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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

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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 0.62 (95% CI 0.50–0.77, $P < 0.0001$). 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 0.99–1.39, $P = 0.07$), 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 1.08–2.34, $P = 0.02$), 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,[1] 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.[2] 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.[3,4] 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)[5] 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.[6,7]

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.[11] The Cochrane Q-statistic ($P \leq 0.05$ was considered significant, whereas $P > 0.05$ was considered as statistically insignificant) and I^2-statistic were used to assess heterogeneity across the trials. I^2 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 I^2 was <50%, a fixed-effect model was used. However, if I^2 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

Table 1

Numbers of DAPT and TT-treated patients, bleeding definition, and endpoints with their corresponding follow-up periods.

| Author | Year | Study population | | | Bleeding definition | Outcomes analyzed | Mean follow-up period, mos |
		Total	DAPT	TT			
Ruiz-Nodar et al[23]	2008	373	178	195	PRISM-PLUS	Major bleeding, MACEs, MI, ST, all-cause mortality	19
Maegdefessel et al[25]	2008	117	103	14	Not specified	Major bleeding, stroke, all-cause mortality	16
Manzano-Fernandez et al[28]	2008	103	53	50	PRISM-PLUS	Major bleeding	12
Gao et al[9]	2010	497	355	142	TIMI	Major bleeding, MACEs, ST, stroke, all-cause mortality	12
Fosbol et al[13]	2012	3572	2841	731	CRUSADE	Major bleeding, MACEs	12
Lamberts et al[24]	2013	5486	3590	1896	HAS-BLED	Major bleeding, stroke, all-cause mortality	12
Suh et al[26]	2013	203	166	37	Intracranial bleeding, clinical bleeding or drop in hemoglobin >2 g/dL needing transfusion	Major bleeding, MACEs, MI, ST, stroke, all-cause mortality	42
Dąbrowska et al[29]	2013	104	60	44	HAS-BLED, GRACE	Major bleeding, MI, ST, all-cause mortality	12
Ho et al[17]	2013	602	220	382	Bleeding requiring subsequent blood transfusion	Major bleeding, MACEs, MI, stroke, all-cause mortality	6
Goto et al[20]	2014	1057	551	506	GUSTO	Major bleeding, MI, stroke, all-cause mortality	12
Rubboli et al[19]	2014	841	162	679	BARC	Major bleeding, MACEs, MI, ST, stroke, all-cause mortality	12
Mennuni et al[21]	2015	859	488	371	BARC	Major bleeding, MACEs	12
Sambola et al[18]	2015	585	266	319	TIMI, PRISM-PLUS	Major bleeding, MACEs, stroke, all-cause mortality	12
Kang et al[8]	2015	367	236	131	Moderate or severe bleeding according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria	Major bleeding, MACEs, MI, stroke, all-cause mortality	24
Kawai et al[22]	2015	95	67	28	TIMI	Major bleeding, MACEs, MI, stroke, all-cause mortality	12
Hess et al[14]	2015	4959	3589	1370	ATRIA	Major bleeding, MACEs, MI, stroke, all-cause mortality	24
Lopes et al[15]	2016	347	198	149	ATRIA, HAS-BLED	Major bleeding, MACEs, MI, all-cause mortality	12
Sambola et al[16]	2016	289	130	159	TIMI, BARC	Major bleeding, MACEs, MI, ST, stroke, all-cause mortality	12

ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation, BARC = Bleeding Academic Research Consortium, GRACE = Global Registry of Acute Coronary Events, CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines, GUSTO = The Global Use of Strategies to Open Occluded Arteries, HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65 years), Drugs/alcohol concomitantly, DAPT = dual antiplatelet therapy, MACEs = major adverse cardiovascular events, MI = myocardial infarction, PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms, ST = stent thrombosis, TIMI = Thrombolysis in Myocardial Infarction, TT = triple therapy.

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
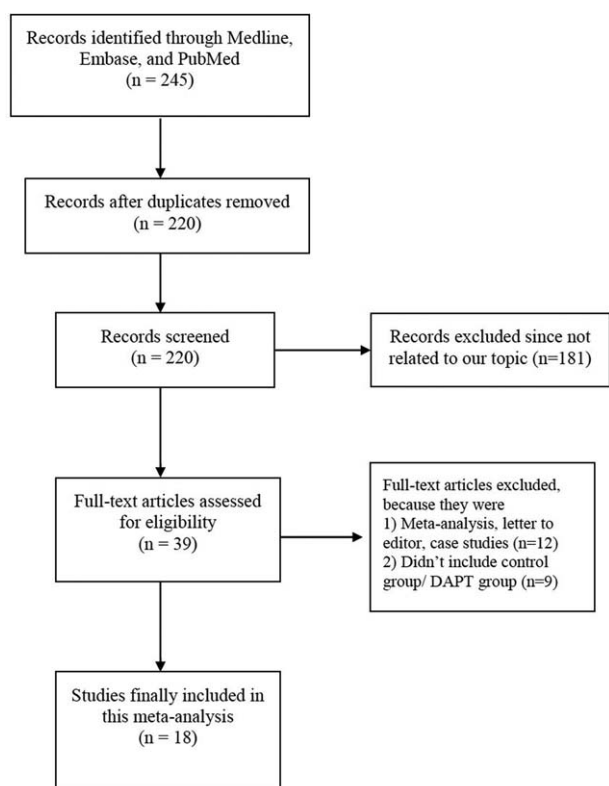
Figure 1. The flow diagram of study selection.

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).[8,9,14,17–19] 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, $P < 0.0001$, $I^2 = 63\%$). ST, stroke, and all-cause mortality were significantly lower in DAPT + VKA group (OR 1.98, 95% CI 1.03–3.81, $P = 0.04$, $I^2 = 0\%$; OR 1.59, 95% CI 1.08–2.34, $P = 0.02$, $I^2 = 56\%$; and OR 1.41, 95% CI 1.03–1.94, $P = 0.03$, $I^2 = 81\%$, 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, $P = 0.15$, $I^2 = 46\%$; and OR 1.17, 95% CI 0.99–1.39, $P = 0.07$, $I^2 = 56\%$, 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),[13,14,24] the risk of major bleeding was similar to previous finding (OR 0.68, 95% CI 0.56–0.82, $P < 0.0001$, $I^2 = 56\%$). 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

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,

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-Nodar 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
Maegdefessel et al[25]	2008	Germany	Retrospective analysis	69.8/68.5	73.5/78.6	91.3/78.6	30.1/7.1	68/64.3	NS
Manzano-Fernandez et al[28]	2008	Spain	Retrospective analysis	74/69*	66/74	54/51	54/51	52/57	36/47
Gao et al[9]	2010	China	Prospective study	71.7/70.9*	71.2/72.2	68/73	35.7/38.3	67.4/71.3	21.6/19.1
Fosbol et al[13]	2012	USA	Retrospective registry	80/78	51/63.7	79.6/82.2	35.1/37.1	52.3/62.2	29.1/29.3
Lamberts et al[24]	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	Retrospective analysis	68.9/65.6	59.6/75.7	71.1/67.6	38/24.3	24.1/16.2	26.7/21.6
Dąbrowska et al[29]	2013	Poland	Prospective, non-randomized registry	71/69	53/66	85/93	28/57*	95/98	NS
Ho et al[17]	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[20]	2014	Japan	Cohort study	73/72*	67/75.7*	84.8/86	33.6/35	NS	39.2/39.7
Rubboli et al[19]	2014	Italy	Prospective study	73/73	65/71	88/84	33/37	67/67	14/21*
Mennuni et al[21]	2015	Italy	Retrospective study	72/73	70/75	92/95	38/43	NS	60/41*
Sambola et al[18]	2015	Spain	Prospective study	73/73	37/20	69.5/79.9*	34.2/40.4	45.4/54.4	56.4/56.3
Kang et al[8]	2015	South Korea	Retrospective study	67.5/69.1	64.4/66.4	75/74	30.5/32.8	46.1/39.6	18.6/39.6*
Kawai et al[22]	2015	Japan	Retrospective study	70.5/71.9	74.6/71.4	89.6/89.3	44.8/42.9	68.9/64.3	NS
Hess et al[14]	2015	USA	Cohort study	78/77*	55.4/63.1*	81.1/83.6*	30/35.5*	62/67.3*	16.9/24.6*
Lopes et al[15]	2016	USA	Prospective study	79/73	64/73	87/92	34/43	89/90	46/46
Sambola et al[16]	2016	Spain	Prospective cohort study	79.8/79.4	69.2/65.4	72.3/84.3	34.6/34.6	NS	26.3/26.8

D/T = DAPT/TT, DAPT = dual antiplatelet therapy, DM = diabetes mellitus, h/o = history of, HF = heart failure, HL = hyperlipidemia, HTN = hypertension, NS = not stated, TT = triple therapy.
* $P < 0.05$.

Table 3

Baseline characteristics of each included study.

Author	h/o-Stroke (%) D/T	CHADS2 score ≥2 (%) D/T	ACS (%) D/T	Smokers (%) D/T	Liver dysfunction (%) D/T	Kidney dysfunction (%) D/T	Permanent/ persistent AF (%) D/T	DES used (%) D/T	GP IIb/IIIa inhibitor (%) D/T
Ruiz-Nodar et al[23]	11.1/19.6*	69	84.4/81.4	NS	NS	22.9/10.9	60.1	40.1	25.7
Maegdefessel et al[25]	8.7/21.4	NS	88.4/80.4	15.5/28.6	NS	NS	NS	NS	NS
Manzano-Fernandez et al[28]	21/27	NS	92.5/88.2	15/27	NS	60/57	NS	62/71	49/29
Gao et al[9]	12.1/16.5	37.8/49.6*	15.3/12.2	36.9/28.7	NS	28.0/21.7	54.2/72.4*	100/100	21.6/16.1
Fosbol et al[13]	15.9/16.7	73.9/76.5	100/100	12.7/7.14*	NS	NS	NS	80.1/80.6	50.4/38.1*
Lamberts et al[24]	10/10	56.3/60.3	100/100	NS	NS	NS	NS	NS	NS
Suh et al[26]	14.5/10.8	64.5/56.8	42.1/32.4	12.7/13.5	NS	10.8/2.7	NS	83.1/81.1	NS
Dabrowska et al[29]	8.3/11.4	93.3/97.7	NS	NS	NS	NS	25/31.7	22/27	8.3/9.1
Ho et al[17]	6.4/14.4*	31.8/50.5*	67.7/70.7	56.4/59.2	NS	1.5/2.2	NS	NS	64.1/64.7
Goto et al[20]	18.2/19	73.7/76.9	40.7/33.2	21.6/23.3	2.4/3.4	10.9/9.3	17.2/40.9*	43.9/52.2*	NS
Rubboli et al[19]	14/17	65/71*	66.1/54.3	9/10	NS	NS	32.7/66.7*	NS	NS
Mennuni et al[21]	14/16	85	57/54	NS	NS	63/63	42/71*	71/61*	NS
Sambola et al[18]	10.5/17.9	44.5/55.5*	79.2/68.3	55.2/45.8*	NS	17.4/15.1	NS	41.2/39.3	NS
Kang et al[8]	11.8/18.3	52.1/68.7*	77.5/77.9	38.9/39.6	NS	10.1/9.1	61.4/85.4*	100/100	NS
Kawai et al[22]	NS	NS	NS	NS	NS	49.3/60.7	37.3/75.0*	77.6/85.7*	NS
Hess et al[14]	10.3/12.8*	73.6/79.0*	100/100	NS	NS	NS	NS	52.2/48.2	49.9/40.2*
Lopes et al[15]	19/21	NS	NS	NS	NS	2/2	NS	28/41	NS
Sambola et al[16]	14.6/21.4	94.6/93.7	81.5/72.3	46.5/39.9	NS	24.6/15.7*	NS	41.4/36.1	NS

ACS = acute coronary syndrome, CHADS2 = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, D/T = DAPT/TT, DAPT = dual antiplatelet therapy, DES = drugs-eluting stent, GP = glycoprotein, h/o = history of, NS = not stated, TT = triple therapy.
* $P < 0.05$.

1.18, 95% CI 0.85–1.63, $P = 0.32$, $I^2 = 88\%$; OR 1.64, 95% CI 0.79–3.14, $P = 0.19$, $I^2 = 90\%$; and OR 1.85, 95% CI 0.61–5.62, $P = 0.28$, $I^2 = 98\%$, respectively). These results have been represented in Fig. 4. Moreover, in long-term[8,14,23,25,26] follow-up period, the risk of major bleeding was significantly higher in DAPT + VKA group (OR 0.55, 95% CI 0.47–0.65, $P < 0.00001$, $I^2 = 24\%$). 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, $P = 0.54$, $I^2 = 65\%$; OR 1.02, 95% CI 0.83–1.26, $P = 0.82$, $I^2 = 0\%$; OR 1.13, 95% CI 0.86–1.50, $P = 0.37$, $I^2 = 0\%$; OR 1.10, 95% CI 0.96–1.26, $P = 0.19$, $I^2 = 41\%$; and OR 1.67, 95% CI 0.35–7.90, $P = 0.52$, $I^2 = 0\%$, 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)".[27] 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 15 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%; $P = 0.1$); 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 ± 1.1 vs 2.3 ± 0.2;

Table 4

Result of this meta-analysis.

Outcomes	Trials analyzed	OR [95% CI]	P	I^2%
Major bleeding	18	0.62 [0.50–0.77]	<0.0001	63
MACEs	14	1.17 [0.99–1.39]	0.07	56
MI	10	1.27 [0.92–1.77]	0.15	46
Stroke	12	1.59 [1.08–2.34]	0.02	56
ST	6	1.98 [1.03–3.81]	0.04	0
All-cause mortality	15	1.41 [1.03–1.94]	0.03	81

CI = confidence interval, MACEs = major adverse cardiovascular events, MI = myocardial infarction, OR = odds ratio, ST = stent thrombosis.

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.

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

Study or Subgroup	DAPT Events	Total	DAPT+VKA Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Year	Odds Ratio M–H, Fixed, 95% CI
Ruiz–Nodar 2008	2	178	2	195	14.2%	1.10 [0.15, 7.87]	2008	
Gao 2010	3	334	1	136	10.6%	1.22 [0.13, 11.87]	2010	
Dabrowska 2013	0	60	0	44		Not estimable	2013	
Suh 2013	6	166	0	37	5.9%	3.04 [0.17, 55.11]	2013	
Goto 2014	14	551	4	506	30.5%	3.27 [1.07, 10.01]	2014	
Rubboli 2014	3	162	9	679	25.6%	1.40 [0.38, 5.25]	2014	
Sabmola 2016	2	130	2	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%
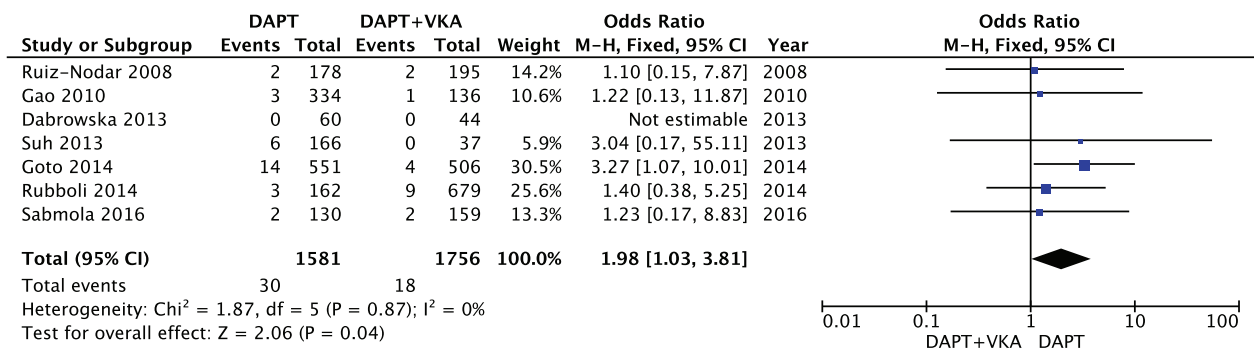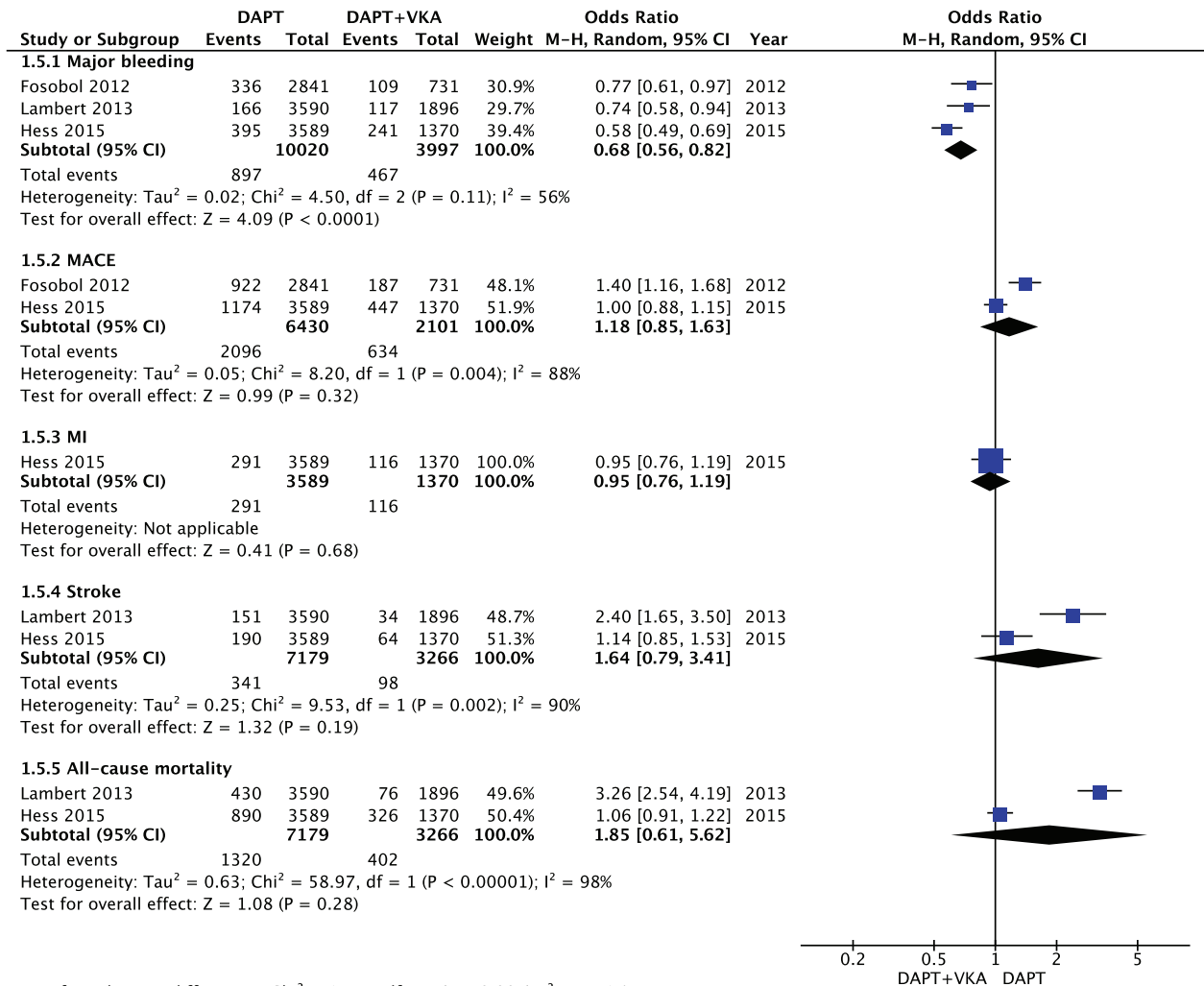Test for overall effect: Z = 2.06 (P = 0.04)

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.

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.[31] Of note, in some studies, anemia also appeared to be a high-risk marker for mortality and hemorrhagic complications

Study or Subgroup	DAPT Events	Total	DAPT+VKA Events	Total	Weight	Odds Ratio M–H, Random, 95% CI	Year	Odds Ratio M–H, Random, 95% CI
1.5.1 Major bleeding								
Fosobol 2012	336	2841	109	731	30.9%	0.77 [0.61, 0.97]	2012	
Lambert 2013	166	3590	117	1896	29.7%	0.74 [0.58, 0.94]	2013	
Hess 2015	395	3589	241	1370	39.4%	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								
Fosobol 2012	922	2841	187	731	48.1%	1.40 [1.16, 1.68]	2012	
Hess 2015	1174	3589	447	1370	51.9%	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	326	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%

Figure 4. Forest plot showing the odds ratio of major bleeding, MACEs, MI, stroke, all-cause mortality in ACS subgroup associated with DAPT + VKA versus DAPT. ACS = acute coronary syndrome, DAPT = dual antiplatelet therapy, MACEs = major adverse cardiovascular events, MI = myocardial infarction, VKA = vitamin K antagonist.

Study or Subgroup	DAPT Events	Total	DAPT+VKA Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Year
1.2.1 Major bleeding							
Maegdefessel 2008	2	103	0	14	0.2%	0.71 [0.03, 15.63]	2008
Ruiz–Nodar 2008	16	178	29	195	6.9%	0.57 [0.30, 1.08]	2008
Suh 2013	1	166	1	37	0.4%	0.22 [0.01, 3.57]	2013
Kang 2015	11	236	22	131	7.4%	0.24 [0.11, 0.52]	2015
Hess 2015	395	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				

Heterogeneity: Chi² = 5.28, df = 4 (P = 0.26); I² = 24%
Test for overall effect: Z = 7.15 (P < 0.00001)

1.2.3 MI							
Ruiz–Nodar 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				

Heterogeneity: Chi² = 2.73, df = 3 (P = 0.43); I² = 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				

Heterogeneity: Chi² = 0.98, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)

1.2.5 All-cause mortality							
Ruiz–Nodar 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				

Heterogeneity: Chi² = 6.74, df = 4 (P = 0.15); I² = 41%
Test for overall effect: Z = 1.31 (P = 0.19)

1.2.6 ST							
Ruiz–Nodar 2008	2	178	2	195	70.7%	1.10 [0.15, 7.87]	2008
Suh 2013	6	166	0	37	29.3%	3.04 [0.17, 55.11]	2013
Subtotal (95% CI)		344		232	100.0%	**1.67 [0.35, 7.90]**	
Total events	8		2				

Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)

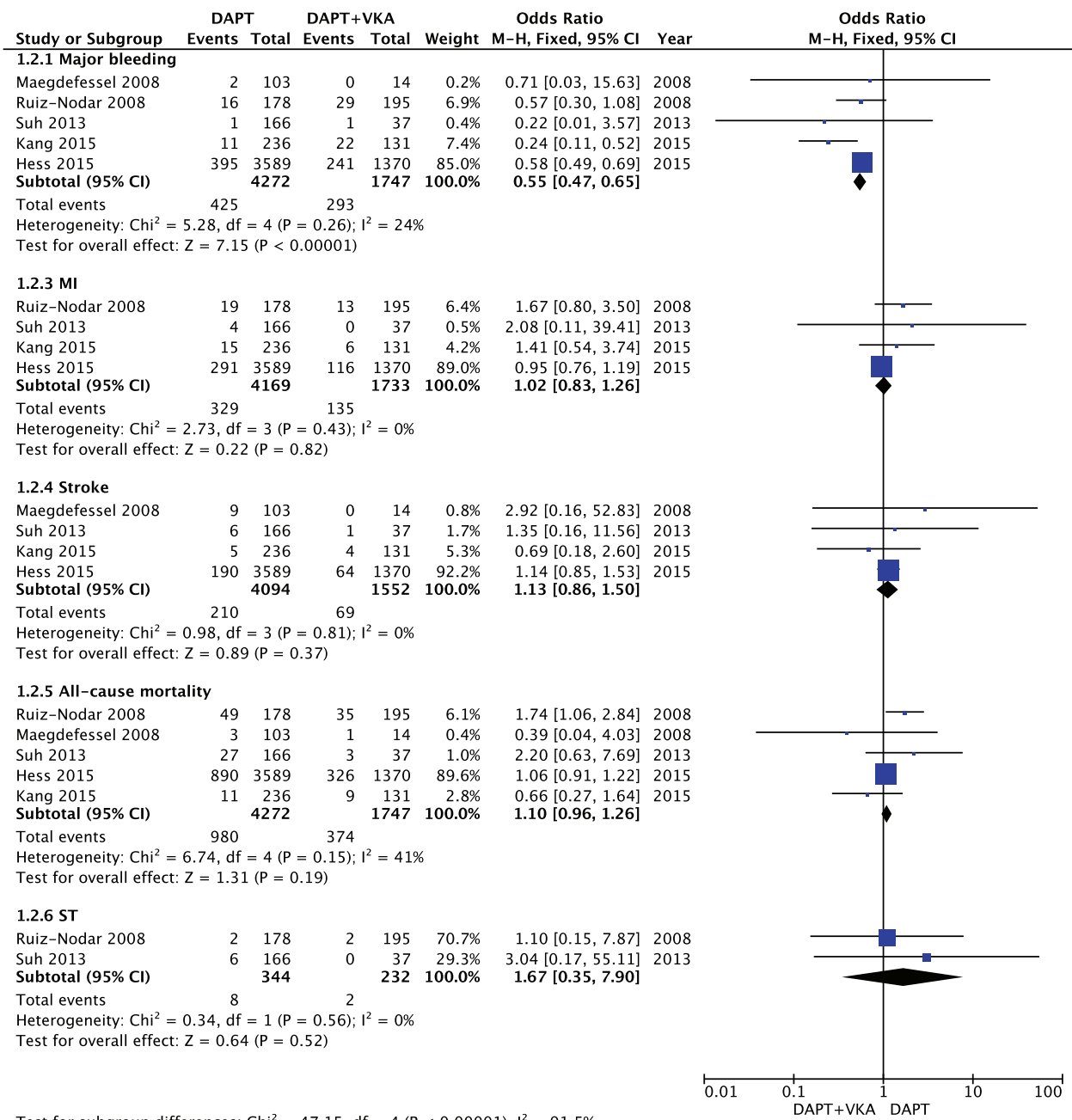Test for subgroup differences: Chi² = 47.15, df = 4 (P < 0.00001), I² = 91.5%

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.

Study or Subgroup	DAPT Events	Total	DAPT+VKA Events	Total	Weight	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–Nodar 2008	69	178	52	195	25.7%	1.74 [1.12, 2.70]	2008
Suh 2013	32	166	1	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, 1.68]**	
Total events	1328		542				

Heterogeneity: Tau² = 0.11; Chi² = 11.57, df = 4 (P = 0.02); I² = 65%
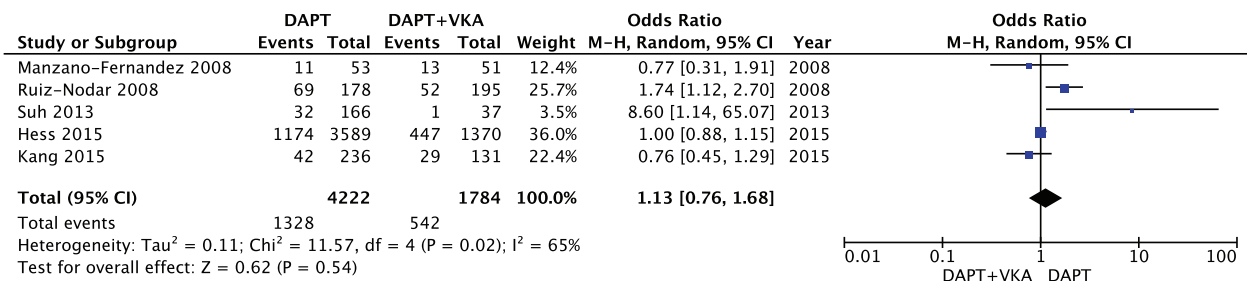Test for overall effect: Z = 0.62 (P = 0.54)

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.
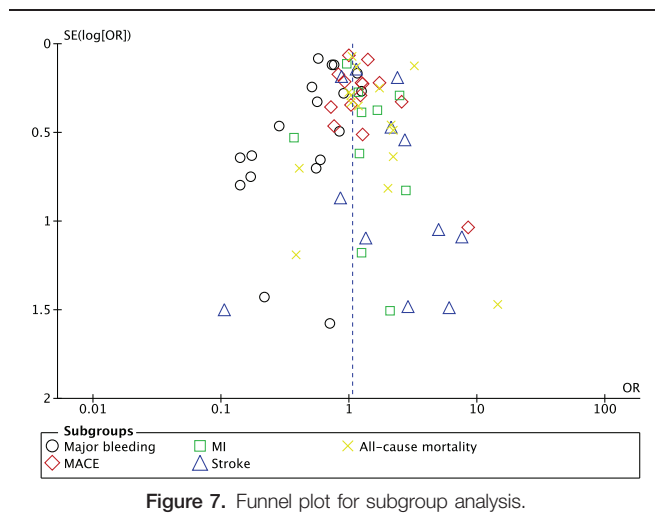
Figure 7. Funnel plot for subgroup analysis.

in patients undergoing PCI.[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.[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.[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.[35–37] 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.[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[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,[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,[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[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.[7,46] 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.[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.[38,46]

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[48] and requires prolonged DAPT up to a year. However, in patients with concomitant OAC, prolonged DAPT may increase the bleeding risk.[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.[7]

Recently, new oral anticoagulants, such as dabigatran, apixaban, and rivaroxaban, have led to a new modern era of novel anticoagulation. New antiplatelet 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,[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.[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.

5. Conclusions

Our analysis suggested that at a mean follow-up period of 15 months DAPT + VKA is efficacious in reducing stroke, ST, and all-cause 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.

Acknowledgments

References

[1] Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA [Internet] 2001;285:2370–5.

[2] Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. Med Clin North Am [Internet] 2008;92:17–40. ix.

[3] Lip GYH, Laroche C, Dan G-A, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. Europace [Internet] 2014;16:308–19.

[4] Kirchhof P, Ammentorp B, Darius H, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events: European Registry in Atrial Fibrillation (PREFER in AF). Europace [Internet] 2014;16:6–14.

[5] King SB, Smith SC, Hirshfeld JW, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol [Internet] 2008;51:172–209.

[6] Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Commi. Eur Heart J [Internet] 2006;27:1979–2030.

[7] Lip GYH, Huber K, Andreotti F, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting. Thromb Haemost [Internet] 2009;103:13–28.

[8] Kang DO, Yu CW, Kim HD, et al. Triple antithrombotic therapy versus dual antiplatelet therapy in patients with atrial fibrillation undergoing drug-eluting stent implantation. Coron Artery Dis [Internet] 2015;26:372–80.

[9] Gao F, Zhou YJ, Wang ZJ, et al. Comparison of different antithrombotic regimens for patients with atrial fibrillation undergoing drug-eluting stent implantation. Circ J [Internet] 2010;74:701–8.

[10] Bavishi C, Koulova A, Bangalore S, et al. Evaluation of the efficacy and safety of dual antiplatelet therapy with or without warfarin in patients with a clinical indication for DAPT and chronic anticoagulation: A meta-analysis of observational studies. Catheter Cardiovasc Interv [Internet] 2016;88:E12–22.

[11] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ [Internet] 2009;339:b2700.

[12] Higgins JP, Green S. Higgins JP, Green S. Assessing risk of bias in included studies [Internet]. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. Chichester, UK:John Wiley & Sons, Ltd; 2008. 187–241.

[13] Fosbol EL, Wang TY, Li S, et al. Safety and effectiveness of antithrombotic strategies in older adult patients with atrial fibrillation and non-ST elevation myocardial infarction. Am Heart J [Internet] 2012;163:720–8.

[14] Hess CN, Peterson ED, Peng SA, et al. Use and outcomes of triple therapy among older patients with acute myocardial infarction and atrial fibrillation. J Am Coll Cardiol [Internet] 2015;66:616–27.

[15] Lopes RD, Rao M, Simon DN, et al. Triple vs Dual Antithrombotic Therapy in Patients with Atrial Fibrillation and Coronary Artery Disease. Am J Med [Internet] 2016;129:592–9. e1.

[16] Sambola A, Mutuberría M, García Del Blanco B, et al. Impact of triple therapy in elderly patients with atrial fibrillation undergoing percutaneous coronary intervention. PLoS One [Internet] 2016;11:e0147245.

[17] Ho KW, Ivanov J, Freixa X, et al. Antithrombotic therapy after coronary stenting in patients with nonvalvular atrial fibrillation. Can J Cardiol [Internet] 2013;29:213–8.

[18] Sambola A, Mutuberría M, García Del Blanco B, et al. Effects of triple therapy in patients with non-valvular atrial fibrillation undergoing percutaneous coronary intervention regarding thromboembolic risk stratification. Circ J [Internet] 2016;80:354–62.

[19] Rubboli A, Schlitt A, Kiviniemi T, et al. One-year outcome of patients with atrial fibrillation undergoing coronary artery stenting: an analysis of the AFCAS registry. Clin Cardiol [Internet] 2014;37:357–64.

[20] Goto K, Nakai K, Shizuta S, et al. Anticoagulant and antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention. Am J Cardiol [Internet] 2014;114:70–8.

[21] Mennuni MG, Halperin JL, Bansilal S, et al. Balancing the risk of bleeding and stroke in patients with atrial fibrillation after percutaneous coronary intervention (from the AVIATOR Registry). Am J Cardiol [Internet] 2015;116:37–42.

[22] Kawai H, Watanabe E, Yamamoto M, et al. Major bleeding complications related to combined antithrombotic therapy in atrial fibrillation patients 12 months after coronary artery stenting. J Cardiol [Internet] 2015;65:197–202.

[23] Ruiz-Nodar JM, Marín F, Hurtado JA, et al. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation implications for bleeding risk and prognosis. J Am Coll Cardiol [Internet] 2008;51:818–25.

[24] Lamberts M, Gislason GH, Olesen JB, et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. J Am Coll Cardiol [Internet] 2013;62:981–9.

[25] Maegdefessel L, Schlitt A, Faerber J, et al. Anticoagulant and/or antiplatelet treatment in patients with atrial fibrillation after percutaneous coronary intervention. A single-center experience. Med Klin (Munich) [Internet] 2008;103:628–32.

[26] Suh SY, Kang WC, Oh PC, et al. Efficacy and safety of aspirin, clopidogrel, and warfarin after coronary artery stenting in Korean patients with atrial fibrillation. Heart Vessels [Internet] 2014;29:578–83.

[27] Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. Kardiol Pol [Internet] 2014;72:1253–379.

[28] Manzano-Fernández S, Pastor FJ, Marín F, et al. Increased major bleeding complications related to triple antithrombotic therapy usage in patients with atrial fibrillation undergoing percutaneous coronary artery stenting. Chest [Internet] 2008;134:559–67.

[29] Dąbrowska M, Ochała A, Cybulski W, et al. Balancing between bleeding and thromboembolism after percutaneous coronary intervention in patients with atrial fibrillation. Could triple anticoagulant therapy be a solution? Adv Interv Cardiol [Internet] 2013;9:234–40.

[30] Rossini R, Musumeci G, Lettieri C, et al. Long-term outcomes in patients undergoing coronary stenting on dual oral antiplatelet treatment requiring oral anticoagulant therapy. Am J Cardiol [Internet] 2008;102:1618–23.

[31] Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. Eur Heart J [Internet] 2007;28:726–32.

[32] DeEugenio D, Kolman L, DeCaro M, et al. Risk of major bleeding with concomitant dual antiplatelet therapy after percutaneous coronary intervention in patients receiving long-term warfarin therapy. Pharmacotherapy [Internet] 2007;27:691–6.

[33] Rubboli A, Colletta M, Herzfeld J, et al. Periprocedural and medium-term antithrombotic strategies in patients with an indication for long-term anticoagulation undergoing coronary angiography and intervention. Coron Artery Dis [Internet] 2007;18:193–9.

[34] Porter A, Konstantino Y, Iakobishvili Z, et al. Short-term triple therapy with aspirin, warfarin, and a thienopyridine among patients undergoing percutaneous coronary intervention. Catheter Cardiovasc Interv [Internet] 2006;68:56–61.

[35] Gardiner C, Williams K, Mackie IJ, et al. Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring. Br J Haematol [Internet] 2005;128:242–7.

[36] Bloomfield HE, Krause A, Greer N, et al. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. Ann Intern Med [Internet] 2011;154:472–82.

[37] Heneghan C, Alonso-Coello P, Garcia-Alamino JM, et al. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. Lancet (London, England) [Internet] 2006;367:404–11.

[38] Gorin L, Fauchier L, Nonin E, et al. Antithrombotic treatment and the risk of death and stroke in patients with atrial fibrillation and a CHADS2 score=1. Thromb Haemost [Internet] 2010;103:833–40.

[39] Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guide. Circulation [Internet] 2011;123: e269–367.

[40] January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol [Internet] 2014;64:e1–76.

[41] Ruiz-Nodar JM, Marín F, Manzano-Fernández S, et al. An evaluation of the $CHADS_2$ stroke risk score in patients with atrial fibrillation who undergo percutaneous coronary revascularization. Chest [Internet] 2011;139:1402–9.

[42] Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. Rev Esp Cardiol (Engl Ed) [Internet] 2015;68:144.

[43] Khurram Z, Chou E, Minutello R, et al. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. J Invasive Cardiol [Internet] 2006;18:162–4.

[44] Zhao H-J, Zheng Z-T, Wang Z-H, et al. Triple therapy" rather than "triple threat": a meta-analysis of the two antithrombotic regimens after stent implantation in patients receiving long-term oral anticoagulant treatment. Chest [Internet] 2011;139:260–70.

[45] Washam JB, Dolor RJ, Jones WS, et al. Dual antiplatelet therapy with or without oral anticoagulation in the postdischarge management of acute coronary syndrome patients with an indication for long term anti-coagulation: a systematic review. J Thromb Thrombolysis [Internet] 2014;38:285–98.

[46] Camm AJ, Kirchhof P, Lip GYH, et al. European Heart Rhythm Association, European Association for Cardio-Thoracic SurgeryGuide-lines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J [Internet] 2010;31:2369–429.

[47] Ruiz-Nodar JM, Marín F, Manzano-Fernández S, et al. An evaluation of the CHADS2 stroke risk score in patients with atrial fibrillation who undergo percutaneous coronary revascularization. Chest [Internet] 2011;139:1402–9.

[48] Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med [Internet] 2007;356:1030–9.

[49] Gilard M, Blanchard D, Helft G, et al. Antiplatelet therapy in patients with anticoagulants undergoing percutaneous coronary stenting (from STENTIng and oral antiCOagulants [STENTICO]). Am J Cardiol [Internet] 2009;104:338–42.

[50] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med [Internet] 2009;361:1139–51.

[51] Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med [Internet] 2011;365:981–92.

[52] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med [Internet] 2011;365: 883–91.

[53] Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation–developed with the special contribution of the European Heart Rhythm Association. Europace [Internet] 2012;14:1385–413.