Dual versus single antiplatelet therapy for patients with long-term oral anticoagulation undergoing coronary intervention: a systematic review and meta-analysis

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Abstract

Objective The main aim of this meta-analysis is to compare the efficacy and safety of dual versus single antiplatelet therapy for patients taking oral anticoagulation (OAC) after coronary intervention. Background The optimal regimen remains controversial for patients taking OAC after coronary intervention. Methods PubMed, Embase and Cochrane Central Register of Controlled Trials were searched for eligible studies including data of triple therapy (TT) versus OAC plus single antiplatelet therapy for patients requiring OAC after coronary intervention. The primary outcome was major adverse cardiac and cerebrovascular event (MACCE). The safety outcome was major bleeding. Results Fourteen studies with 32,825 patients were included. Among prospective studies, patients with TT had a trend toward a higher risk of major bleeding [odds ratios (OR): 1.56, 95% confidence interval (CI): 0.98–2.49, \(P = 0.06\)] and a markedly higher risk of all-cause death (OR; 2.11, 95% CI: 1.10–4.06 \(P = 0.02\)) compared with OAC plus clopidogrel. Meanwhile, TT was associated with decreased risks of MACCE (OR: 0.63, 95% CI: 0.51–0.77 \(P < 0.0001\)), all-cause death (OR: 0.45, 95% CI: 0.20–0.97, \(P = 0.04\)), and stroke/transient ischemic attack (TIA)/peripheral embolism (PE) (OR: 0.29, 95% CI: 0.09–0.96, \(P = 0.04\)) compared with OAC plus aspirin. Conclusions For patients requiring OAC after coronary intervention, OAC plus clopidogrel may bring more clinical net benefit than TT, whereas OAC plus aspirin should be the last choice. More large-size randomized control trials are needed to confirm these findings.

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1 Introduction

Long-term treatment of oral anticoagulation (OAC) is essential for prevention of thromboembolic events in patients with atrial fibrillation (AF), deep venous thrombosis, and other diseases.[1,2] About 20%–30% of these patients also have an indication of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel due to percutaneous coronary intervention (PCI) with stenting.[3] The concomitant use of aspirin and OAC does not effectively prevent stent thrombosis (ST). In addition, DAPT is not effective enough to prevent thromboembolic risk without OAC. Triple therapy (TT) with OAC plus DAPT was recommended to prevent stent thrombosis and systemic embolism.[4] In the past decade, many studies, most of which were retrospective and small-size, showed that TT could reduce the risk of adverse cardiovascular events, while at the cost of increasing bleeding risk, compared with DAPT.[5–8]

Choosing the optimal antithrombotic regimens for patients with OAC and coronary intervention is very challenging. Triple therapy was preferred until the first prospective, open-label, multicenter, randomized controlled trial (RCT)——What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting (WOEST) study, was published.[9] The results of this study indicated that dual therapy with OAC and clopidogrel was associated with a significantly lower risk of bleeding complications, and no increase in the risk of thrombotic events than TT. This trial opened a new door for determining the antithrombotic therapy for patients with OAC after coronary intervention. Based on that, the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) Guideline recommended concomitant use of clopidogrel (75 mg once daily) and OAC in these patients (class IIb, level of evi-
dence B).[10]

The combination of OAC plus single antiplatelet agent has attracted increasing attention and investigations in several studies, most of which were also observational and retrospective.[11,12] And these studies still could not get a consistent result, so the choice of the treatment regimen for patients with long-term OAC after coronary intervention is still perplexing clinicians. Therefore, this up-dated meta-analysis was performed to assess the safety and efficacy of OAC plus single antiplatelet agent compared with TT.

2 Methods

2.1 Search strategy

Literature search was performed in PubMed, Embase and Cochrane Central Register of Controlled Trials from January 2005 to March 2017 with no language limitation. In order to include all relevant studies, we used search keywords with “anticoagulation” or “atrial fibrillation” or “warfarin” and “antiplatelet therapy” or “dual therapy” or “clopidogrel” and “percutaneous coronary intervention” or “coronary stenting” or “myocardial infarction” or “PCI” or “myocardial infarction (MI)”. Subsequently, a hand search of references from reviews and selected articles was performed for further screening.

2.2 Inclusion and exclusion criteria

The inclusion criteria were: (1) clinical trials comparing triple therapy and dual therapy with OAC and single antiplatelet; (2) patients taking long-term OAC with coronary intervention; (3) ≥6 months of follow-up. The exclusion criteria were:

(1) reviews, meta-analyses, case reports, letters, abstracts, and editorials; (2) articles with duplicate publication and studies from the same sample.

2.3 Data extraction

All eligible studies were reviewed and data were extracted by two authors (JY and CZ) independently. Any disagreement was resolved by a third author (GY). The extracted data included: name of study, publication date, first author, patients’ baseline characteristics, study endpoints and clinical outcomes.

2.4 Quality assessment

Two authors (JY and WL) assessed the quality of included studies. Any disagreement was resolved by consensus. Methodological quality of randomized trial was assessed by the Cochrane’s risk-of-bias handbook.[13] Includ-

ing seven specific domains. Each domain was judged by ‘Low risk’ of bias, ‘High risk’ of bias, or ‘Unclear risk’ of bias. One point was assigned for each judgment of ‘Low risk’ of bias and the maximum score was 7 points. Studies with a score ≥5 points were considered as high quality, while those with a score <5 were considered as low quality. The Newcastle-Ottawa scale (NOS) was used to assess the methodological quality of observational studies.[14] This scale consists of 8 specific criteria and the score varies from 0–8. Studies with a score ≥6 points were divided into high quality group, otherwise, were divided into low quality group.

2.5 Study endpoints

The primary endpoint was major adverse cardiac/cerebrovascular events (MACCE). The secondary endpoints included all-cause death, MI, ST, stroke/transient ischemic attack (TIA)/peripheral embolism (PE), and major bleeding. The rate of stroke/TIA/PE could be replaced by thromboembolic events, when no relevant data reported.

2.6 Statistical analysis

This meta-analysis was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta analysis (PRISMA) statements.[15] Dichotomous outcomes were expressed by calculating pooled odds ratios (ORs) with 95% confidence intervals (CI), and the statistical significance level was set at P value < 0.05. The heterogeneity was performed by Cochran’s Q test and I-squared statistics. A fixed-effect model was used when the P value ≥0.1 or I² value ≤25%. Otherwise, the random-effect model was conducted.[16,17] In cases of significant heterogeneity, we conducted sensitivity analysis by deselecting each study at a time to assess the robustness of the results. In addition, we performed the subgroup analysis in prospective studies and retrospective studies if the number of corresponding studies is enough. All statistical analysis was performed using Revman 5.3.

3 Results

3.1 Literature selection

The screening process of the eligible studies is shown in Figure 1. A total of 445 studies were identified in initial research. Literatures that did not meet the inclusion criteria and duplicated publications were eliminated. Overall, 14 eligible studies,[3,9,11,12,18–27] with a total of 32825 patients were included in this meta-analysis.

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3.2 Study characteristics

The general characteristics of included studies are listed in Table 1. Of the 14 studies, three were RCT, five were prospective cohort trial, and 6 were retrospective cohort trial. The mean age of all patients was 71.2 years old. There were 6142 patients in the TT group with a mean age of 70.7 and 23631 patients in the OAC plus single antiplatelet group with a mean age of 71.3, respectively. The warfarin was used as the oral anticoagulant in most trial, whereas one study used rivaroxaban in OAC plus single antiplatelet group. The mean period of follow-up was 12.9 months. 13 studies were assessed as high quality, while only one study was divided into low quality group.

| Study            | Year | Design | N   | OSA Regimen | Age (TT/OSA) | AF % | Indication of antiplatelet | Definition of MACCE | Definition of Bleeding | Follow-up (months) | Quality |
|------------------|------|--------|-----|-------------|--------------|------|----------------------------|----------------------|-----------------------|---------------------|---------|
| Karjalainen      | 2007 | R      | 106/78 | OA, OC     | 70            | 70   | PCI                        | Death, MI, TVR, ST  | PRISM-PLUS            | 12                  | H       |
| Nguyen           | 2007 | R      | 580/220 | OA, OC    | 64/66         | 40   | Coronary stenting          | NA                   | GRACE                | 6                   | H       |
| Sambola          | 2009 | P      | 278/46 | OA, OC    | 70/72         | 64   | PCI                        | CV death, MI, TVR, stroke | PRISM-PLUS             | 6                   | H       |
| Gao              | 2010 | P      | 142/125 | OA, OC    | 71.0/72.8     | 100  | Drug-eluting stent         | Death, MI, TVR, ST, stroke | TIMI                 | 12                  | H       |
| Hansen           | 2010 | R      | 1261/19775 | OA, OC | 69.9/70.8 | 100  | ACS                        | Death, MI            | ICD-10 codes          | 40                  | H       |
| Persson          | 2011 | R      | 404/565 | OA, OC    | 68/68         | NA   | PCI                        | Death                | ICD-10 codes          | 12                  | H       |
| REAL             | 2012 | P      | 205/111 | OA        | 73            | 58   | PCI                        | CV death, MI, TVR, stroke | Not defined            | 12                  | H       |
| WOEST            | 2013 | RCT    | 284/279 | OA         | 69.5/70.3     | 69   | PCI                        | Death, MI, TVR, stroke | TIMI, GUSTO, BARC     | 12                  | H       |
| Lamberts         | 2013 | R      | 1896/2052 | OA, OC    | 72.6/75.1    | 100  | MI or PCI                  | MI, coronary death   | ICD-10 codes          | 12                  | H       |
| AFCAS            | 2014 | P      | 679/73  | OC         | 73/74         | 100  | PCI                        | Death, MI, TVR, ST, stroke/STIA | BARC                 | 12                  | H       |
| ISAR-TRIPLE      | 2015 | RCT    | 307/307 | OA*        | 73.3/73.9     | 84   | Drug-eluting stent         | Death, MI, ST, stroke | TIMI, BARC            | 9                   | H       |
| ORBIT-AF         | 2016 | P      | 149/1431 | OA, OC    | 73/76         | 100  | CAD                        | Stroke, TIA, MI, TVR | ISTH                 | 12                  | H       |
| PIONEER AF-PCI   | 2016 | RCT    | 697/696 | OC#        | 69.9/70.4     | 100  | PCI                        | CV death, MI, stroke | TIMI                 | 12                  | H       |
| Vecchis          | 2016 | R      | 48/31   | OA, OC    | 72/73         | 90   | PCI                        | NA                   | NA                   | 12                  | L       |

*a6-week clopidogrel; b6-week clopidogrel plus Prasugrel; ACS: acute coronary syndrome; AF: atrial fibrillation; BARC: bleeding academic research consortium; CV: cardiovascular; CAD: coronary artery disease; GUSTO: global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries; GRACE: global registry of acute coronary events; H: high quality; ICD: international classification of diseases; ISAR-TRIPLE: intracoronary stenting and anti-thrombotic regimen—a comparison of a 6-week versus a 6-month clopidogrel treatment regimen in patients with concomitant aspirin and oral anticoagulant therapy following drug-eluting stent implantation; ISTH: international society of thrombosis and haemostasis; L: low quality; MACCE: major adverse cardiac/cerebrovascular event; MI: myocardial infarction; NA: not reported; OSA: oral anticoagulant + aspirin; OSA: oral anticoagulant + single antiplatelet agent; PIONEER AF-PCI: open-Label, randomized, controlled, multi-center study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vita-min K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention; P: prospective; PRISM-PLUS: platelet receptor inhibition in ischemic syndrome management in patients limited by unstable signs and symptoms; R: retrospective; RCT: randomized control trial; REAL: registro angioplastiche emilia-romagna; SA: single antiplatelet; ST: stent thrombosis; TIA: transient ischemic attack; TIMI: thrombolysis in myocardial infarction; TT: triple therapy (warfarin + clopidogrel + aspirin); TVR: target vessel revascularization; WOEST: what is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting.
3.3 Primary endpoint-MACCE

Eleven studies reported the risk of MACCE, as shown in Figure 2A. There were no significant differences in the risk of MACCE between TT and OAC plus clopidogrel/aspirin (OR: 0.97, 95% CI: 0.68–1.38, \(P = 0.85\)). Meanwhile, both OAC plus clopidogrel and OAC plus aspirin regimens had a similar risk of MACCE compared with TT (OR: 1.00, 95% CI: 0.69–1.46, \(P = 1.00\); OR: 0.85, 95% CI: 0.56–1.29, \(P = 0.45\), respectively). There were high level of heterogeneities among these 11 studies (\(I^2 = 79\%\), \(I^2 = 68\%\), \(I^2 = 69\%\), respectively). However, TT was associated with a significantly lower risk of MACCE than OAC plus aspirin in retrospective studies (OR: 0.63, 95% CI: 0.51–0.77, \(P < 0.0001\)). Moreover, the \(I^2\) decreased from 69% to 0% in subgroups.

Figure 2. Forest plots of MACCE in 11 studies. (A): prospective studies; (B): retrospective studies (C): identified in this meta-analysis. AFCAS: atrial fibrillation undergoing coronary artery stenting; CI: confidence interval; ISAR-TRIPCE: intracoronary stenting and anti-thrombotic regimen–testing of a 6-week versus a 6-month clopidogrel treatment regimen in patients with concomitant aspirin and oral anticoagulant therapy following drug-eluting; MACCE: major adverse cardiac and cerebrovascular events; OAC: oral anticoagulation; ORBIT AF: Outcome registry for better informed treatment of atrial fibrillation; PIONEER AF-PCI: open-Label, randomized, controlled, multi-center study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vita-min K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention; REAL: registro angioplastiche emilia-romagna; SA: single antiplatelet; TT: triple therapy (warfarin + clopidogrel + aspirin); WOEST: what is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting.
3.4 Secondary endpoints

3.4.1 All-Cause death

Ten studies reported the risk of all-cause death, as shown in Figure 3A. Patients in TT group showed a comparable risk of all-cause death compared with OAC plus clopidogrel/aspirin (OR: 0.90, 95% CI: 0.52–1.56, \( P = 0.71 \)) with a high level of heterogeneity (I² = 80%) among these 10 studies. However, TT was significantly associated with a higher risk of all-cause death when compared with OAC plus clopidogrel (OR: 2.11, 95% CI: 1.10–4.06, \( P = 0.02 \)) with a low level of heterogeneity (I² = 0%) in prospective studies. Whereas, TT showed a decreased risk of all-cause death compared with OAC plus aspirin (OR: 0.45, 95% CI: 0.20–0.97, \( P = 0.04 \)) with a high level of heterogeneity (I² = 78%) in retrospective studies.

3.4.2 MI

Nine studies reported the data of MI, as illustrated in Figure 4A. TT showed an inconclusive decreased risk of MI when compared with the other 3 antithrombotic groups: OAC plus clopidogrel/aspirin (OR: 0.80, 95% CI: 0.62–1.04, \( P = 0.09 \)), OAC plus clopidogrel (OR: 0.84, 95% CI: 0.61–1.15, \( P = 0.27 \)) and OAC plus aspirin (OR: 0.71, 95% CI: 0.49–1.04, \( P = 0.08 \)). There was a low level of heterogeneity (I² = 12%; 10%; 20%, respectively). In addition, TT showed a significantly lower risk of MI compared with OAC plus clopidogrel/aspirin (OR: 0.63, 95% CI: 0.43–0.92, \( P = 0.02 \)) and OAC plus clopidogrel (OR: 0.58, 95% CI: 0.37–0.90, \( P = 0.02 \)), both with low level of heterogeneity.

Figure 3. Forest plots of risks of all-cause death in 10 studies. (A): prospective studies; (B): retrospective studies; (C): identified in this meta-analysis. AFCAS: atrial fibrillation undergoing coronary artery stenting; CI: confidence interval; ISAR-TRIPCE: intracoronary stenting and antithrombotic regimen–testing of a 6-week versus a 6-month clopidogrel treatment regimen in patients with concomitant aspirin and oral anticoagulant therapy following drug-eluting; OAC: oral anticoagulation; ORBIT AF: Outcome registry for better informed treatment of atrial fibrillation; PIONEER AF-PCI: open-Label, randomized, controlled, multi-center study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vita-min K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention; REAL: registro angioplastiche emilia-romagna; SA: single antiplatelet; TT: triple therapy (warfarin + clopidogrel + aspirin); WOEST: what is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting.

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Figure 4. Forest plots of risks of MI in 9 studies. (A): prospective studies; (B): retrospective studies; (C): identified in this meta-analysis. AFCAS: atrial fibrillation undergoing coronary artery stenting; CI: confidence interval; ISAR-TRIPCE: intracoronary stenting and anti-thrombotic regimen–testing of a 6-week versus a 6-month clopidogrel treatment regimen in patients with concomitant aspirin and oral anticoagulant therapy following drug-eluting; MACCE: major adverse cardiac and cerebrovascular events; OAC: oral anticoagulation; ORBIT AF: Outcome registry for better informed treatment of atrial fibrillation; PIONEER AF-PCI: open-Label, randomized, controlled, multi-center study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vita-min K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention; REAL: registro angioplastiche emilia-romagna; SA: single antiplatelet; TT: triple therapy (warfarin + clopidogrel + aspirin); WOEST: what is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting.

$\left( I^2 = 0\% \right)$, in retrospective studies.

3.4.3 Stroke/TIA/PE

Ten studies showed the data of Stroke/TIA/PE, as illustrated in Figure 5A. The risk of Stroke/TIA/PE in TT group did not differ significantly with the other 3 groups (OR: 0.76, 95% CI: 0.42–1.38, $P = 0.36$; OR: 1.00, 95% CI: 0.58–1.72, $P = 0.99$; OR: 0.49, 95% CI: 0.22–1.09, $P = 0.08$, respectively) using a random-effect model ($\hat{I}^2 = 41\%$; $I^2 = 9\%$; $I^2 = 45\%$, respectively). However, in retrospective studies, TT had a decreased risk of Stroke/TIA/PE compared with OAC plus clopidogrel/aspirin (OR: 0.43, 95% CI: 0.30–0.62, $P < 0.00001$) and OAC plus aspirin (OR: 0.29, 95% CI: 0.09–0.96, $P = 0.04$), with low level of heterogeneity ($\hat{I}^2 = 25\%$; $\hat{I}^2 = 43\%$, respectively).

3.4.4 ST

As illustrated in Figure 6A, 9 studies reported the risk of ST. TT showed a trend of decreased risk of ST when compared with OAC plus clopidogrel/aspirin (OR: 0.78, 95% CI: 0.46–1.30, $P = 0.33$) and OAC plus aspirin (OR: 0.40, 95% CI: 0.15–1.11, $P = 0.08$), whereas no differences in TT and OAC plus clopidogrel (OR: 1.14, 95% CI: 0.54–2.40, $P = 0.73$). Meanwhile, the results in subgroup of prospective
studies kept consistent to those in overall analyses, with low level of heterogeneity ($I^2 = 16\%$; $I^2 = 11\%$; $I^2 = 23\%$, respectively) (Figure 6B).

### 3.4.5 Major bleeding

There were 12 studies showed the result of major bleeding, as shown in Figure 7A. Overall, TT showed a similar risk of major bleeding compared with OAC plus clopidogrel/aspirin (OR: 1.11, 95% CI: 0.82–1.51, $P = 0.49$), OAC plus clopidogrel (OR: 1.13, 95% CI: 0.79–1.61, $P = 0.49$) and OAC plus aspirin (OR: 1.11, 95% CI: 0.58–2.10, $P = 0.75$). However, among prospective studies, TT regimen had a trend toward increased risk of major bleeding than OAC plus clopidogrel (OR: 1.56, 95% CI: 0.98–2.49, $P = 0.06$), with a low level of heterogeneity ($I^2 = 0\%$) (Figure 7B).

### 3.5 Sensitivity analysis

There were no significant changes and reverse results in all comparisons after deselecting one study at one time. When comparing the rates of MACCE and ST between TT and OAC plus aspirin, the $I^2$ decreased from 69% to 0% and from 61% to 0%, respectively, after deselecting the REAL study.[23] In addition, when comparing the rates of all-cause

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**Figure 5. Forest plots of risks of Stroke/TIA/PE in 10 studies.** (A): prospective studies; (B): retrospective studies; (C): identified in this meta-analysis. AFCAS: atrial fibrillation undergoing coronary artery stenting; CI: confidence interval; ISAR-TRIPCE: intracoronary stenting and antithrombotic regimen–testing of a 6-week versus a 6-month clopidogrel treatment regimen in patients with concomitant aspirin and oral anticoagulant therapy following drug-eluting; MACCE: major adverse cardiac and cerebrovascular events; OAC: oral anticoagulation; ORBIT AF: Outcome registry for better informed treatment of atrial fibrillation; PIONEER AF-PCI: open-Label, randomized, controlled, multi-center study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vita-min K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention; REAL: registro angioplastiche emilia-romagna; SA: single antiplatelet; TT: triple therapy (warfarin+clopidogrel+aspirin); WOEST: what is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting.
death in TT and OAC plus aspirin, the I² decreased from 87% to 0% after deselecting the study of Lamberts, et al.[24] The sensitivity analysis indicated that these two studies might be the main sources of the heterogeneities.

4 Discussion

As far as we know, up to now, there has been no consensus about the optimal treatment regimen for patients with chronic OAC after coronary stenting. The biggest challenge is the balance between the risks of ischemic events and bleeding. Numbers of studies have shown the effectiveness of TT compared with DAPT, nevertheless, based on retrospective, observational, and underpowered data.[28–30] However, there have still been many concerns about TT due to the high risk of bleeding.[31] Many meta-analyses have collected data comparing the efficacy and safety of TT and DAPT and reported the pooled outcomes, which also could not reach an agreement.[12,33]

The results of our meta-analysis were similar to that of the WOEST study, while not in complete accordance with other similar meta-analyses.[34–36] Palla, et al.[35] found no significant difference in all-cause mortality, major bleeding, MI, stroke, and ST between TT and OAC plus clopidogrel. Results of analysis performed by Briasoulis, et al.[36] showed that TT was associated with a decreased risk of MI, without increasing in risks of major bleeding or death compared with OAC plus single antiplatelet therapy. The main reasons causing these discrepancies could be the difference of included studies and different subgroups. In addition, one RCT PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multi-center Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) involved in the novel oral anticoagulant rivaroxaban was included in this present meta-analysis.[12]

This trial enrolled 2124 participants with nonvalvular AF after PCI with stenting and randomly assigned them to three
groups, Vitamin K antagonist (VKA) plus DAPT, low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor, or very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT. Within the follow-up period of 12 months, the rates of major bleeding in the two groups receiving rivaroxaban were significantly lower than the group receiving standard TT. However, there was no significant difference in the rates of cardiovascular death, MI, or stroke between the three groups. The PIONEER trial showed that the addition of low-dose rivaroxaban or very-low-dose rivaroxaban to single or dual antiplatelet agents could reduce the rate of major bleeding without reducing the effectiveness compared with TT in patients with AF after PCI. However, the costly prices of New oral anticoagulants (NOACs) have hindered the extensive usage in clinic, and the strategies combining NOACs with antiplatelet agents still need more data to be further verified.

The findings of this updated meta-analysis indicated that OAC plus clopidogrel may bring the most net benefit for patients requiring OAC after coronary intervention, whereas OAC plus aspirin should be the worst choice. However, due to the limited number of high-quality, large-size trials, there is still no consensus on the optional antithrombotic regimen in these patients. Careful risk stratifications of stroke and bleeding should be conducted before making a decision of optimal antithrombotic regimen. CHA2DS2-VASc score is the most common score to predict the stroke risk for AF
patients.\(^{[37]}\) OAC is essential for AF patients with a score ≥ 1 point.\(^{[38]}\) As for the bleeding risk, the HAS-BLED is the most wide-used score in AF,\(^{[39]}\) which refers to, Hypertension; abnormal renal or liver function; stroke; bleeding tendency or predisposition; labile international normalized ratio (INRs, if on warfarin); age (eg, > 65, frail condition); drugs (eg, concomitant antiplatelet or NSAIDs) or alcohol excess/abuse. HAS-BLED categorizes bleeding risks into low (score 0–2) or high (≥ 3). However, a high HAS-BLED score is not a sign of withholding OAC, but a warning for physicians to monitor (INR) more frequently and adjusted the dose (if warfarin) more carefully. It is essential to balance the risk of stroke and bleeding by using CHA\(_2\)DS\(_2\)-VASc score and HAS-BLED score before the initiation of antithrombotic therapy. In addition, the duration of TT still remained questionable. The European Society of Cardiology (ESC) guideline recommended TT for one month after PCI, and 1–6 months after PCI for patients with acute coronary syndrome (ACS).\(^{[40]}\) Whatever, an individualized strategy weighing the effectiveness and risk sufficiently should be used for patients who need OAC and coronary stenting.

### 4.1 Limitations

There are several limitations in this meta-analysis. First, the definitions about MACCE and bleeding were not consistent among studies, which might result in bias. Next, the heterogeneity among studies was at a high level in the overall analyses. The REAL and the study of Lamberts, \textit{et al.}\(^{[24]}\) may be the main source of heterogeneities, because of the design differences and definition differences of MACCE and major bleeding. Therefore, the random-effect model was used in the overall analyses. Subsequently, subgroup analyses were performed based on trial design and studies in subgroups had a remarkably lower level of heterogeneity, which demonstrated that design differences were the main resource of heterogeneity. Third, there existed lots of potential confounding factors, such as the duration of each therapy, other concurrent drugs, and the periprocedural treatment, which might impact us on the assessment about the results. We wanted to conduct more subgroup analyses to find more potential sources of heterogeneity and provide more information about the comparison between TT and OAC plus single antiplatelet agent. However, the data available were so limited that further subgroup analyses could not be performed.

### 4.2 Conclusions

Our meta-analysis revealed that OAC plus clopidogrel has a trend of decreased risk of major bleeding and significantly decreased risk of all-cause death, without a markedly increased risk of MACCE in comparison with TT. TT is associated with lower risks of MACCE, all-cause death, and stroke/TIA/PE, and equivalent risk of major bleeding compared with OAC plus aspirin. Therefore, for patients requiring OAC after coronary intervention, OAC plus clopidogrel may bring more net benefit than TT, whereas OAC plus aspirin should be the last choice. More large-size randomized control trials are needed to confirm these findings.

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