Comparing the clinical outcomes in patients with atrial fibrillation receiving dual antiplatelet therapy and patients receiving an addition of an anticoagulant after coronary stent implantation

A systematic review and meta-analysis of observational studies

Nabin Chaudhary, MD, Pravesh Kumar Bundhun, MD, He Yan, MD, PhD

Abstract

Background: Data regarding the clinical outcomes in patients with atrial fibrillation (AF) receiving dual antiplatelet therapy (DAPT) and an anticoagulant in addition to DAPT (DAPT + vitamin K antagonist [VKA]) after coronary stent implantation are still controversial. Therefore, in order to solve this issue, we aim to compare the adverse clinical outcomes in AF patients receiving DAPT and DAPT + VKA after percutaneous coronary intervention and stenting (PCI-S).

Methods: Observational studies comparing the adverse clinical outcomes such as major bleeding, major adverse cardiovascular events, stroke, myocardial infarction, all-cause mortality, and stent thrombosis (ST) in AF patients receiving DAPT + VKA therapy, and DAPT after PCI-S have been searched from Medline, EMBASE, and PubMed databases. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to express the pooled effect on discontinuous variables, and the pooled analyses were performed with RevMan 5.3.

Results: Eighteen studies consisting of a total of 20,456 patients with AF (7203 patients received DAPT + VKA and 13,253 patients received DAPT after PCI-S) were included in this meta-analysis. At a mean follow-up period of 15 months, the risk of major bleeding was significantly higher in DAPT + VKA group, with OR 1.98 (95% CI 1.03–3.19, P = 0.07), respectively. There was no significant differences in myocardial infarction and major adverse cardiovascular event between DAPT + VKA and DAPT, with OR 1.27 (95% CI 0.92–1.77, P = 0.15) and OR 1.17 (95% CI 0.90–1.39, P = 0.07), respectively. However, the ST, stroke, and all-cause mortality were significantly lower in the DAPT + VKA group, with OR 1.98 (95% CI 1.03–3.81, P = 0.04), 1.59 (95% CI 1.08–3.34, P = 0.02), and 1.41 (95% CI 1.03–1.94, P = 0.03), respectively.

Conclusion: At a mean follow-up period of 15 months, DAPT + VKA was associated with significantly lower risk of stroke, ST, and all-cause mortality in AF patients after PCI-S compared with DAPT group. However, the risk of major bleeding was significantly higher in the DAPT + VKA group.

Abbreviations: ACS = acute coronary syndrome, AF = atrial fibrillation, CAD = coronary artery disease, DAPT = dual antiplatelet therapy, DES = drug-eluting stent, INR = international normalized ratio, MACEs = major adverse cardiovascular events, MI = myocardial infarction, NOAC = new oral anticoagulation, OAC = oral anticoagulation, PCI = percutaneous coronary intervention, ST = stent thrombosis, TT = triple therapy, VKA = vitamin K antagonist.

Keywords: atrial fibrillation, dual antiplatelet therapy, meta-analysis, percutaneous coronary intervention, triple therapy

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence ranging from less than 1% among people younger than 60 years to approximately 10% of patients who are older than 80 years. Co-existence of AF and coronary artery disease (CAD) is common. Approximately 20% to 35% of all patients with AF have CAD, and up to half of these patients have had a myocardial infarction (MI) that required coronary revascularization. Among patients with AF, the risk of stroke and thromboembolism is high. However, among patients with stent implantation, the risk of stent thrombosis (ST) is high. CAD patients with AF can suffer from stroke, thromboembolism, and also ST after stent implantation.

For patients undergoing stent implantation, dual antiplatelet therapy (DAPT) is the mainstay of the treatment to reduce the risk of ST. However, to prevent stroke and thromboembolism in patients with AF, chronic oral anticoagulation (OAC) therapy
with warfarin or Coumadin is recommended as the optimal therapy. For CAD patients with AF, who undergo stent implantation, warfarin, in addition to DAPT, has been considered in high-risk situations. However, the adverse outcomes in patients with AF, receiving DAPT, and an addition of an OAC after coronary stent implantation are still controversial. For example, the study conducted by Kang et al[8] showed that in CAD patients with AF, who underwent stent implantation, the risk for major bleeding was higher in triple therapy (TT) group (combination of vitamin K antagonist [VKA]+DAPT) compared with the DAPT group. On the contrary, the study by Gao et al[9] showed that the incidence of major bleeding was comparable between TT and DAPT groups. Moreover, recently, a meta-analysis conducted by Bavishi et al[10] stated that TT was associated with higher major bleeding when compared with the DAPT group. However, in his study, he has included the studies in which the indication of OAC is not only for AF but also for prosthetic metal valves, thromboembolism, and intracardiac thrombus. In our study, we have excluded those studies in which metallic prosthetic heart valves, intracardiac thrombi, and thromboembolism were also the indication of OAC, which can increase the risk of thromboembolic events in patients.

To solve this issue, we, therefore, sought to undertake a meta-analysis of clinical trials that compared DAPT with TT regarding clinical outcomes after stent implantation in CAD patients with AF.

2. Methods

2.1. Data sources and search strategy

We have searched Medline, EMBASE, and PubMed databases for relevant studies comparing DAPT with DAPT+VKA in CAD patients with AF after stent implantation, by typing the words “dual antiplatelet therapy,” “oral anticoagulation,” “percutaneous coronary intervention,” and “atrial fibrillation.” To further enhance this search, the abbreviations “DAPT,” “OAC,” “PCI,” and “AF” have also been used. References have also been checked for relevant studies. No language restriction was applied.

2.2. Inclusion and exclusion criteria

Studies were included if:
(1) they were dealing with CAD patients with AF;
(2) they compared TT (DAPT+VKA) with DAPT (aspirin+P2Y12 inhibitors) after percutaneous coronary intervention and stenting (PCI-S);
(3) adverse outcomes (major bleeding, major adverse cardiovascular events [MACEs], MI, ST, stroke, or all-cause mortality) were reported in these patients; and
(4) they had a mean follow-up period of ≥6 months after PCI.

Studies were excluded if:
(1) adverse outcomes were not among the clinical endpoints;
(2) an indication of OAC was the mechanical valve, thromboembolism, deep vein thrombosis, dilated cardiomyopathy, intracardiac thrombus, or others rather than AF;
(3) they were case studies, meta-analyses, or letter to editors;
(4) no control group/DAPT-treated patients were absent; and
(5) duplicates.

2.3. Definitions, outcomes, and follow-up

Adverse clinical outcomes such as major bleeding, all-cause mortality, MACEs, MI, ST, and stroke were considered as the clinical endpoints in this study. Analyzed clinical outcomes and follow-up periods have been represented in Table 1.

The definition of “major bleeding” is given in Table 1.

The term “major adverse cardiovascular events” is defined as the death of cardiac or noncardiac, MI, ST, and repeat target lesion revascularization after stent implantation. Major adverse cardiovascular and cerebrovascular events (MACCEs) have also been considered together in this section.

Myocardial infarction is defined as re-infarction, which occurs in AF patients after PCI. It could be Q-wave and non-Q-wave MI together, ST elevation MI and Non-ST elevation MI together, or fatal and nonfatal MI.

Stent thrombosis, as defined according to the Academic Research Consortium classification, including probable and definite ST, and also subacute ST, has been considered in this study.

Stroke is defined as a permanent, focal, neurological deficit adjudicated by a neurologist and confirmed by computed tomography/magnetic resonance imaging.

All-cause mortality is defined as mortality including cardiac and noncardiac death. If death was not clearly defined, whether it was cardiac or noncardiac or both, we have assumed it to be a death of all causes and have used the data in our study.

The long-term follow-up period was defined as a follow-up at >12 months.

2.4. Methodological quality and statistical analysis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was considered for this meta-analysis. The Cochrane Q-statistic (P ≤ 0.05 was considered significant, whereas P > 0.05 was considered as statistically insignificant) and I²-statistic were used to assess heterogeneity across the trials. I² described the percentage of total variation across studies, that is, due to heterogeneity rather than chance. A value of 0% indicated no heterogeneity, and larger values, especially from 50% and above, indicated increasing heterogeneity. If I² was < 50%, a fixed-effect model was used. However, if I² was > 50%, a random-effect model was considered. Publication bias was visually estimated by assessing funnel plots. We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) for categorical variables. The pooled analyses were performed with RevMan 5.3 software.

2.5. Ethics

Since this is a systematic review and meta-analysis, ethical approval was not required.

2.6. Data extraction and quality assessment

Two authors (NC and PKB) independently reviewed the data, and assessed the eligibility and methodological quality of each eligible trial. Information regarding the author names, the study type, year of publication, the total number of AF patients with CAD, the patient characteristics, and the adverse clinical outcomes reported, and also the follow-up periods was systematically extracted. If any of the 2 authors disagreed about the information or data extracted, disagreements were discussed between the authors, and if they could not reach a decision, it was
discussed and resolved by the third author (HY). The bias risk of trials was assessed with the components recommended by the Cochrane Collaboration.[12]

3. Results

3.1. Study selection

In all, 245 articles were identified by title and abstract. After elimination of duplicates, 220 articles were further screened. Among them, 181 articles were excluded since they were not related to the title of our study. Finally, 39 full-text articles were assessed for eligibility, of which, 21 were further excluded for several reasons: they were case studies, meta-analyses, or letters to the editor, in some trials DAPT+VKA-treated group was compared with either single antiplatelet therapy group or warfarin+single antiplatelet-treated group. Finally, 18 studies had been selected and included in this meta-analysis. The flow diagram for this study selection has been illustrated in Fig. 1.

3.2. General characteristics of included trials

Table 1 reports the general features of all the 18 studies included in this present meta-analysis. Features such as the number of the population involved in DAPT group, the number of population involved in DAPT+VKA group, bleeding definition, follow-up periods, and outcomes analyzed have been summarized in Table 1.

3.3. Baseline characteristics

These 18 studies which have been included in this systematic review and meta-analysis consisted of a total of 20,456 CAD patients with AF; among them, 13,253 patients received DAPT...
Records identified through Medline, Embase, and PubMed (n = 245)

Records after duplicates removed (n = 220)

Records screened (n = 220)

Records excluded since not related to our topic (n=181)

Full-text articles assessed for eligibility (n = 39)

Full-text articles excluded, because they were:
1. Meta-analysis, letter to editor, case studies (n=12)
2. Didn’t include control group/DAPT group (n=9)

Studies finally included in this meta-analysis (n = 18)

Figure 1. The flow diagram of study selection.

and remaining 7203 patients received DAPT+VKA treatment after PCI-S. The baseline features of each included study have been shown in Tables 2 and 3. Data from each study have been reported. Publication year, design of studies, mean age of patients, percentage of male patients, percentage of patients with hypertension, percentage of patients with diabetes mellitus, percentage of patients with dyslipidemia, percentage of patients with the history of heart failure and stroke, liver dysfunction, and kidney dysfunction, percentage of patients with drug-eluting stent (DES) used, and glycoprotein IIb/IIIa inhibitors used and active smokers have been listed in Tables 2 and 3.

In this present meta-analysis, the mean follow-up duration ranged from 6 to 42 months. The mean ages of the patients ranged from 65 to 80 years. Among 18 studies, 4 studies reported that the age of patients was ≥75 years.[13–16] The percentage of men were 20% to 78.6%. In 6 studies, those who received TT had a higher CHADS2 score [≥2][8,9,14–19] Moreover, in 6 studies, the proportion of patients with persistent or permanent AF was higher in TT group.[8,9,19–22] In 3 studies, the proportion of patients with the history of stroke was higher in TT group.[14,17,23]

3.4. Main results of this meta-analysis

At a mean follow-up period of 15 months, the pooled result of this meta-analysis showed that TT was associated with a significantly higher incidence of the major bleeding (OR 0.62, 95% CI 0.50–0.77, P < 0.0001, I² = 63%). ST, stroke, and all-cause mortality were significantly lower in DAPT+VKA group (OR 1.98, 95% CI 1.03–3.81, P = 0.04, I² = 0%; OR 1.59, 95% CI 1.08–2.34, P = 0.02, I² = 56%; and OR 1.41, 95% CI 1.03–1.94, P = 0.03, I² = 81%, respectively). There was no significant differences in the risk of MI and MACEs between DAPT+VKA and DAPT (OR 1.27, 95% CI 0.92–1.77, P = 0.15, I² = 46%; and OR 1.17, 95% CI 0.99–1.39, P = 0.07, I² = 56%, respectively). The adverse clinical outcomes have been summarized in Table 4. The detailed results for all adverse events have been represented in Figs. 2 and 3.

In the subgroup analysis of acute coronary syndrome (ACS),[13,14,17,24] the risk of major bleeding was similar to previous finding (OR 0.68, 95% CI 0.56–0.82, P < 0.0001, I² = 56%). However, there was no significant difference in the risk of MI, MACE, stroke, and all-cause mortality between DAPT+VKA and DAPT groups (OR 0.95, 95% CI 0.76–1.19, P = 0.68; OR

### Table 2

Baseline characteristics of each included study.

| Author            | Year | Country | Design                  | Age, y (D/T) | Male (%) D/T | HTN (%) D/T | DM (%) D/T | HL (%) D/T | h/o-HF (%) D/T |
|-------------------|------|---------|-------------------------|--------------|--------------|-------------|------------|------------|----------------|
| Ruiz-Nadar et al[23] | 2008 | UK      | Retrospective registry  | 71.2/71.6    | 70.4/70.7    | 72.1/81.6   | 41.8/42.5  | NS         | 22.8/29.2   |
| Magedorfussel et al[3] | 2008 | Germany | Retrospective analysis  | 69.8/68.5    | 73.5/78.6    | 91.3/78.6   | 30.1/71    | 68/64.3    | NS            |
| Marciano-Fernandez et al[24] | 2008 | Spain   | Retrospective analysis  | 74.6/74      | 64/74        | 54/51       | 54/51      | 52/57       | 36/47         |
| Gao et al[4]     | 2010 | China   | Prospective study       | 71.7/70.9    | 71/72.2      | 68/73       | 35.7/38.3  | 67/47.1    | 21.6/19.1    |
| Fosbol et al[3]  | 2012 | USA     | Retrospective registry  | 80/78        | 51/63.7      | 79.6/82.2   | 35.1/37.1  | 52/62.2    | 29/29.3       |
| Lamberts et al[25] | 2013 | UK      | Retrospective study     | 72.1/71.3    | 61.8/73.9    | 67.3/77.2   | NS         | NS         | 22.5/27       |
| Suh et al[26]    | 2013 | South Korea | Prospective, non-retrospective study | 68.9/65.6  | 59.6/75.7   | 71.1/67.6   | 38/24.3    | 24/116.2   | 26/27.2       |
| Djibrweska et al[27] | 2013 | Poland  | Prospective, non-retrospective study | 71/69       | 53/66       | 85/93      | 28/57      | 95/98      | NS            |
| Ho et al[7]      | 2013 | Canada  | Retrospective study     | 70.5/72.9    | 65.9/74.3    | 82.3/76.4   | 32.3/36.9  | 75.5/75.9  | 36.9/72.3*   |
| Goto et al[3]    | 2014 | Japan   | Cohort study            | 73/72        | 67/75.7      | 84.8/86     | 33.6/55    | NS         | 39.2/39.7    |
| Rubboli et al[8] | 2014 | Italy   | Prospective study       | 73/73        | 65/71.1      | 88/84       | 33/37      | 67/67      | 14/21*        |
| Minnuni et al[6] | 2015 | Italy   | Retrospective study     | 72/73        | 70/75       | 92/95       | 38/43      | NS         | 60/41         |
| Sambola et al[28] | 2015 | Spain   | Retrospective study     | 73.7/73      | 37/20.1      | 69.5/79.9   | 34/24.4    | 45/45.4    | 56/45.3       |
| Kang et al[9]    | 2015 | South Korea | Retrospective study     | 67.6/65.1    | 64/66.4      | 75/74       | 30.5/32.8  | 46/38.6    | 18.6/39.6     |
| Kawai et al[10]  | 2015 | Japan   | Retrospective study     | 70.5/71.9    | 74.6/71.4    | 80/69.3     | 44.8/42.9  | 68.9/64.3  | NS            |
| Hess et al[11]   | 2015 | USA     | Cohort study            | 78/77*       | 55.4/63.1    | 81.1/83.6   | 30/55*     | 62.6/67.3*  | 16.9/24.6*    |
| Lopes et al[12]  | 2016 | USA     | Prospective study       | 79/73        | 64/73       | 87/92       | 34/43      | 89/90      | 46/46         |
| Sambola et al[13] | 2016 | Spain   | Prospective cohort study| 79/80.4     | 69.2/65.4    | 72.3/84.3   | 34.6/34.6  | NS         | 26.2/26.8    |

D/T = DAPT/TT, DAPT = dual antiplatelet therapy, DM = diabetes mellitus, h/o = history of, HF = heart failure, HTN = hypertension, NS = not stated, TT = triple therapy.

* P < 0.05.
1.18, 95% CI 0.85–1.63, P = 0.32, I² = 88%; OR: 1.64, 95% CI 0.79–3.14, P = 0.19, I² = 90%; and OR: 1.85, 95% CI 0.61–5.62, P = 0.28, I² = 98%, respectively). These results have been represented in Fig. 4. Moreover, in long-term follow-up period, the risk of major bleeding was significantly higher in DAPT + VKA group (OR: 0.55, 95% CI 0.47–0.65, P < 0.00001, I² = 24%). MACE, MI, stroke, all-cause mortality, and ST in DAPT + VKA group was comparable with that in the DAPT group (OR: 1.13, 95% CI 0.76–1.68, P = 0.54, I² = 65%; OR: 1.02, 95% CI 0.83–1.26, P = 0.82, I² = 0%; OR: 1.13, 95% CI 0.86–1.50, P = 0.37, I² = 0%; OR: 1.10, 95% CI 0.96–1.26, P = 0.19, I² = 41%; and OR: 1.67, 95% CI 0.35–7.90, P = 0.52, I² = 0%, respectively). Details of long-term results have been represented in Figs. 5 and 6.

For all of the above analyses, sensitivity analysis yielded consistent results. Based on a visual inspection of the funnel plot, there has been no evidence of publication bias for the included studies that assessed the adverse clinical endpoints. The funnel plot has been represented in Fig. 7.

4. Discussion

To our knowledge, till date, there is no consensus on the optimal strategy for antithrombotic therapy in patients who require anticoagulation treatment after coronary stenting. The European Society of Cardiology (ESC) 2014 guidelines for the management of patients with AF and ACS/PCI briefly addresses this issue: “After elective PCI, TT should be considered in the short term, followed by long-term therapy (up to 12 months) with VKA plus clopidogrel 75 mg per day (or, alternatively, aspirin 75–100 mg daily, plus gastric protection with PPIs, H2 antagonists, or antacids).” However, there is still no large-scale, randomized, controlled trial on TT and DAPT in these patients. For AF patients requiring OAC after coronary stenting, TT has been increasingly prescribed in the current clinical practice. There are various studies, mainly observational, that have been recently conducted on this topic.[8,9,13–26,28,29] However, single studies were underpowered for clinical endpoints, and only pooled analyses of data from multiple studies can help in clarifying the issue of safety and effectiveness of TT. Therefore, we performed this present analysis.

The main findings of this meta-analysis were that TT was associated with a significantly higher risk of major bleeding compared with DAPT group, with a mean follow-up period of 1.5 months. Although MACE and MI were similar in both groups, DAPT was associated with a significantly higher risk of ST, stroke, and all-cause mortality compared with TT group. However, in ACS subgroup and long-term follow-up group, the risk of MI, MACE, stroke, all-cause mortality, and ST were comparable between TT and DAPT groups. Several reasons have been thought to be responsible for this significantly higher rate of major bleeding in AF patients after coronary stenting. First of all, almost all major bleeding events occurring in TT group were often associated with supratherapeutic international normalized ratio (INR) levels.[30] A study conducted by Rossini et al.[30] in 2008 showed that at a mean follow-up period of 18 months, the risk of bleeding was higher in the TT compared with the DAPT group (10.8% vs 4.9%; P = 0.01); however, the result was statistically nonsignificant. Moreover, according to the study conducted by Rossini et al, bleeding was higher in those patients with significantly higher INR values (2.8±0.1 vs 2.3±0.2;
P=0.0001). INR values >2.6 were the only independent predictors of bleeding in their study. A meta-analysis conducted by Bavishi et al[10] showed that patients treated with TT had a significantly higher risk of major bleeding (8.8% vs 7.7%) compared with DAPT. However, in his study, the indication of OAC is not only AF but also prosthetic heart valve, thromboembolism, left ventricular aneurysm, ejection fraction <30%, or intracardiac thrombus. It is important that

Figure 2. Forest plot showing the odds ratio of major bleeding, MACEs, myocardial infarction, stroke, all-cause mortality associated with DAPT + VKA versus DAPT. DAPT = dual antiplatelet therapy, MACEs = major adverse cardiovascular events, VKA = vitamin K antagonist.
our study exclude those patients with metallic prosthetic heart valves, intracardiac thrombi, and thromboembolism, who would be at significantly increased risk of thromboembolic events if anticoagulation was to be discontinued after PCI. Reasons for the higher bleeding events in TT have not been specifically studied. However, they could be likely multifactorial due to various therapeutic and clinical characteristics. Possible explanations are female sex, advanced age, high prevalence of comorbidities (eg, previous major bleeding and renal dysfunction), peri-interventional administration of glycoprotein IIb/IIIa inhibitors, and smoking. Of note, in some studies, anemia also appeared to be a high-risk marker for mortality and hemorrhagic complications.

| Study or Subgroup | DAPT Events | DAPT+VKA Events | Odds Ratio M-H, Fixed, 95% CI Year |
|-------------------|-------------|----------------|----------------------------------|
| Ruiz–Nodar 2008   | 2           | 178            | 14.2% 1.10 [0.15, 7.87] 2008      |
| Gao 2010          | 3           | 334            | 136 10.6% 1.22 [0.13, 11.87] 2010  |
| Dabrowska 2013    | 0           | 60             | 0 44 Not estimable 2013          |
| Sub 2013          | 6           | 166            | 37 5.9% 3.04 [0.17, 55.11] 2013    |
| Goto 2014         | 14          | 551            | 506 30.5% 3.27 [1.07, 10.01] 2014  |
| Rubboi 2014       | 3           | 162            | 679 25.6% 1.40 [0.38, 5.25] 2014   |
| Salomona 2016     | 2           | 130            | 159 13.3% 1.23 [0.17, 8.83] 2016   |
| **Total (95% CI)** | **1581**   | **1756**       | **100.0% 1.98 [1.03, 3.81]**     |

| Total events     | 30          | 18             |
| Heterogeneity: Chi² = 1.87, df = 5 (P = 0.87); I² = 0% |
| Test for overall effect: Z = 2.06 (P = 0.04) |

**Figure 3.** Forest plot showing the odds ratio of stent thrombosis associated with DAPT + VKA versus DAPT. DAPT = dual antiplatelet therapy, VKA = vitamin K antagonist.

| Study or Subgroup | DAPT Events | DAPT+VKA Events | Odds Ratio M-H, Fixed, 95% CI Year |
|-------------------|-------------|----------------|----------------------------------|
| **1.5.1 Major bleeding** |
| Fosbol 2012       | 336         | 2841           | 109 30.9% 0.77 [0.61, 0.97] 2012       |
| Lambert 2013      | 166         | 3590           | 117 29.7% 0.74 [0.58, 0.94] 2013       |
| Hess 2015         | 395         | 3589           | 241 33.4% 0.58 [0.49, 0.69] 2015       |
| Subtotal (95% CI) | 10020       | 3997           | 100.0% 0.68 [0.56, 0.82]              |
| Total events      | 897         | 467            |
| Heterogeneity: Tau² = 0.02; Chi² = 4.50, df = 2 (P = 0.11); I² = 56% |
| Test for overall effect: Z = 4.09 (P < 0.0001) |

| **1.5.2 MACE** |
| Fosbol 2012       | 922         | 2841           | 187 48.1% 1.40 [1.16, 1.68] 2012       |
| Hess 2015         | 1174        | 3589           | 447 31.9% 1.00 [0.88, 1.15] 2015       |
| Subtotal (95% CI) | 6430        | 2101           | 100.0% 1.18 [0.85, 1.63]              |
| Total events      | 2096        | 634            |
| Heterogeneity: Tau² = 0.05; Chi² = 8.20, df = 1 (P = 0.004); I² = 88% |
| Test for overall effect: Z = 0.99 (P = 0.32) |

| **1.5.3 MI** |
| Hess 2015         | 291         | 3589           | 116 1370 100.0% 0.95 [0.76, 1.19] 2015 |
| Subtotal (95% CI) | 3589        | 1370           | 100.0% 0.95 [0.76, 1.19]              |
| Total events      | 291         | 116            |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.41 (P = 0.68) |

| **1.5.4 Stroke** |
| Lambert 2013      | 151         | 3590           | 34 1896 48.7% 2.40 [1.65, 3.50] 2013 |
| Hess 2015         | 190         | 3589           | 64 1370 51.3% 1.14 [0.85, 1.53] 2015 |
| Subtotal (95% CI) | 7179        | 3266           | 100.0% 1.64 [0.79, 3.41]             |
| Total events      | 341         | 98             |
| Heterogeneity: Tau² = 0.25; Chi² = 9.53, df = 1 (P = 0.002); I² = 90% |
| Test for overall effect: Z = 1.32 (P = 0.19) |

| **1.5.5 All-cause mortality** |
| Lambert 2013      | 430         | 3590           | 76 1896 49.6% 3.26 [2.54, 4.19] 2013 |
| Hess 2015         | 890         | 3589           | 526 1370 50.4% 1.06 [0.91, 1.22] 2015 |
| Subtotal (95% CI) | 7179        | 3266           | 100.0% 1.85 [0.61, 5.62]             |
| Total events      | 1320        | 402            |
| Heterogeneity: Tau² = 0.63; Chi² = 58.97, df = 1 (P < 0.00001); I² = 98% |
| Test for overall effect: Z = 1.08 (P = 0.28) |

Test for subgroup differences: Chi² = 15.44, df = 4 (P = 0.004); I² = 74.1%
### Table

| Study or Subgroup | DAPT Events | DAPT+VKA Events | Odds Ratio M-H, Random, 95% CI Year |
|-------------------|-------------|-----------------|-----------------------------------|
| **1.2.1 Major bleeding** | | | |
| Maegdefessel 2008 | 2 | 103 | 0.2% | 0.71 [0.03, 15.63] 2008 |
| Ruiz-Nadar 2008 | 16 | 178 | 6.9% | 0.57 [0.30, 1.08] 2008 |
| Suh 2013 | 1 | 166 | 137 | 0.9% | 0.22 [0.03, 1.57] 2013 |
| Kang 2015 | 1 | 236 | 131 | 7.4% | 0.24 [0.11, 0.52] 2015 |
| Hess 2015 | 39 | 3589 | 241 | 1370 | 85.0% | 0.58 [0.49, 0.69] 2015 |
| **Subtotal (95% CI)** | 4272 | 1747 | 100.0% | 0.55 [0.47, 0.65] |
| Total events | 425 | 293 | 193 | 24% | Test for overall effect: Z = 7.15 (P < 0.00001) |
| **1.2.3 MI** | | | |
| Ruiz-Nadar 2008 | 19 | 178 | 13 | 195 | 6.4% | 1.67 [0.80, 3.50] 2008 |
| Suh 2013 | 4 | 166 | 0 | 37 | 0.5% | 2.08 [0.11, 39.41] 2013 |
| Kang 2015 | 15 | 236 | 6 | 131 | 4.2% | 1.41 [0.54, 3.74] 2015 |
| Hess 2015 | 291 | 3589 | 116 | 1370 | 89.0% | 0.95 [0.76, 1.19] 2015 |
| **Subtotal (95% CI)** | 4169 | 1733 | 100.0% | 1.02 [0.83, 1.26] |
| Total events | 329 | 135 | 135 | 0% | Test for overall effect: Z = 0.22 (P = 0.82) |
| **1.2.4 Stroke** | | | |
| Maegdefessel 2008 | 9 | 103 | 0 | 14 | 0.8% | 2.92 [0.16, 52.83] 2008 |
| Suh 2013 | 6 | 166 | 1 | 37 | 1.7% | 1.35 [0.16, 11.56] 2013 |
| Kang 2015 | 5 | 236 | 4 | 131 | 5.3% | 0.69 [0.18, 2.60] 2015 |
| Hess 2015 | 190 | 3589 | 64 | 1370 | 92.2% | 1.14 [0.85, 1.53] 2015 |
| **Subtotal (95% CI)** | 4094 | 1552 | 100.0% | 1.13 [0.86, 1.50] |
| Total events | 210 | 69 | 69 | 0% | Test for overall effect: Z = 0.37 (P = 0.71) |
| **1.2.5 All-cause mortality** | | | |
| Ruiz-Nadar 2008 | 49 | 178 | 35 | 195 | 6.1% | 1.74 [1.06, 2.84] 2008 |
| Maegdefessel 2008 | 3 | 103 | 1 | 14 | 0.4% | 0.39 [0.04, 4.03] 2008 |
| Suh 2013 | 27 | 166 | 3 | 37 | 1.0% | 2.20 [0.63, 7.69] 2013 |
| Hess 2015 | 890 | 3589 | 326 | 1370 | 89.6% | 1.06 [0.91, 1.22] 2015 |
| Kang 2015 | 11 | 236 | 9 | 131 | 2.8% | 0.66 [0.27, 1.64] 2015 |
| **Subtotal (95% CI)** | 4272 | 1747 | 100.0% | 1.10 [0.96, 1.26] |
| Total events | 980 | 374 | 374 | 0% | Test for overall effect: Z = 1.31 (P = 0.19) |
| **1.2.6 ST** | | | |
| Ruiz-Nadar 2008 | 2 | 178 | 2 | 195 | 70.7% | 1.10 [0.15, 7.87] 2008 |
| Suh 2013 | 6 | 166 | 0 | 37 | 3.3% | 3.04 [0.17, 55.11] 2013 |
| **Subtotal (95% CI)** | 344 | 252 | 100.0% | 1.67 [0.35, 7.90] |
| Total events | 8 | 2 | 2 | 0% | Test for overall effect: Z = 0.64 (P = 0.52) |

Test for subgroup differences: Chi² = 47.15, df = 4 (P < 0.00001), I² = 91.5%

Figure 5. Forest plot showing the odds ratio of major bleeding, MI, stroke, all-cause mortality, and ST at long-term follow-up associated with DAPT + VKA versus DAPT. DAPT = dual antiplatelet therapy, MI = myocardial infarction, ST = stent thrombosis, VKA = vitamin K antagonist.

### Table

| Study or Subgroup | DAPT Events | DAPT+VKA Events | Odds Ratio M-H, Random, 95% CI Year |
|-------------------|-------------|-----------------|-----------------------------------|
| **Manzano–Fernandez 2008** | 11 | 53 | 13 | 51 | 12.4% | 0.77 [0.31, 1.91] 2008 |
| **Ruiz–Nadar 2008** | 69 | 178 | 52 | 195 | 25.7% | 1.74 [1.12, 2.70] 2008 |
| **Suh 2013** | 52 | 166 | 5 | 37 | 3.5% | 8.60 [1.14, 65.07] 2013 |
| **Hess 2015** | 1174 | 3589 | 447 | 1370 | 36.0% | 1.00 [0.88, 1.15] 2015 |
| **Kang 2015** | 42 | 236 | 29 | 131 | 22.4% | 0.76 [0.45, 1.29] 2015 |
| **Total (95% CI)** | 4222 | 1784 | 100.0% | 1.13 [0.76, 1.66] |
| Total events | 1328 | 542 | 542 | 0% | Test for overall effect: Z = 0.62 (P = 0.54) |

Figure 6. Forest plot showing the odds ratio of MACEs at long-term follow-up associated with DAPT + VKA versus DAPT. DAPT = dual antiplatelet therapy, MACEs = major adverse cardiovascular events, VKA = vitamin K antagonist.
in patients undergoing PCI.\cite{32-34} In addition, gastrointestinal bleeding events were common and occurred in patients with baseline anemia, emphasizing the importance of a thorough search for predisposing bleeding sites and/or hemorrhagic diatheses.\cite{25} On the contrary, some studies showed that patients receiving TT with an INR of lower therapeutic range (2.0–2.5) had a bleeding risk comparable with that of patients receiving dual therapy.\cite{19,30} It is difficult to maintain INR within the therapeutic range (2.0–2.5). However, regular self-monitoring of prothrombin time (PT) and/or INR provides comparable or better outcomes, in terms of therapeutic range of INR levels, decreased thromboembolic events, all-cause mortality, and major hemorrhage.\cite{33-37} Therefore, if we can maintain the INR in the target range and assess patients using the CHADS2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category) score, the difference between TT and DAPT in major bleeding events may disappear.\cite{38-42}

In our meta-analysis, MACEs were higher in DAPT group (29% vs 23.6%), but were not statistically significant. The occurrence of MI was similar in both groups (8% vs 7.1%), however, the occurrences of ST (1% vs 1.9%) and all-cause mortality (12.5% vs 17.6%) in TT group were significantly lower than the ones in the DAPT group. A study conducted by Khurram et al.\cite{43} evaluated 107 patients who were treated up to a year with TT after PCI-S (DES in 50% of cases). The incidences of both major and minor hemorrhages were significantly higher in the TT group than in the DAPT group (6.6% vs 0%; $P=0.03$, and 14.9% vs 3.8%; $P=0.01$). TT was found associated with about 5-fold increase in hemorrhages as compared with DAPT (hazard ratio [HR] 5.44, 95% CI 2.03–14.53, $P=0.001$). All major bleedings occurred between 2 and 10 months, suggesting that the duration of the TT should be decreased, for example, by avoiding the use of DES. Moreover, in the study, neither ST nor thromboembolic events were observed during the triple antithrombotic therapy. The meta-analysis by Zhao et al.,\cite{44} which included 9 studies, demonstrated that TT was more efficacious in reducing mortality and cardiovascular events, at the price of an increased bleeding risk. Additionally, a study published by Washam et al.,\cite{45} which compared the safety and efficacy of DAPT and TT in patients with ACS, has shown that mortality and stroke were comparable between DAPT and TT groups, whereas nonfatal MI and major bleeding were significantly higher in TT group. In the study, the indication of OAC was AF, venous thromboembolism, or mechanical heart valve. The ESC Working Group on Thrombosis published an expert consensus\cite{7} which suggested that the use of aspirin and warfarin could not provide sufficient protection against the risk of ST. Patients undergoing stent-based PCI should be treated with triple therapy consisting of aspirin, clopidogrel, and warfarin. However, prolonged duration of triple therapy might be associated with an increased risk of bleeding; therefore, in the document of ESC expert consensus and ESC guidelines for the management of AF, it is recommended that triple therapy should be used for 4 weeks after bare metal stent (BMS) implantation, and longer duration for DES (at least 3–6 months), followed by dual antithrombotic therapy with warfarin and 75 mg clopidogrel, or 75 to 100 mg aspirin, plus gastric protection agents.\cite{17,46} Careful risk stratification should be made on an individual basis before the initiation of antithrombotic therapy to balance the risk of bleeding and ischemic events. Recent trials have suggested that even patients with low to moderate risk of thromboembolism assessed by CHADS2 score can largely benefit from chronic OAC.\cite{38,47} Therefore, the new ESC guidelines have recommended a novel risk score system, CHADS2-VASc schema, to evaluate the individual risk of thromboembolism accurately.\cite{18,46}

The use of DES in reducing restenosis has been well-documented. However, the main problem of DES is that it is potentially associated with the increased risk of late ST\cite{48} and requires prolonged DAPT up to a year. However, in patients with concomitant OAC, prolonged DAPT may increase the bleeding risk.\cite{49} Therefore, the use of DES should be limited to situations such as long lesions, small vessels, and diabetes, where a significant benefit is expected as compared with BMS.\cite{7}

Recently, new oral anticoagulants, such as dabigatran, apixaban, and rivaroxaban, have led to a new modern era of novel anticoagulation. New antplatelet drugs including ticagrelor and prasugrel have also emerged. These novel anticoagulants have been introduced as an alternative to warfarin, the standard OAC therapy for patients with AF. Three large-phase randomized controlled trials, RE-LY trial, ARISTOTLE trial, and ROCKET-AF,\cite{50-52} have examined the long-term use of new anticoagulants. Concerning combined stroke and systemic embolism, the new oral anticoagulants were more efficacious than warfarin and were associated with a decreased risk of intracranial bleeding. However, the data on TT with a new oral anticoagulation (NOAC) are still limited.\cite{53} Enough trials should be conducted in the future to understand the efficacy and safety of TT with the NOAC.

### 4.1. Limitations

The present meta-analysis has several limitations. The articles included in the analysis were not randomized controlled trials; therefore, there is a possibility of selection bias. The trials were significantly heterogeneous from each other as evidenced by high $I^2$ value for the all-cause mortality. The follow-up periods were not similar in all the articles. Also, bleeding was defined differently in each article. There was an unequal distribution of patients with DAPT and TT groups. Time in therapeutic INR range (TTR), which plays an important role in both thromboembolic and adverse bleeding events, was not reported in this study. Moreover, ST, stroke, and MI were less well studied than the bleeding events. The best way to answer these shortcomings is a randomized control trial.
The risk of bleeding complications can be lowered. Significantly reduced mortality in AF patients after PCI-S, when compared with DAPT group. However, the risk of major bleeding is significantly higher in the DAPT+VKA group. If we pay more attention to the INR and keep it within the target range (2.0–2.5), the risk of bleeding complications can be lowered.

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