months and 3.3 years and the mean ages were from 65 to 77.5 years. Six studies were monocentric trials and 6 studies were multicenter trials. Most of the patients in our analysis had CHADS2 scores ≥2 and all patients in the TT groups were receiving a combination of warfarin, aspirin, and clopidogrel. The DT group patients were receiving a combination of warfarin and a single antiplatelet drug (mainly aspirin or clopidogrel). Three studies reported short-term follow-up outcomes and 9 studies reported long-term follow-up outcomes. The quality assessment of these studies showed that 1 study[8] had a high risk of bias, but the remaining studies had low risks of bias (see Table 1).

3.2. Major adverse cardiovascular events

There were no detectable differences in MACE between the TT and DT regimens (RR = 0.82, 95% CI: 0.58–1.17; $I^2 = 87.3\%$). High heterogeneity was identified between the studies (Fig. 2) and similar results were observed in the 2 subgroups. The funnel plot showed obvious asymmetry in Egger test ($P = .02$), but the sensitivity analysis did not find an impact of any individual trials on the MACE results.

3.3. Stroke

No significant differences were found in stroke between the TT and DT regimens (RR = 1.08, 95% CI; 0.56–2.07), with significant heterogeneity between the studies ($I^2 = 65.5\%$, $P = .002$). Similar results were observed in the 2 subgroups (Fig. 3). The funnel plot did not show asymmetry in Egger test ($P = .184$).

3.4. Myocardial infarction

The results of our analysis showed that TT elicited a greater reduction in MI than in the DT regimen (RR = 0.59, 95% CI: 0.50–0.70), without significant heterogeneity between the trials ($I^2 = 31.1\%$, $P = .169$). A similar finding was observed in the long-term follow-up group (RR = 0.60, 95% CI: 0.51–0.71), but no significant difference was found in the short-term follow-up group (RR = 0.47, 95% CI; 0.21–1.07), The data are presented in

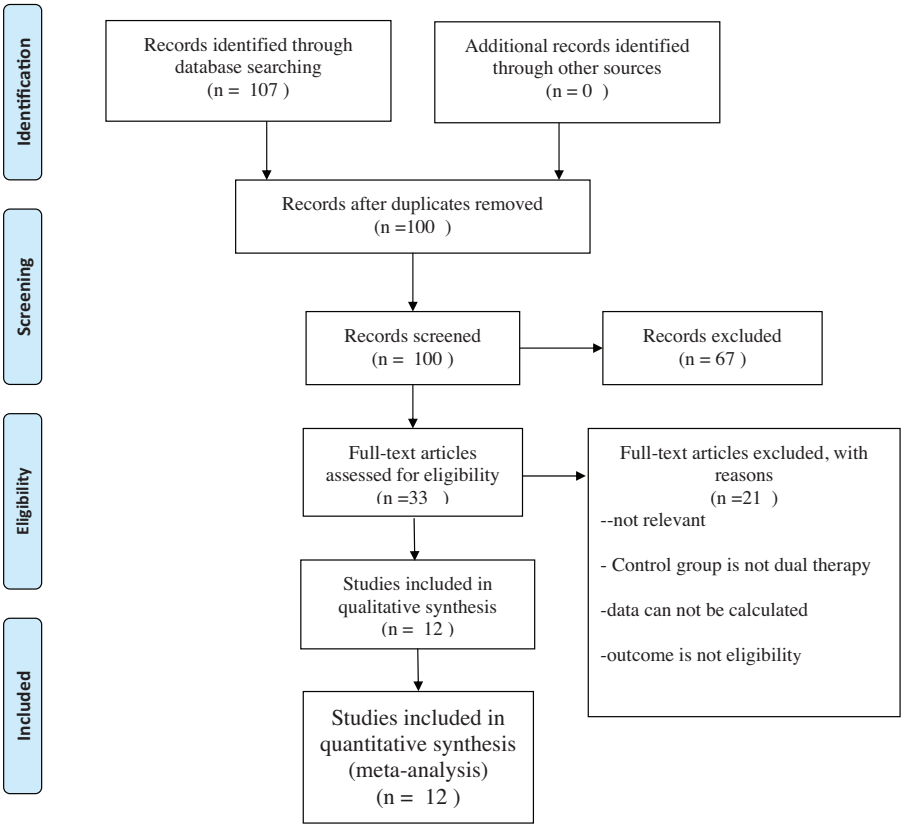

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Figure 1. Flow diagram of the systematic overview process.

Fig. 4. The funnel plot did not show asymmetry in Egger test ($P = .293$).

3.5. All-cause mortality

No significant differences were found in all-cause mortality between the TT and DT regimens (RR = 0.90, 95% CI: 0.54–1.51; $I^2 = 79.1\%$), with significant heterogeneity between the studies (Fig. 5). Similar findings were observed in the subgroup analyses. The funnel plot showed obvious asymmetry in Egger test ($P = .002$), but the sensitivity analysis did not find an impact of any individual trial on the mortality result.

3.6. Major bleeding

A significantly decreased risk of major bleeding was found between the TT and DT regimens (RR = 0.86, 95% CI: 0.74–0.99; Fig. 6), but significant heterogeneity was not found ($I^2 = 24.3\%$, $P = .205$).

Table 1

Baseline characteristics of the included studies.

Study	Year	Study design	Sample size	Country	Mean age, y	CHADS2 score ≥2 (TT/DT)%	TT	DT	Mean follow-up	Risk of bias
WOEST	2013	RCT	581	Multicenter	70.3	88/88	OAC+A+C	OAC+C	1 y	Low
ISAR-TRIPLE	2015	RCT	614	Multicenter	73.6	78.9/83.4	OAC+A+C	OAC+C	9 mo	Low
Lamberts et al[19]	2013	Retrospective cohort study	3948	Denmark	71.3	90.1/90.7	OAC+A+C	OAC+A; OAC+C	1 y	Low
Rubboli et al[21]	2014	Prospective Cohort study	752	Multicenter	73.5	71/77	OAC+A+C	OAC+C	1 year	Low
Gao et al[8]	2010	Prospective Cohort study	257	China	71.8	49.6/60.9	OAC+A+C	OAC+A; OAC+C	1 year	High
Nguyen et al[20]	2007	Retrospective cohort study	800	Multicenter	65	NR	OAC+A+C	OAC+A; OAC+C	6 mo	Low
Sambola et al[10]	2009	Prospective Cohort study	324	Multicenter	71	66.2/58.7	OAC+A+C	OAC+A; OAC+C	6 mo	Low
Persson et al[22]	2011	Prospective Cohort study	658	Sweden	68	NR	OAC+A+C	OAC+C	1 y	Low
Claudio et al	2016	Retrospective cohort study	79	Italy	73	NR	OAC+A+C	OAC+A; OAC+C	378 d	Low
Renato et al	2016	Prospective Cohort study	1623	Multicenter	77.5	NR	OAC+A+C	OAC+AA	2 y	Low
Karjalainn et al	2007	Retrospective cohort study	151	Finland	70	NR	OAC+A+C	OAC+C	1 y	Low
Hansen et al[24]	2010	Retrospective cohort study	21036	Denmark	70	NR	OAC+A+C	OAC+A; OAC+C	3.3 y	Low

A = aspirin, AA = any antiplatelet, C = clopidogrel, DT = dual therapy, OAC = oral anticoagulant, RCT = randomized controlled trials, TT = triple therapy.

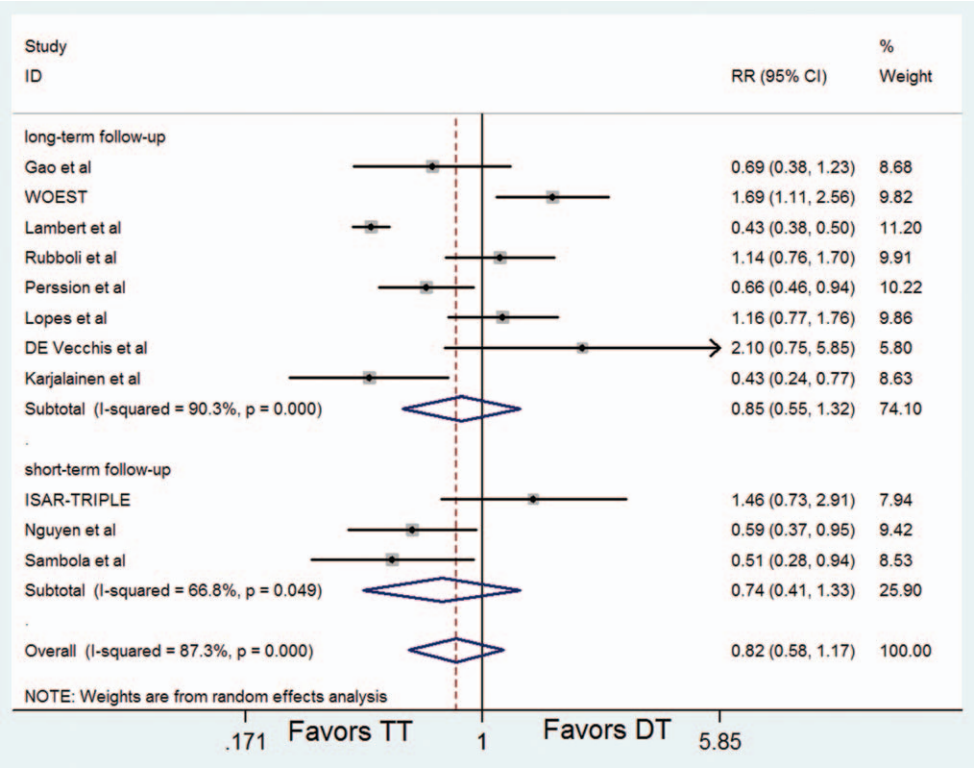

Figure 2. Forest plot of MACE. CI = confidence intervals, DT = dual therapy, MACE = major adverse cardiovascular events, RR = relative risk, TT = triple therapy.

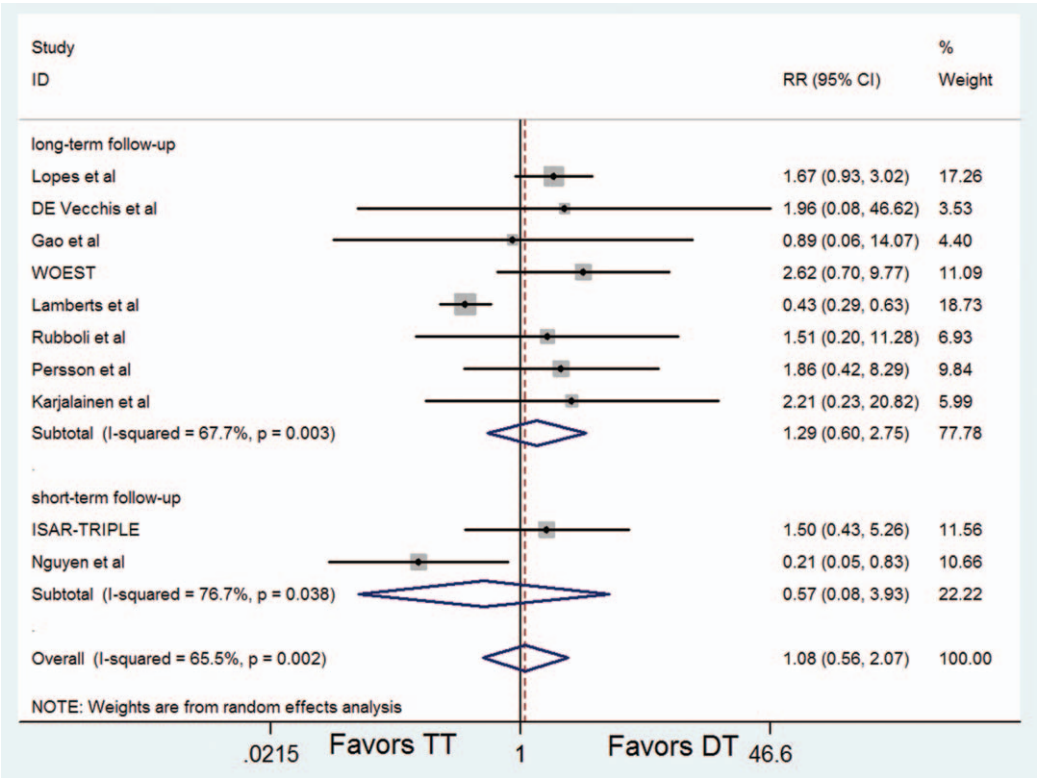

Figure 3. Forest plot of stroke. CI = confidence intervals, DT = dual therapy, RR = relative risk, TT = triple therapy.

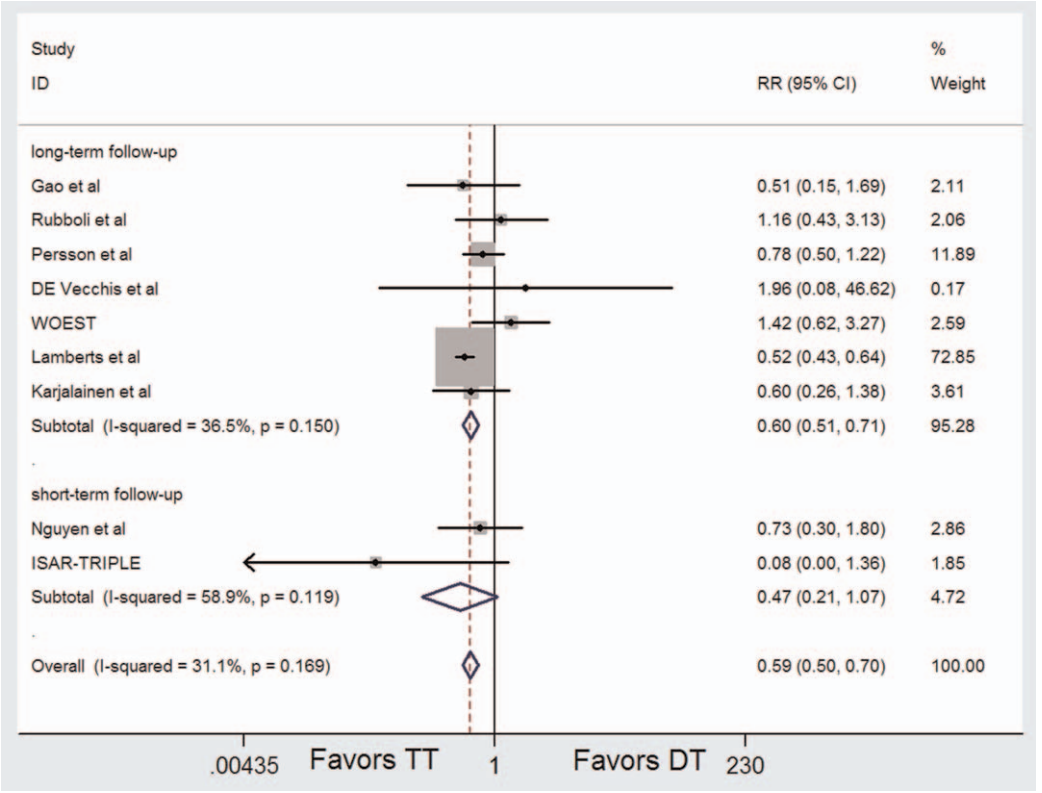

Figure 4. Forest plot of MI. CI = confidence intervals, DT = dual therapy, MI = myocardial infarction, RR = relative risk, TT = triple therapy.

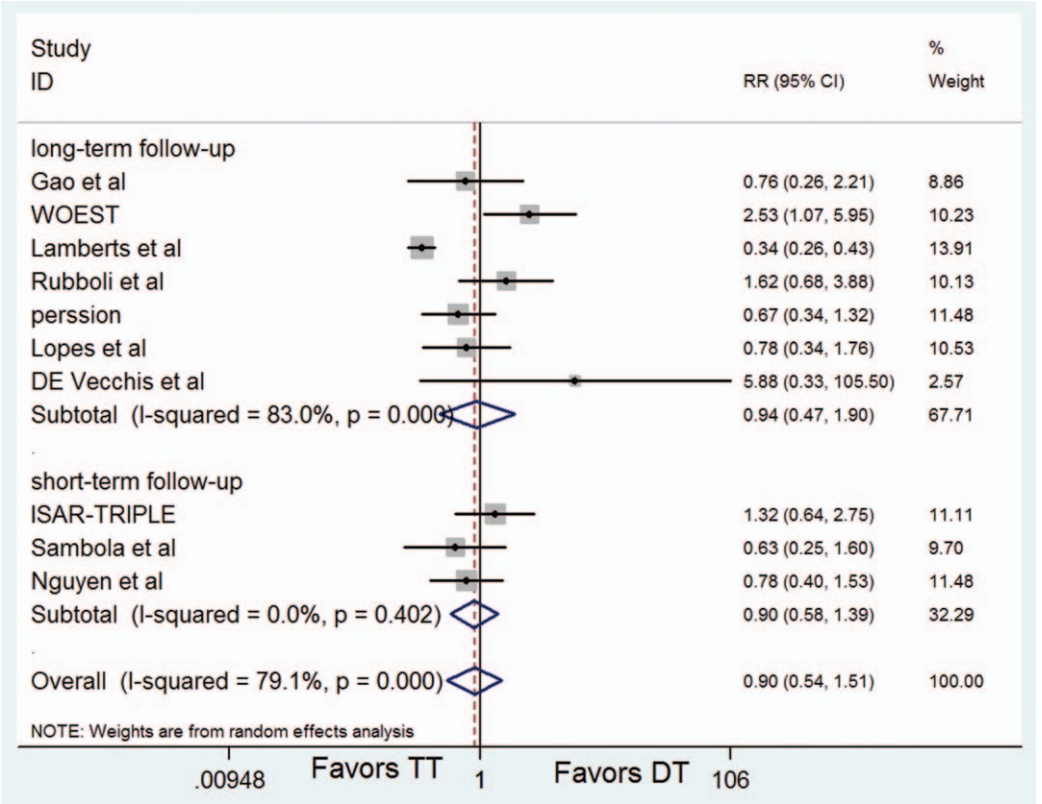

Figure 5. Forest plot of all-cause mortality. CI = confidence, DT = dual therapy, RR = relative risk, TT = triple therapy.

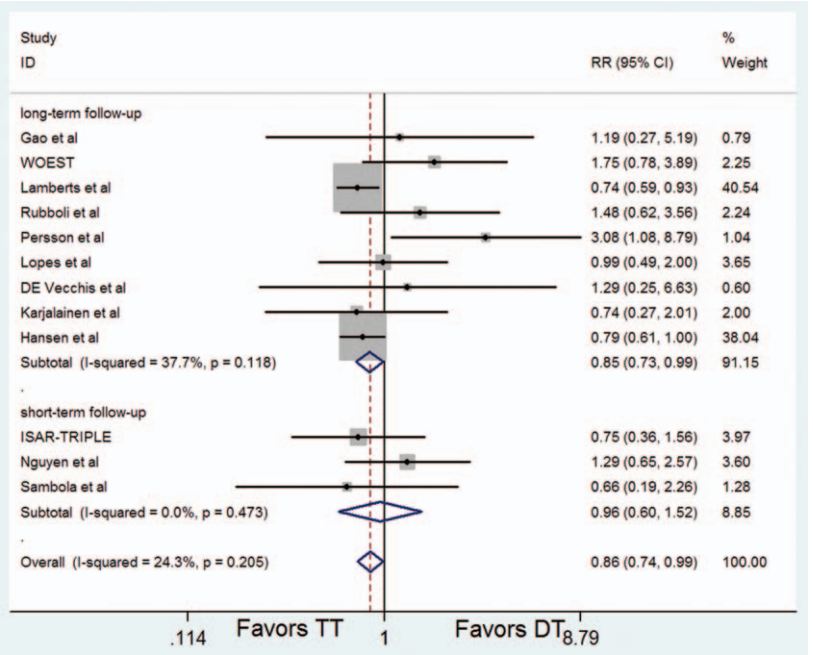

Figure 6. Forest plot of major bleeding. CI = confidence intervals, DT = dual therapy, RR = relative risk, TT = triple therapy.

A similar finding was observed in the long-term follow-up group (RR = 0.85, 95% CI: 0.73–0.99), but no significant difference was found in the short-term follow-up group (RR = 0.96, 95% CI: 0.60–1.52). The funnel plot showed obvious asymmetry in Egger test ($P = .025$), but the sensitivity analysis did not find an influence of any individual trial on the result of major bleeding.

3.7. Stent thrombosis

The risk of stent thrombosis was not significantly different between the TT and DT regimens (RR = 0.71, 95% CI: 0.41–1.24; $I^2 = 12.7\%$, $P = .333$), without significant heterogeneity between the trials (Fig. 7). Similar findings were observed in the 2 subgroup analyses. The funnel plot did not show asymmetry in Egger test ($P = .619$).

3.8. TT versus OAC and clopidogrel

We also compared TT with OAC and clopidogrel in terms of MACE, stroke, MI, all-cause mortality, major bleeding, and stent thrombosis. No significant differences were found (see Figure A-F, Supplemental Content, http://links.lww.com/MD/B862), but significant heterogeneity was found for MACE and all-cause mortality ($I^2 = 73.6\%$, $P = .004$; and $I^2 = 63.9\%$, $P = .040$; respectively). After removing the source of heterogeneity (WOEST investigators),[9] this heterogeneity was reduced to $I^2 = 53.7\%$ and $I^2 = 28.4\%$, in the MACE group and all-cause mortality group, respectively.

4. Discussion

The main results of the present meta-analysis were that no significant differences were found in the rates of MACE, all-cause mortality, stroke, or stent thrombosis between the TT and DT regimens, but significantly lower risks of MI and major bleeding were identified with TT. Furthermore, the results of the comparison of TT with OAC and clopidogrel showed that OAC and clopidogrel treatment had similar efficacy and safety outcomes compared with TT.

The optimal antithrombotic regimen for patients on long-term oral anticoagulants undergoing coronary stent implantation remains controversial. There is enough evidence to demonstrate that OAC is necessary for AF patients. In general, compared with placebo, OAC can reduce the risk of stroke and systemic embolism by approximately 60%[25] and by approximately 40% compared with aspirin.[26] The current guidelines recommend that DAPT is the standard treatment for patients after undergoing coronary stenting or for those experiencing ACS.[27] DAPT is less effective in stroke prevention compared with OAC and OAC are less effective in stent thrombosis prevention than DAPT. Therefore, TT has been used as the optimal antithrombotic treatment in patients who are on OAC and require PCI. Indeed, TT is associated with a lower risk of cardiovascular events, but at the cost of an increased risk of major bleeding.[28,29] This conclusion has been confirmed by previous meta-analyses.[30,31] The reduction in ischemic stroke with TT was balanced by the reduction in bleeding with DAPT. More and more studies consider that TT cannot be used as a standard treatment for patients with indications for OAC who have undergone PCI with stent implantation. Therefore, many studies have assessed the benefits and risks of DT compared with TT, but the results have been inconsistent. The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) trials, which represented the first open-label, randomized, multicenter study, demonstrated that OAC with clopidogrel treatment was associated with a significantly lower rate of bleeding, without increasing the rate of thrombotic events.[11] Moreover, the prospective observational AFCAS trial[21] and the large nationwide Danish registry[19] confirmed that OAC with clopidogrel treatment was similar or better in terms of both efficacy and safety outcomes than TT in real-world populations.

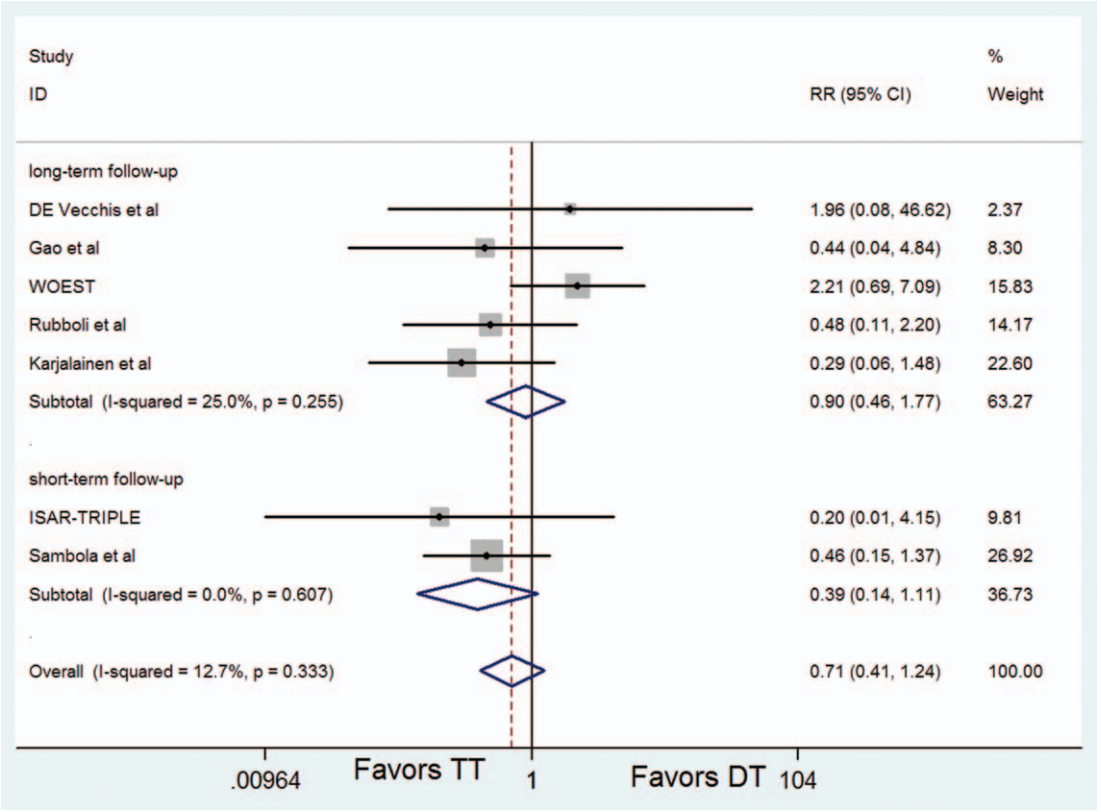

Figure 7. Forest plot of stent thrombosis. CI = confidence intervals, DT = dual therapy, RR = relative risk, TT = triple therapy.

However, our study was different from several previous meta-analyses relative to the comparison of TT with OAC and a single antiplatelet.[6,12,13,31] Compared with other meta-analyses, our study had apparent advantages. First, the present meta-analysis included 12 studies with a total of 30,823 patients, representing far more subjects than these previous meta-analyses. Second, these recently published meta-analyses had data selection biases, such as the inclusion of the data on OAC with clopidogrel alone even though the included studies provided data on both OAC and aspirin and OAC with clopidogrel, respectively,[13] leading to results that indicated that TT showed a greater reduction in major bleeding than the DT regimen. Furthermore, after eliminating 2 studies (Lamberts et al[19] and Hansen et al[24]), no significant differences were found in major bleeding between the TT and DT regimens. We think that the main reason for this phenomenon is that the weight of the 2 studies is too large.

The studies included in our analysis did not report international normalized ratio (INR) values. In fact, warfarin with a lower INR (1.6–2.5) combined with DAPT has a similar bleeding risk compared with DAPT.[32,33] In our study, only 6 studies assessed the risk of stroke with CHADS2 scores and 2 studies assessed the risk of bleeding with HAS-BLED scores, but we know that detailed risk stratification should be carried out to balance the risks of stroke and bleeding before initiating antithrombotic therapy. Finally, we did not analyze the effect of newer P2Y12 inhibitors (prasugrel or ticagrelor), which are associated with more obvious platelet inhibition and higher bleeding rates than clopidogrel.[34,35] Furthermore, novel oral anticoagulants have demonstrated their superiority over warfarin in AF patients.[36–38] These drugs may be the best replacements for warfarin and could improve the risk/benefit ratio. A recent study showed that among participants with atrial fibrillation who underwent PCI with stenting, the administration of either rivaroxaban along with a P2Y12 inhibitor or rivaroxaban along with DAPT was associated with a lower rate of clinically significant bleeding than standard therapy with a vitamin K antagonist plus DAPT,[39] but a high INR (2.0–3.0) may limit this power.

Our study has some limitations. First, the present meta-analysis could not obtain individual data. Second, although the results of our study were robust, a publication bias was identified. Therefore, we should interpret the results carefully and more well-designed studies are needed. Third, different studies with different inclusion criteria, different designs and clinical characteristics, and different endpoint definitions, leading to significant heterogeneity, were included in our article. Fourth, although these data suggest that the TT may reduce the incidence of MI, the result is heavily dependent on 1 study (Lamberts et al[19]). Finally, most studies were from western countries, with only 1 study from Asian countries, so we cannot conclude on whether the results of our article apply to Asian populations.

5. Conclusion

In patients on OAC undergoing PCI with stent implantation, TT shows equal effectiveness in terms of MACE, stroke, all-cause mortality, and stent thrombosis and lower risks of MI and major bleeding than does DT. However, compared with OAC and clopidogrel treatment, TT was associated with similar efficacy and safety outcomes.

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