Reviews

Antithrombotic Regimens for Patients Taking Oral Anticoagulation After Coronary Intervention: A Meta-analysis of 16 Clinical Trials and 9185 Patients

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ABSTRACT

The optimal antithrombotic regimen remains controversial in patients taking oral anticoagulation (OAC) undergoing coronary stenting. This study sought to compare efficacy and safety outcomes of triple therapy (OAC, aspirin, and clopidogrel) vs dual therapy (clopidogrel with aspirin or OAC) in these patients. We hypothesize OAC plus clopidogrel could be the optimal regimen for patients with indications for OAC receiving stent implantation. Medline, the Cochrane Library, and other Internet sources were searched for clinical trials comparing the efficacy and safety of triple vs dual therapy for patients taking OAC after coronary stenting. Sixteen eligible trials including 9185 patients were identified. The risks of major adverse cardiac events (odds ratio [OR]: 1.06, 95% confidence interval [CI]: 0.82-1.39, $P = 0.65$), all-cause mortality (OR: 0.98, 95% CI: 0.76-1.27, $P = 0.89$), myocardial infarction (OR: 1.01, 95% CI: 0.77-1.31, $P = 0.97$), and stent thrombosis (OR: 0.91, 95% CI: 0.49-1.69, $P = 0.75$) were similar between triple and dual therapy. Compared with dual therapy, triple therapy was associated with a reduced risk of ischemic stroke (OR: 0.57, 95% CI: 0.35-0.94, $P = 0.03$) but with higher major bleeding (OR: 1.52, 95% CI: 1.11-2.10, $P = 0.01$) and minor bleeding (OR: 1.59, 95% CI: 1.05-2.42, $P = 0.03$). Subgroup analysis indicated there were similar ischemic stroke and major bleeding outcomes between triple therapy and therapy with OAC plus clopidogrel. Treatment with OAC and clopidogrel was associated with similar efficacy and safety outcomes compared with triple therapy. Triple therapy could be replaced by OAC plus clopidogrel without any concern about additional risk of thrombotic events.

Introduction

Long-term oral anticoagulation (OAC) is an essential treatment for prevention of thromboembolic complication in patients with atrial fibrillation (AF), mechanical heart valves, and other conditions.[1,2] Of note, about 30% of these patients also have indication for additional dual antiplatelet therapy (DAPT) because of percutaneous coronary intervention (PCI).[3] Determining the most effective antithrombotic regimens for patients with OAC after coronary intervention could be challenging, and triple therapy including OAC and DAPT was the preferred treatment compared with DAPT alone. In the past decade, several clinical trials[4–7] and meta-analyses,[8,9] most of which were retrospective, small-scale, and single-center studies, indicated that triple therapy could reduce cardiovascular events, at the cost of increasing major bleeding risk compared with DAPT treatment. Therefore, before 2014, North American and European expert consensus statements recommended the combination of OAC and DAPT in the majority of AF patients receiving coronary stenting.[10,11] However, this triple therapy has never been investigated by a prospective, multicenter, randomized controlled trial (RCT) until the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) study, published recently.[12] This study indicates that dual therapy, including OAC and clopidogrel without aspirin (OAC/C), is associated with a >50% reduction in bleeding complications and no increase in the rate of thrombotic events. In addition, several recent registries suggested that the combination of OAC plus clopidogrel appeared both safe and effective compared with triple therapy.[13–15] For this reason,

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the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) Guideline recommended the use of clopidogrel (75 mg once daily) concurrently with OAC but without aspirin in these patients (class IIb, level of evidence B).[16] Therefore, we performed this updated meta-analysis to represent the largest analysis comparing efficacy and safety between triple and dual therapy after stent implantation in patients receiving long-term OAC.

Methods

Literature Search

Clinical trials comparing antithrombotic regimens for patients taking OAC after coronary stent implantation were acquired through searching Medline, Scopus, and the Cochrane Controlled Trials Registry from January 2000 to December 2014. To include all relevant studies, we used combinations of various keywords, including "anticoagulation," "warfarin," "percutaneous coronary intervention," "coronary stenting," "antiplatelet," "aspirin," "clopidogrel," and "clinical trial." References from reviews and selected articles were further screened.

Inclusion and Exclusion Criteria

The inclusion criteria were: (1) clinical trials comparing triple and dual therapy; (2) patients taking OAC with coronary stent implantation; and (3) ≥30 days of clinical follow-up. The exclusion criteria were: (1) <30 patients receiving triple or dual therapy; (2) non–English-language studies; and (3) studies with duplicate publication or different studies from the same sample origin.

Data Extraction and Quality Assessment

All relevant articles were independently reviewed by 2 investigators (GXF and CY) to assess the eligibility of each article and abstract with standardized data-abstraction forms. Disagreement was resolved by a third investigator (FZG). The following data were extracted from each included study: study's name, first author, publication date, baseline demographics, and clinical outcomes at follow-up. The quality of the retrieved studies was assessed to ensure minimization of bias, but no formal scoring system was used.

Study Endpoints

The efficacy endpoints included major adverse cardiovascular events (MACE), all-cause mortality, myocardial infarction (MI), stent thrombosis (ST), and ischemic stroke. The safety endpoints at follow-up included major and minor bleeding. The rates of all-cause mortality and ischemic stroke could be replaced by cardiovascular death and thromboembolic events, if no relevant data existed.[7] The definitions of each endpoint were slightly different across studies, and we used the trial-specific definitions.

Statistical Analysis

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statements.[17] Dichotomous variables

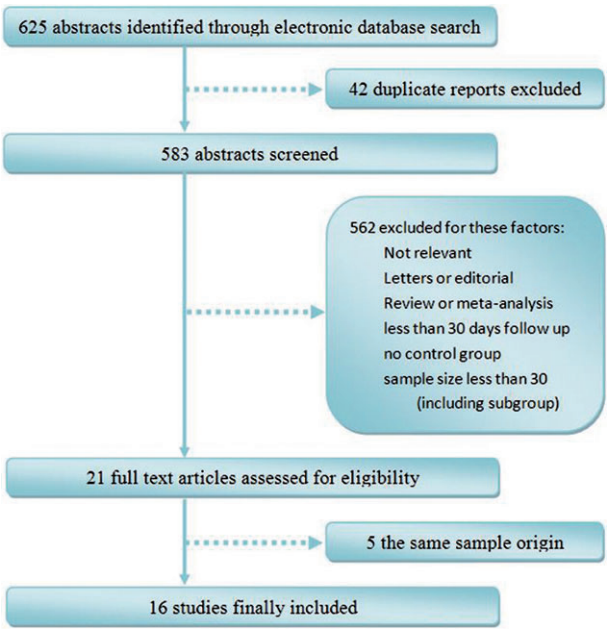

Figure 1. Flowchart of the meta-analysis.

are expressed as odds ratio (OR) and 95% confidence interval (CI). The heterogeneity among trials was evaluated with the Cochrane Q test and I^2 statistic, and high heterogeneity was considered present with Q test $P < 0.10$ and/or $I^2 \geq 50\%$. The random-effects model was used if there was high heterogeneity across trials. If not, the fixed-effects model with the Mantel-Haenszel method was performed. Publication bias was examined by means of the Egger test (P for significant asymmetry <0.1).[18] Sensitivity analyses (exclusion of 1 study at a time) were performed to determine the stability of the overall effects. All P values were 2-tailed with the statistical significance set at <0.05. Statistical analyses were conducted using STATA software version 12.0 (StataCorp, College Station, TX).

Results

Eligible Studies and Patient Characteristics

From 625 initial citations, 16 eligible studies including a total of 9185 patients were identified in the present meta-analysis,[4–7,12,14,15,19–27] with 5680 patients in the triple therapy group and 3505 in the dual therapy group (Figure 1).

Characteristics of the included studies and patients are summarized in Tables 1 and 2. Of these 16 studies, only the WOEST trial[12] is a prospective, randomized trial that assessed the use of warfarin plus clopidogrel after coronary stenting in patients with OAC treatment. The other 15 studies were prospective or retrospective observational studies.

Two subanalyses were performed according to the inclusion criteria in each study: DAPT and OAC/C subgroups (stratified by the patients receiving DAPT or OAC plus clopidogrel treatment). Finally, 12 studies were identified in the DAPT subgroup,[4–7,19–26] with the other 4 studies included in the OAC/C subgroup.[12,14,15,27]

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Table 1. General Characteristics of the Included Studies

Study	Year	Country	Design	Control Group	Indication for Anticoagulation	Indication for Antiplatelet	Definition of MACE	Definition of Major Bleeding	Mean Follow-up
DeEugenio et al	2007	United States	Retrospective	DAPT	AF (59%)	Stent	NA	STEEPLE	182 days
Karjalainen et al	2007	Finland	Retrospective	DAPT	AF (70%)	Stent	Death, MI, TVR, ST	PRISM-PLUS	12 months
Khurram et al	2006	United States	Retrospective	DAPT	AF (80%)	Stent	NA	CURE	>6 months
Manzano-Fernández et al	2008	United Kingdom	Retrospective	DAPT	AF (100%)	Stent	CV death, MI, TVR, ST, thromboembolic complications	PRISM-PLUS	12 months
Mattichak et al	2005	United States	Retrospective	DAPT	AF (43%), LVT (48%)	Stent	Death, reinfarction	Not defined	12 months
Rossini et al	2008	Italy	Prospective	DAPT	AF (67%)	Stent	Death, stroke, MI	TIMI	18 months
Ruiz-Nodar et al	2008	Spain, United Kingdom	Retrospective	DAPT	AF (100%)	Stent	Death, MI, TVR	PRISM-PLUS	595 days
Sarafoff et al	2008	Germany	Prospective	DAPT	AF (67%)	Stent	Death, MI, ST, stroke	TIMI	2 years
STENTICO	2009	France	Prospective	DAPT	AF (63%)	Stent	NA	GUSTO	12 months
Fosbol et al	2013	Multicenter	Retrospective	DAPT	AF (100%)	Stent	Death, MI, ischemic stroke	ICD-9 codes	12 months
MUSICA	2009	Multicenter	Prospective	DAPT	AF (68%)	Stent	ST, MI, TVR, stroke/peripheral embolism, CV death	PRISM-PLUS	6 months
WAR-STENT	2014	Multicenter	Prospective	DAPT	AF (78%)	Stent	Death, MI, TVR, ST, stroke, DVT/PE	TIMI	12 months
Nguyen et al	2007	Multicenter	Retrospective	WS (48.6% for ASA and 51.6% for thienopyridine)	AF (40%), MI (43%)	Stent	NA	GRACE	6 months
Lamberts et al	2013	Denmark	Retrospective	WS (OAC + clopidogrel)	AF (100%)	Stent, MI	MI, coronary death	ICD-10 codes	12 months
AFCAS	2014	Multicenter	Prospective	WS (OAC + clopidogrel)	AF (100%)	Stent	Death, MI, TVR, ST, stroke/TIA	BARC	12 months
WOEST	2013	Multicenter	RCT	WS (OAC + clopidogrel)	AF (69%)	Stent	Death, MI, TVR, stroke, ST	TIMI, GUSTO, and BARCBARC	12 months

Abbreviations: AF, atrial fibrillation; AFCAS, Atrial Fibrillation Undergoing Coronary Artery Stenting; ASA, acetylsalicylic acid (aspirin); BARC, Bleeding Academic Research Consortium; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; CV, cardiovascular; DAPT, dual antiplatelet therapy (ASA + clopidogrel); DVT, deep vein thrombosis; GRACE, Global Registry of Acute Coronary Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; ICD, International Classification of Diseases; LVT, left ventricular thrombus; MACE, major adverse cardiac events; MI, myocardial infarction; MUSICA, Anticoagulation in Stent Intervention; NA, not available; OAC, oral anticoagulation; PE, pulmonary embolism; PRISM-PLUS, Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; RCT, randomized controlled trial; ST, stent thrombosis; STEEPLE, Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation; STENTICO, Stenting and Oral Anticoagulants; TIA, transient ischemic attack; TIMI, Thrombolysis In Myocardial Infarction; TVR, target-vessel revascularization; WAR-STENT, Warfarin and Coronary Stenting; WOEST, What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting; WS, OAC with a single antiplatelet.

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Table 2. Baseline Characteristics of the Included Patients

Study	No. Patients, n (TT/DT)	Age, y (TT/DT)	M, n (TT/DT)	Hypertension, n (TT/DT)	DM, n (TT/DT)	LVEF, % (TT/DT)	DES, n (TT/DT)	Mean INR of Major Bleeding in TT	History of Major Bleeding, n (TT/DT)
DeEugenio et al	97/97	69.9/69.8	56/57	64/66	31/33	NA	24/31	3.4	7/4
Karjalainen et al	106/34	~70	~74%	~67%	~30%	~50	~40%	NA	NA
Khurram et al	107/107	69/74	73/68	88/73	33/43	NA	54/107	2.3	1/2
M-Fernandez et al	51/53	69/74	38/35	44/40	26/28	50/55	36/33	The majority were within 2 to 3	7/7
Mattichak et al	40/42	67/59	15/19	29/22	NA	39/45	NA	NA	NA
Rossini et al	102/102	67.9/68.2	82/81	52/56	23/24	47.6/48.1	48/49	3.3	NA
Ruiz-Nodar et al	242/184	71.6/71.2	171/130	197/133	103/77	NA	~40%	NA	NA
Sarafoff et al	306/209	71.4/72.4	231/157	270/188	80/59	47.3/48.9	306/209	5.4 for GI tract, 2.8 for puncture site, 1.8 for urogenital tract	NA
STENTICO	125/234	71/72	104/196	74/153	32/69	NA	31/78	NA	NA
Fosbol et al	448/1200	77/78	288/673	373/953	163/391	NA	361/961	NA	NA
MUSICA	278/81	70/72	82/80	184/55	100/21	53.5/55.5	134/40	NA	NA
WAR-STENT	339/42	74/76	88/11	284/34	121/13	47/46	115/14	NA	11/0
Nguyen et al	580/220	64/66	432/129	331/129	130/49	NA	28%/22%	NA	NA
Lamberts et al	1896/548	71/71 (M)	1401/402	1464/419	NA	NA	NA	NA	NA
AFCAS	679/73	73/74	482/52	568/60	252/27	49/48	NA	NA	24/3
WOEST	284/279	69.5/70.3	234/214	193/193	72/68	47/46	183/181	NA	14/14

Abbreviations: AFCAS, Atrial Fibrillation Undergoing Coronary Artery Stenting; DES, drug-eluting stent; DM, diabetes mellitus; DT, dual therapy; GI, gastrointestinal; INR, international normalized ratio; LVEF, left ventricular ejection fraction; M, male; MUSICA, Anticoagulation in Stent Intervention; NA, not available; STENTICO, Stenting and Oral Anticoagulants; TT, triple therapy; WAR-STENT, Warfarin and Coronary Stenting; WOEST, What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting.
Values are presented as number, percent, or mean.

Major Adverse Cardiac Events

Triple therapy has a similar risk of MACE compared with dual therapy (OR: 1.06, 95% CI: 0.82-1.39, $P = 0.65$), with significant heterogeneity among studies ($P = 0.01$, $I^2 = 55.1\%$). No publication bias was found for MACE (Egger test $P = 0.37$). The data are illustrated in Figure 2A.

All-Cause Mortality, Myocardial Infarction, and Stent Thrombosis

The risk of all-cause mortality, MI, and ST did not significantly differ between the triple and dual therapy groups (all-cause mortality, OR: 0.98, 95% CI: 0.76-1.27, $P = 0.89$; MI, OR: 1.01, 95% CI: 0.77-1.31, $P = 0.97$; ST, OR: 0.91, 95% CI: 0.49-1.69, $P = 0.75$; Figure 2B–D). No evidence of statistical heterogeneity or publication bias was noted among the included studies with all-cause mortality ($P = 0.14$, $I^2 = 30.4\%$; Egger test $P = 0.13$), MI ($P = 0.65$, $I^2 = 0.0\%$; Egger test $P = 0.37$), and ST ($P = 0.47$, $I^2 = 0.0\%$; Egger test $P = 0.50$).

Ischemic Stroke

Triple therapy was associated with a significantly lower incidence of ischemic stroke (OR: 0.57, 95% CI: 0.35-0.94, $P = 0.03$; Figure 2E), and no significant heterogeneity or publication bias was found ($I^2 = 31.1\%$, $P = 0.13$; Egger test $P = 0.28$). Omission of a single study from the overall analysis had no significant impact on the pooled results of ischemic stroke.

Major and Minor Bleeding

There was significantly increased major bleeding in the triple therapy group compared with the dual therapy group (OR: 1.52, 95% CI: 1.11-2.10, $P = 0.01$; Figure 3A), as well as minor bleeding (OR: 1.59, 95% CI: 1.05-2.42, $P = 0.03$; Figure 3B), but with significant heterogeneity (major bleeding, $I^2 = 44.5\%$, $P = 0.03$; minor bleeding, $I^2 = 54.1\%$, $P = 0.03$). No publication bias for major bleeding (Egger test $P = 0.38$) and minor bleeding (Egger test $P = 0.54$) was found. Omission of a single study from the overall analysis had no significant impact on the pooled results of major and minor bleeding.

Subgroup Analysis

In the DAPT subgroup analysis, there were no significant differences in MACE, all-cause mortality, MI, and ST (Figure 2A–D) between triple therapy and DAPT therapy. Triple therapy was associated with the lower risk of ischemic stroke (OR: 0.46, 95% CI: 0.27-0.76, $P = 0.003$; Figure 2E) but with higher risk of major bleeding (OR: 1.88, 95% CI: 1.18-2.99, $P = 0.008$; Figure 3A) compared with DAPT therapy. In addition, there was a trend toward a higher incidence of minor bleeding in patients with triple therapy (OR: 1.61, 95% CI: 0.99-2.63, $P = 0.057$; Figure 3B).

In the OAC/C subgroup, the risks of all-cause mortality, MI, ST, ischemic thrombosis, and major and minor bleeding were comparable (Figure 2B–3B) between triple therapy and OAC/C therapy. However, there was a trend toward lower incidence of MACE in the OAC/C subgroup compared with the triple therapy group (OR: 1.22, 95% CI: 0.93-1.60, $P = 0.15$; Figure 2A).

Discussion

The major finding of this updated meta-analysis indicated that triple therapy could reduce ischemic stroke with increased major bleeding risk compared with dual therapy for patients taking OAC after PCI. Subgroup analyses revealed that the combination of OAC plus clopidogrel has at least similar efficacy and safety outcomes compared with triple therapy. There was no evident benefit for adding aspirin to the OAC plus clopidogrel regimen, which challenges current guidelines that prefer triple therapy for these specific patients.

Determining the most effective antithrombotic regimens for patients with OAC and coronary intervention can be challenging, and several meta-analyses[8,9] and expert consensus satetments[10,11] demonstrated that "triple is better" for these patients, mostly due to the decrease of cardiovascular and cerebrovascular events compared with the DAPT regimen. So far, there has been sufficient evidence to support the indispensability of OAC among patients with AF. Traditionally, OAC could reduce the risk of stroke and systemic embolism by about 60% compared with placebo,[28,29] and by about 40% compared with aspirin.[30] Data from the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W) study showed that OAC was superior to clopidogrel plus aspirin for prevention of vascular events in patients with AF, and withholding OAC in patients with AF led to an increased rate of stroke.[1] The reason might be that the type of thrombosis in AF is abundant in fibrin, and platelet activation is not the predominant pathway in the pathogenesis of stroke in AF, in which OAC could be more effective than antiplatelet alone. Overall, the current data indicated that triple therapy has the superior effect for stroke prevention in comparison with an antiplatelet regimen, due to the powerful antithrombotic effect of OAC.

Indeed, the triple therapy regimen was associated with less ischemic stroke, but at the cost of higher major bleeding risk, which was in line with our data. Major bleeding has been the Achilles' heel of triple therapy for patients with indications for OAC receiving coronary stenting, and a triple therapy regimen could produce a high annual bleeding risk up to 44.4%.[12] In fact, the reduction of ischemic stroke with triple therapy was balanced by the reduction of bleeding with dual therapy. Data from the Atrial Fibrillation Undergoing Coronary Artery Stenting (AFCAS) trial demonstrated that total events, including stroke and bleeding, were comparable between triple therapy and dual therapy groups.[15] It should be noted that similar results were found in other studies.[14,23] Moreover, several studies[14,31,32] found that major bleeding was associated with increased risk of death, and bleeding was dangerous not only because of the hemorrhage itself but also because it forced the discontinuation of necessary anticoagulation, which might induce higher rates of thrombotic events. Disturbingly, bleeding events might be underestimated in studies, and the impact of bleeding could be even larger in real life than reported in these studies, because these studies were not specifically designed to detect bleeding events; this could explain why the rate of bleeding events reported in the WOEST trial[12] was much higher than those in other studies.[6,15,19,20,22] In addition, it has led to an increased

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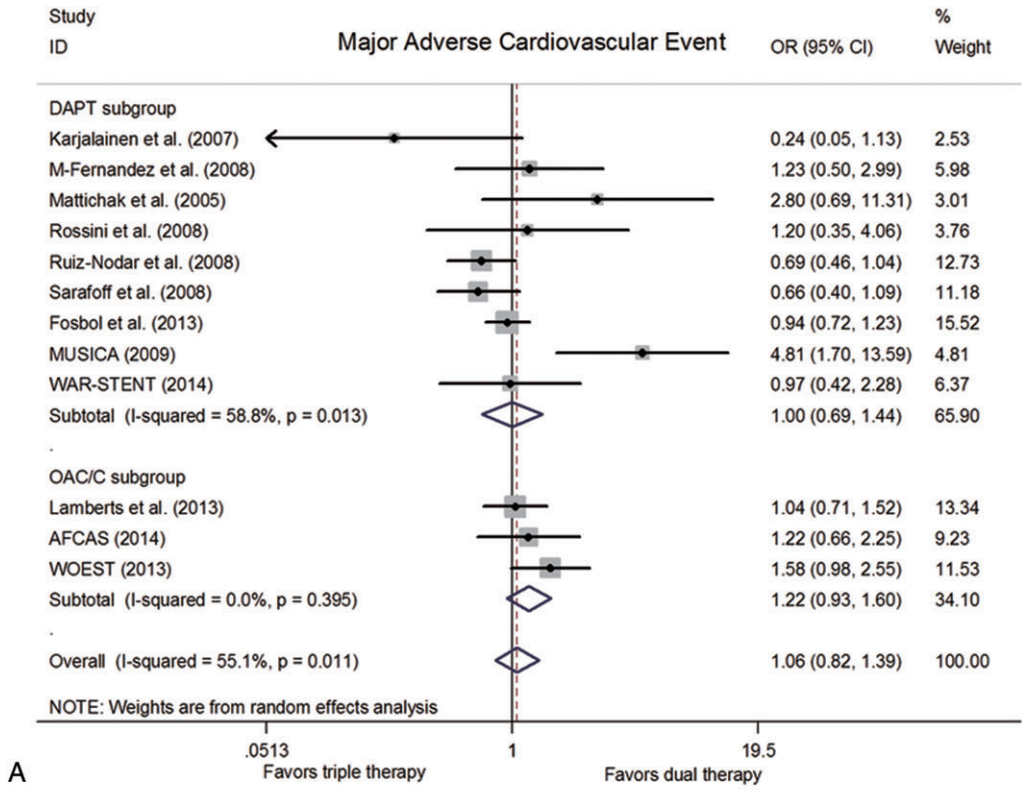

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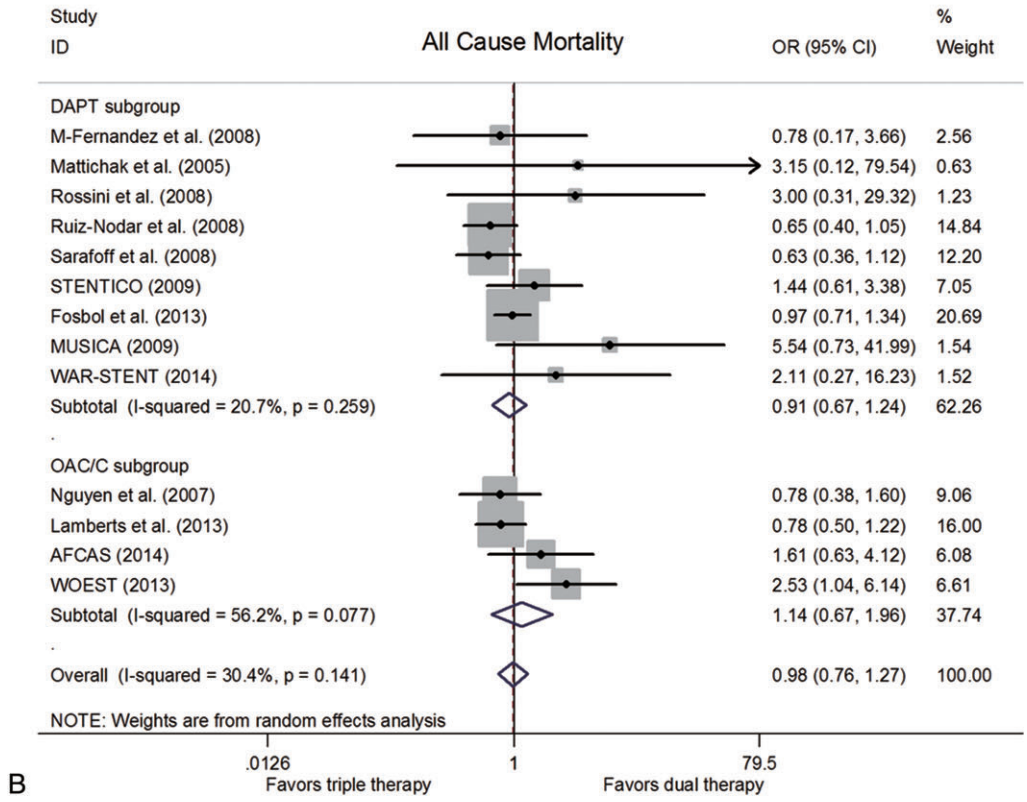

B

Figure 2. Forest plots from the included trials. Odds ratios of MACE (A), all-cause mortality (B), MI (C), ST (D), and ischemic stroke (E), associated with triple therapy vs dual therapy, stratified by different dual regimen. Abbreviations: AFCAS, Atrial Fibrillation Undergoing Coronary Artery Stenting; CI, confidence interval; DAPT, dual antiplatelet therapy; MACE, major adverse cardiovascular events; MI, myocardial infarction; MUSICA, Anticoagulation in Stent Intervention; OAC/C, oral anticoagulation and clopidogrel without aspirin; OR, odds ratio; ST, stent thrombosis; STENTICO, Stenting and Oral Anticoagulants; WAR-STENT, Warfarin and Coronary Stenting; WOEST, What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting.

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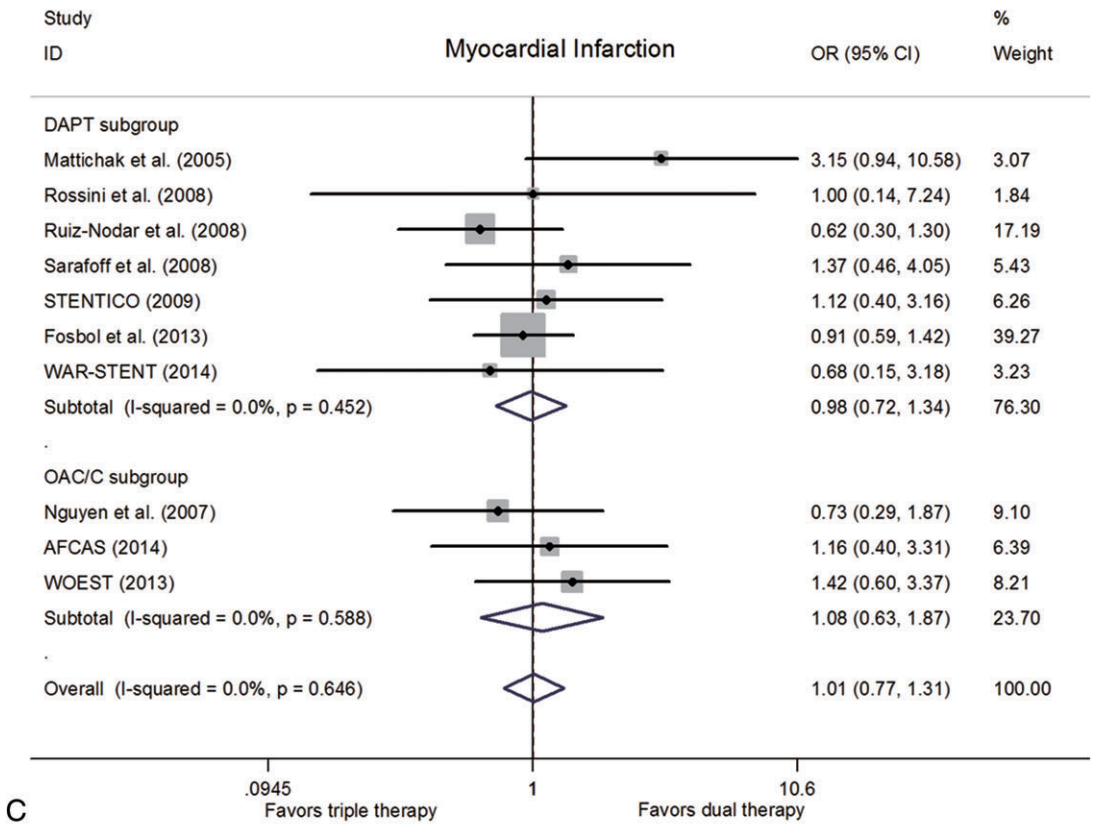

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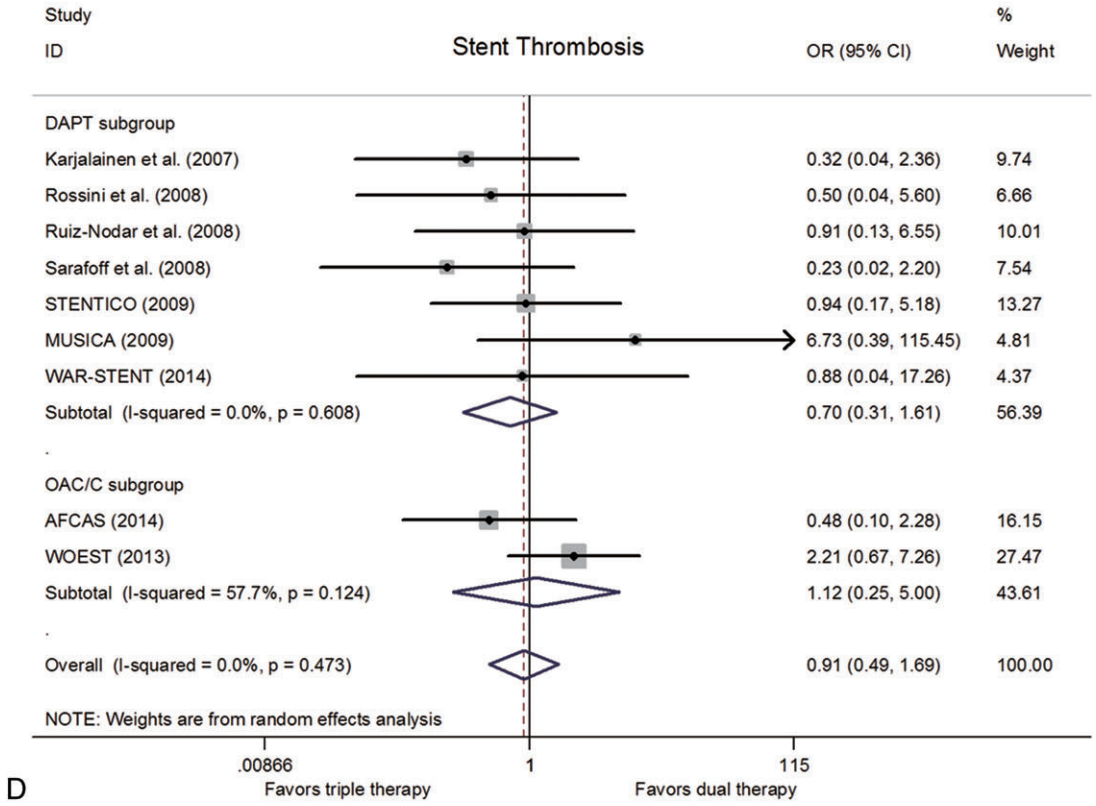

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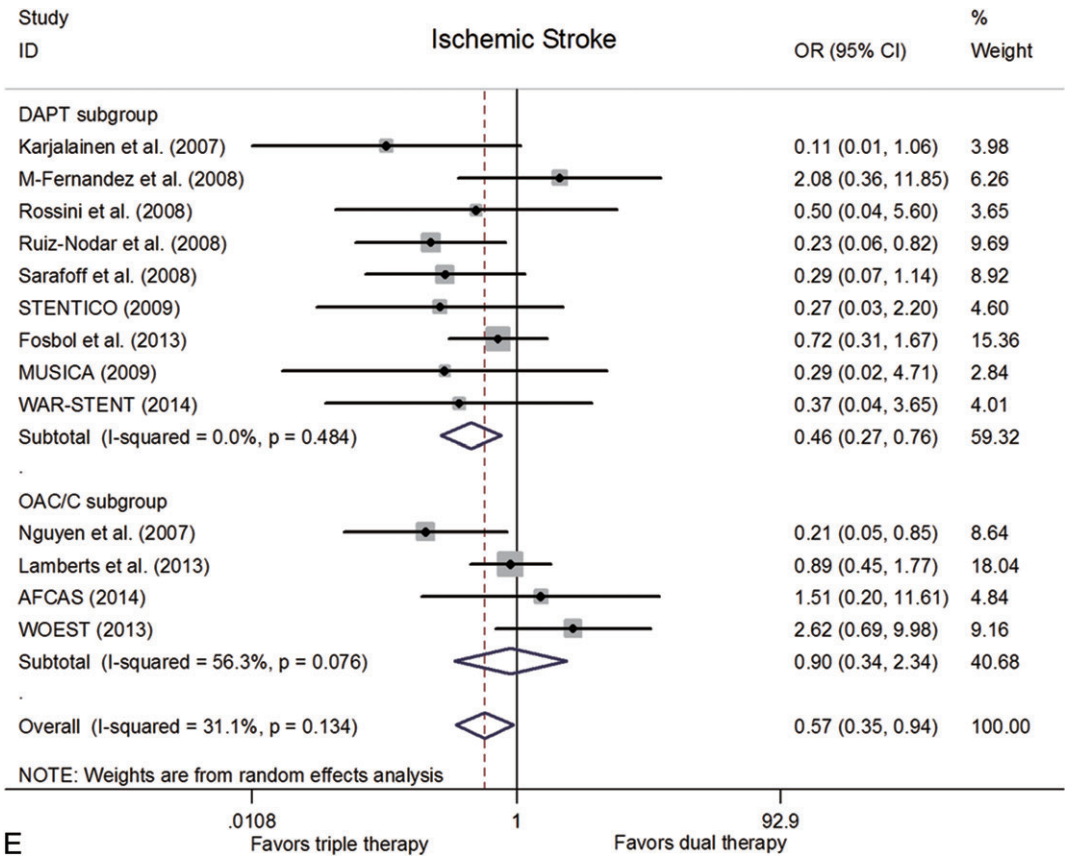

Figure 2. Continued.

awareness of this problem. A survey among US cardiologists showed that as many as 30% of patients with OAC who are admitted for PCI are discharged without it, and many more physicians are now ready to drop triple therapy because of the major bleeding risk. In fact, an earlier guideline has indicated that the triple therapy regimen contributed more bleeding risks than benefits.[33] All these results strongly support that major bleeding has become one of the biggest obstacles to recommending widespread use of the triple therapy regimen.

Transradial PCI is associated with significant reductions in procedural-related bleeding complications and improved patient satisfaction compared with transfemoral access. Of note, it has been proven that transradial PCI is feasible and associated with similar procedural success rates, as well as comparable long-term clinical safety and efficacy for complex lesions and unprotected left main coronary artery disease.[34,35] Just as previously mentioned, patients taking OAC undergoing PCI receiving the triple therapy regimen were exposed to a high risk of bleeding, so that the current guidelines recommended the radial approach in these patients, due to concern about increased bleeding associated with femoral access.

More and more evidence, including our data, has shown that the triple therapy regimen was not the most suitable treatment for patients with OAC after coronary stenting. If that is the case, then what is the optimal regimen to prevent thromboembolic events without increasing bleeding risk? The WOEST trial, as the first multicenter RCT addressing this issue, indicated that OAC plus clopidogrel could be the optimal regimen for these patients, instead of triple therapy.[12] A total of 573 patients receiving OAC undergoing PCI were randomized to triple therapy or OAC/C therapy. The primary outcome was any bleeding event, assessed by intention to treat. At 1-year follow-up, the risk of any bleeding event was 19.4% in the OAC/C therapy group compared with 44.4% in the triple therapy group ($P < 0.001$). Furthermore, the combined secondary endpoint of death, MI, stroke, target-vessel revascularization, and ST was reported in 11.1% of patients in the OAC/C group and in 17.6% in the triple therapy group ($P = 0.025$), in which the stroke risk was comparable between the 2 groups (1.1% vs 2.8%; $P = 0.128$). The WOEST trial strongly confirmed that dropping aspirin from triple therapy led to a >50% reduction in bleeding risk, without affecting stroke. Moreover, real-world data from the nationwide registries, enrolling a total of 12 165 patients, supported the findings of the WOEST trial.[14] After 1 year, no increased risk of recurrent coronary events was seen for OAC/C compared with triple therapy, and bleeding risk was also nonsignificantly lower for OAC/C therapy. Notably, the risk of all-cause death was comparable between OAC/C and triple therapy but significantly increased for OAC plus aspirin. This nationwide registry provided powerful evidence that OAC plus clopidogrel was sufficient to reduce the risk of death and stroke in real-world patients. The reason for dropping

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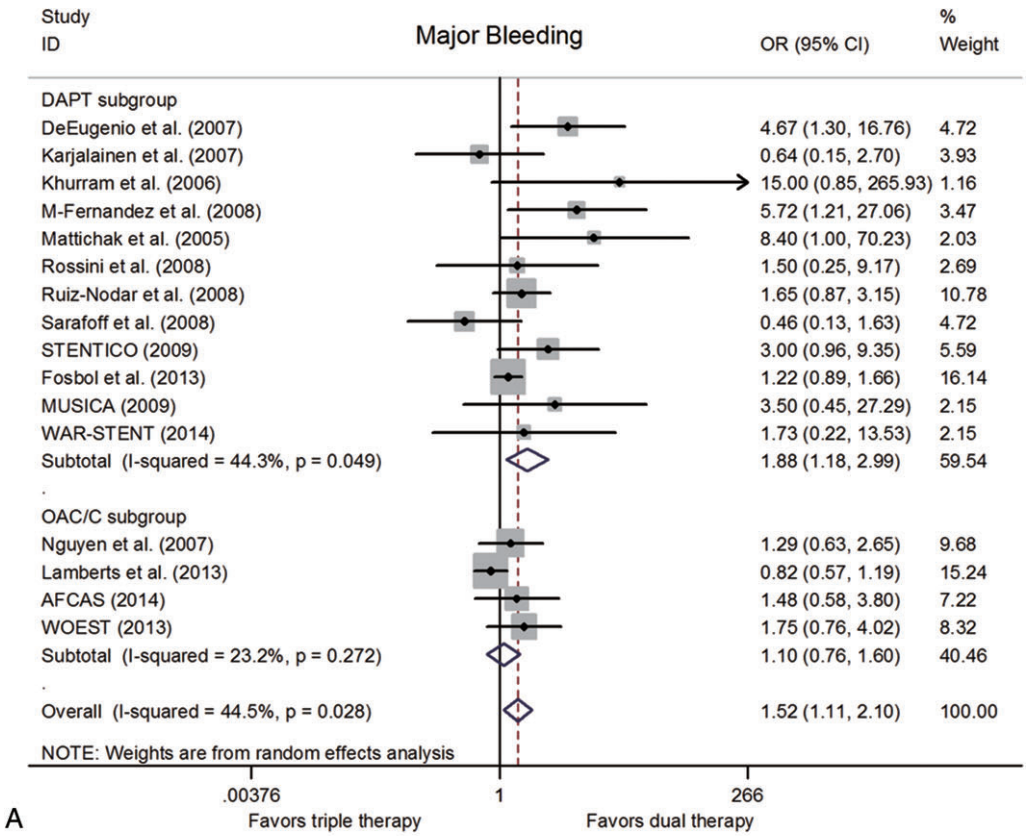

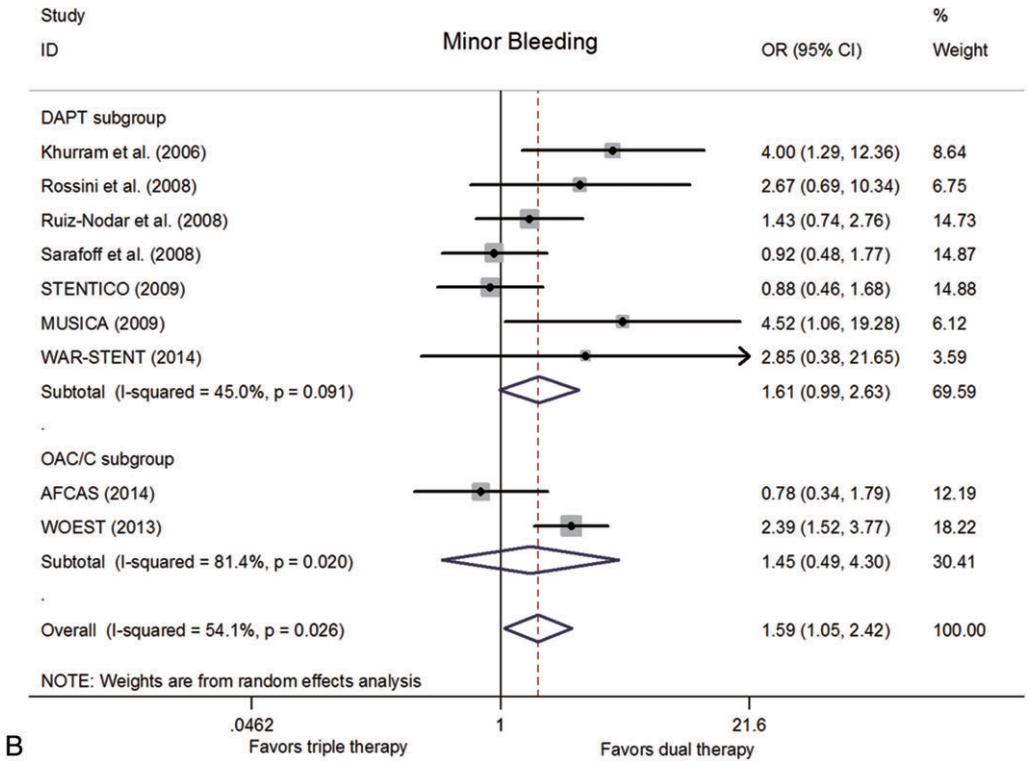

Figure 3. Forest plots from the included trials. Odds ratios of major bleeding (A) and minor bleeding (B), associated with triple therapy vs dual therapy stratified by different dual regimen. Abbreviations: AFCAS, Atrial Fibrillation Undergoing Coronary Artery Stenting; CI, confidence interval; DAPT, dual antiplatelet therapy; MUSICA, Anticoagulation in Stent Intervention; OAC/C, oral anticoagulation and clopidogrel without aspirin; OR, odds ratio; STENTICO, Stenting and Oral Anticoagulants; WAR-STENT, Warfarin and Coronary Stenting; WOEST, What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting.

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aspirin might be that thrombin inhibition with OAC and inhibition of adenosine diphosphate with clopidogrel could decrease the importance of inhibiting cyclooxygenase-1 by aspirin.[36] By and large, these studies, including our meta-analysis, suggest that OAC plus clopidogrel, dropping aspirin, was equal to or better than triple therapy in both benefit and safety outcomes for patients with OAC and coronary stenting.

Careful risk stratification should be made to balance the risk of stroke and bleeding before the initiation of antithrombotic therapy. The most widely used score to predict stroke risk in patients with AF is the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age $\geq$75 years [2 points], diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism [2 points], vascular disease, age 65–74 years, sex category).[2] Oral anticoagulation is necessary in AF patients with a CHA_2DS_2-VASc score $\geq$1, and high scores are associated with a stroke risk of up to 15% per year.[2] The HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [>65 years], drugs/alcohol concomitantly) is the most validated bleeding-risk score in AF.[37] A HAS-BLED score$\geq$3 indicates a high bleeding risk; however, it could not be depended on, on its own, to exclude patients from OAC.[38] There is a large overlap between the CHA_2DS_2-VASc and HAS-BLED score, and individualized strategies balancing stroke and bleeding risk are needed.

Several questions remain unanswered. First, there are insufficient data to assess the optimal duration of triple and dual therapy regimens. Most guidelines recommended triple therapy for 3 to 6 months, depending on stent type and bleeding risk of patients,[10,11] but it is really unknown whether shorter duration of triple therapy is also effective with the new generation of stent implantation. The second unanswered question focuses on how to overcome the resistance to clopidogrel. Newer $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) might be good alternatives for reducing thrombosis risk, but the paucity of data supports the combination of OAC and newer $P2Y_{12}$ inhibitors, and more major bleeding events could also be the hidden trouble. The third dilemma is the type and dose of OAC to optimize the risk/benefit ratio. Current recommendations advise keeping the INR between 2.0 and 2.5 instead of 2.0 to 3.0, concerning the bleeding risk with the combination of warfarin and antiplatelet therapy.[10,11] Novel oral anticoagulants such as dabigatran, rivaroxaban, and apixaban have demonstrated their superiority over warfarin in patients with AF, and these might be the optimal choice to replace warfarin to combine DAPT or clopidogrel to improve the risk/benefit ratio. However, none of these novel oral anticoagulants have been tested in AF patients who need coronary stenting, and several ongoing trials could provide more information to guide future clinical practice.

Study Limitations

Our study has several limitations. First, this meta-analysis is not based on individual patient data. Second, different studies used different bleeding definitions, as noted in our results, which might be an important source of bias. Third, lack of other potential confounding factors, such as the periprocedural use of bridging therapy, duration of triple and dual therapy, and INR values during follow-up, did not allow us to investigate the detailed impact of antithrombotic regimens on clinical endpoints and the underlying mechanisms. Finally, the follow-up period in all enrolled studies was relatively different for comparison of triple therapy vs dual therapy.

Conclusion

In patients taking oral anticoagulants and undergoing coronary intervention, treatment with OAC plus clopidogrel was associated with at least similar efficacy and safety outcomes compared with triple therapy. This meta-analysis suggests that triple therapy regimens could be replaced by OAC plus clopidogrel without any concern about additional risk of thrombotic events.

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