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SYSTEMATIC REVIEW

Meta-Analysis of Oral Anticoagulants with Dual versus Single Antiplatelet Therapy in Patients after Percutaneous Coronary Intervention

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Abstract

Background The combined use of dual antiplatelet therapy with oral anticoagulation (OAC) is required after coronary artery stenting or acute coronary syndromes (ACS).

Methods and Results We performed a meta-analysis (Embase and MEDLINE search) of the comparative effects of triple antithrombotic therapy (TT) versus OAC with single antiplatelet therapy (dual therapy [DT]) on all-cause mortality, stroke, cardiovascular death, myocardial infarction (MI), target vessel revascularization, and major bleeding. Three prospective controlled studies and five cohort studies compared TT versus DT. We identified three prospective controlled and five cohort studies with 4564 patients on TT and 1848 on DT with an average follow-up duration of 10.1 months. TT is associated with similar rates of all-cause mortality, stroke, and major bleeding but significantly lower rates of MI compared with DT.

Conclusions Triple antithrombotic therapy is associated with similar mortality and bleeding rates but fewer MIs compared with OAC and single antiplatelet therapy.

Key Points

The combined use of dual antiplatelets with oral anticoagulants is required after coronary artery stenting or acute coronary syndromes.

Our analysis suggests that triple antithrombotic therapy is associated with similar mortality and bleeding rates but fewer myocardial infarctions compared with oral anticoagulation and single antiplatelet therapy.

1 Introduction

Current guidelines recommend 12 or more months of dual antiplatelet therapy (DAPT) with aspirin and $P2Y_{12}$ receptor antagonists after coronary artery stenting with drug-eluting stents (DES) or acute coronary syndrome (ACS) [1]. Of these patients, 10 % have atrial fibrillation, mechanical heart valves, or venous thromboembolic disease and require treatment with oral anticoagulants (OACs) for prevention of thromboembolic events [2]. The combination of aspirin with OAC does not effectively prevent stent thrombosis. Moreover, DAPT is less effective in thromboembolic risk prevention than OAC. Therefore, for patients requiring OAC, triple antithrombotic therapy (TT),

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usually including a vitamin K antagonist (VKA) and DAPT, is indicated. The safety and efficacy of TT compared with OAC and single antiplatelet therapy (usually clopidogrel) have been evaluated in prospective controlled [3–5] and observation cohort [6–10] studies. The results of the first prospective open-label controlled WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) trial suggested that aspirin may not be necessary in patients requiring OAC and antiplatelet therapy [3]. In addition, recent cohort studies indicated that the combination of OAC plus clopidogrel compared with TT was safe and effective compared with triple therapy [6–11].

We performed an updated systematic review and meta-analysis to assess the effects of TT over dual therapy (VKAs plus antiplatelet therapy) on cardiovascular outcomes and the risk of bleeding in patients requiring anticoagulation after stenting.

2 Methods

2.1 Search Strategy

We performed a systematic electronic search on MEDLINE (PubMed interface), Embase, and CENTRAL (Cochrane Central Register of Controlled Trials) with no language limitations. We searched with the medical subject heading (MESH) terms 'triple antithrombotic therapy', 'oral anticoagulation with antiplatelet therapy', and 'atrial fibrillation' or 'mechanical valves' or 'thromboembolic disease'. Two reviewers (AB and NP) independently screened titles and abstracts based on inclusion and exclusion criteria. We reviewed full-text reports after eliminating irrelevant studies. Review articles and studies comparing oral anticoagulation with antiplatelets versus DAPT were excluded. Subsequently, we performed a hand search of all included randomized controlled trials and cohort studies until no further relevant studies were identified. Disagreements between the two reviewers were resolved by the third reviewer. Finally, eight studies were identified. The electronic search was last updated on 15 May 2015.

2.2 Study Selection

We included all studies that had been published as original articles in peer-reviewed scientific journals. Of the eight studies identified, three were prospective controlled trials [3–5] and five were non-randomized observational cohort studies and registries [6–10]. The population consisted of patients with mainly atrial fibrillation but also mechanical valves and venous thromboembolic disease who were receiving OAC and who underwent DES implantation. We excluded studies in non-human subjects. We did not restrict eligibility based on study outcomes.

2.3 Outcomes Assessed

The primary outcome measures were all-cause mortality, cardiovascular death, myocardial infarction (MI), target vessel revascularization, stroke, and major bleeding. Cardiovascular death was not reported in the ISAR-TRIPLE study or the GRACE and AFCAS registries. MI was not reported in MUSICA and Lamberts et al. [7] registries. Target vessel revascularization was not reported in the ISAR-TRIPLE study or the GRACE, AFCAS, or Lamberts et al. [7] registries. Stroke was not reported in the MUSICA registry. Bleeding outcome was assessed based on TIMI (Thrombolysis In Myocardial Infarction) and BARC (Bleeding Academic Research Consortium) criteria. We assessed major bleeding events as a safety endpoint.

2.4 Risk of Bias

The individual risk of bias was assessed in each prospective randomized study using Cochrane's risk-of-bias tool [18]. We used the Newcastle–Ottawa tool to assess the quality of cohort studies. Two authors (AB and NP) independently assessed the risk of bias and the quality of studies in each eligible trial. Studies with two or more quality assessment criteria qualifying as high or unclear risk of bias were classified as 'low quality'. The small study effect, including publication bias, was tested using funnel plot with Duval and the Egger's test.

2.5 Data Analysis, Summary Measures, and Synthesis of Results

This systematic review and meta-analysis was conducted in compliance with the Cochrane Collaboration and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Meta-analyses were performed using the Review Manager (RevMan) version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, 2012, Copenhagen, Denmark). The Chi squared test of heterogeneity and I^2 statistic of inconsistency were used to assess heterogeneity between studies. I^2 values of 25, 50, and 75 % were considered as low, moderate, and high heterogeneity, respectively. Heterogeneity was considered significant if the p value was <0.05 or an I^2 statistic was >25 %. Pooled effect of intervention was measured using odds ratio (OR) with 95 % confidence interval (CI). The Mantel–Haenszel fixed-effects model was used to estimate the pooled effect measure. A DerSimonian–Laird random-effects model for ORs estimation of all outcomes

Table 1 Characteristics of the included studies

Study	Design	Sample size		Mean age (years)	Sex (male %)	Indications for DAPT	Indication for anticoagulation (% of pts)	Type of stents (% of pts)	Definition of bleeding	Follow-up (months)	Risk of bias
		TT	DT								
WOEST [3]	RCT	284	279	70.3	79	CS	AF (69 %), MV (11 %)	DES (65 %), BMS (32 %)	TIMI, GUSTO	12	Low
Gao et al. [4]	PC	136	121	71.8	71	DES	AF	DES	TIMI	12	High
ISAR-TRIPLE [5]	RCT	307	307	73.6	76.7	DES	AF (85 %), MV (9.1 %)	DES	TIMI, BARC	9	Low
MUSICA [6]	OC	278	46	71	80	CS or ACS	AF (64.7 %), MV (28.3 %)	DES (48.2 %), BMS (51.8 %)		6	Low
Lamberts et al. [7]	OC	1896	548	71.3	73.7	CS or ACS	AF	–		12	Low
Nguyen et al. [8]	OC	453	184	65	72	CS or ACS	AF (80 %), MV (9 %)	DES (28 %)		6	Low
Rubboli et al. [9]	OC	75	73	73.5	71	CS or ACS	AF	DES (24 %), BMS (76 %)	BARC	12	Low
Persson et al. [10]	OC	404	254	68	75	DES	AF	DES		12	Low

ACS acute coronary syndrome, *AF* atrial fibrillation/atrial flutter, *BARC* Bleeding Academic Research Consortium, *BMS* bare metal stents, *CS* coronary stenting, *DAPT* dual antiplatelet therapy, *DES* drug-eluting stents, *DT* OAC+ single antiplatelet, *MV* mechanical valves, *OAC* oral anticoagulant, *OC* observational cohort, *PC* prospective controlled, *RCT* randomized double-blind clinical trial, *TIMI* Thrombolysis in Myocardial Infarction, *TT* OAC+ dual antiplatelet

was used in the presence of heterogeneity. Reported values are two-tailed, and hypothesis-testing results were considered statistically significant at $p < 0.05$. Sensitivity analysis was performed by eliminating each study at a time to assess the influence of any included study on the results and the robustness of results. Significant heterogeneity between the studies was further explored using subgroup analyses. Each of these analyses was conducted for all the endpoints that showed significant heterogeneity.

3 Results

We identified three prospective controlled studies [3–5] and five cohort studies [6–10] that investigated TT compared with dual therapy (DT) (Table 1). The main antiplatelet used in the single antiplatelet arm was clopidogrel. The WOEST [3] study and the AFCAS registry [9] used clopidogrel in all patients receiving OAC and single antiplatelet therapy. We selected the OAC plus clopidogrel group included in the Danish registry [7] and compared it with TT. The study by Gao et al. [4] and the MUSICA registry [6] used clopidogrel in 87 and 82.6 % of patients in the single-antiplatelet arm, respectively. However, in the GRACE registry [8], only 51 % of patients receiving OAC plus single antiplatelet therapy received clopidogrel. Finally, in the ISAR-TRIPLE trial, patients continued to receive aspirin and OAC after discontinuing clopidogrel [5]. The baseline characteristics of the included studies are summarized in Table 1. All were reported between 2007 and 2014. These studies enrolled 4564 patients receiving TT and 1848 receiving DT. The average follow-up time was 10.1 months. With the exception of AFCAS and ISAR-TRIPLE studies, TT and DT were continued throughout follow-up. In the AFCAS trial, aspirin and VKA were prescribed lifelong, whereas clopidogrel was prescribed for up to 6 months in three-quarters of patients. In the ISAR-TRIPLE study, the follow-up period was extended for 3 months after the 6-month duration of TT.

On the basis of quality assessment, one study [4] was deemed to be at high risk of bias and the remaining studies at low risk (Table 1).

No significant difference in all-cause mortality between TT and DT was noted in the prospective controlled studies (OR 1.52; 95 % CI 0.92–2.51; $p = 0.1$; Fig. 1a) without significant heterogeneity between trials ($I^2 = 35$ %, $p = 0.22$). In the subgroup of cohort studies, no difference between groups was found (OR 0.82; 95 % CI 0.60–1.11; p = 0.19; Figs. 1b, 6) without significant heterogeneity between trials ($I^2 = 0$ %, $p = 0.53$).

Only two studies in each subgroup reported data on cardiovascular death. No significant differences between the TT and DT were found, without significant

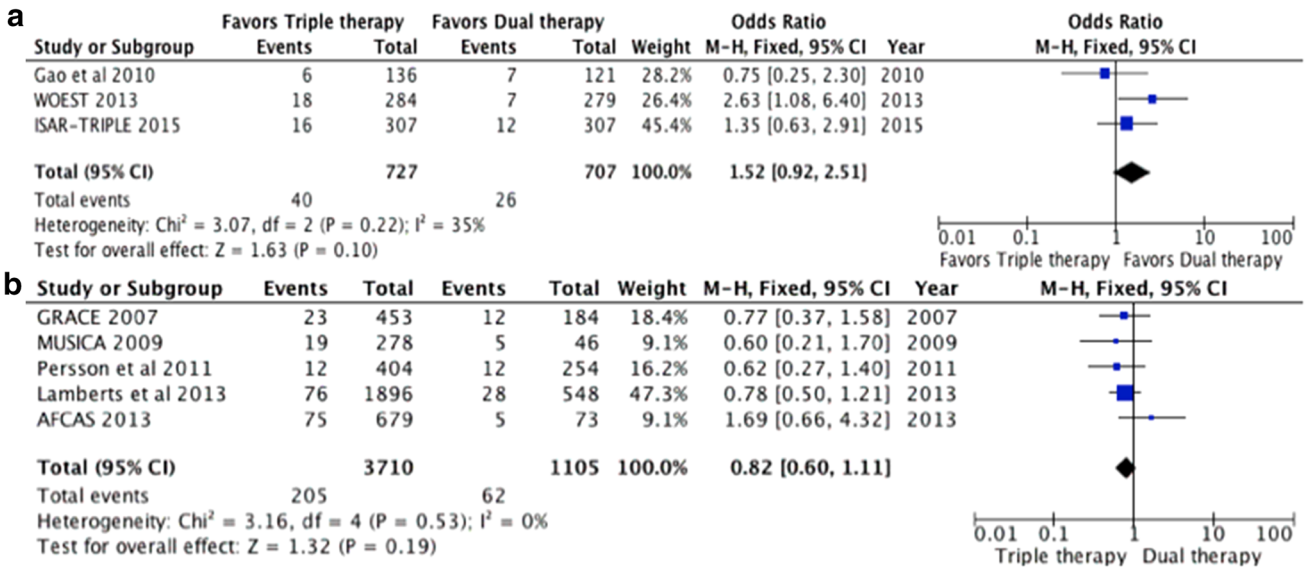

Fig. 1 Fixed-effect meta-analysis for all-cause mortality. The figure presents number of events, number of patients in treatment and control groups, odds ratio and 95 % confidence interval for each trial, overall odds ratio estimate with 95 % confidence interval and *p* value for association test, *p* value for heterogeneity test, and between-trial inconsistency (I^2) measures. *CI* confidence interval, *M–H* Mantel–Haenszel

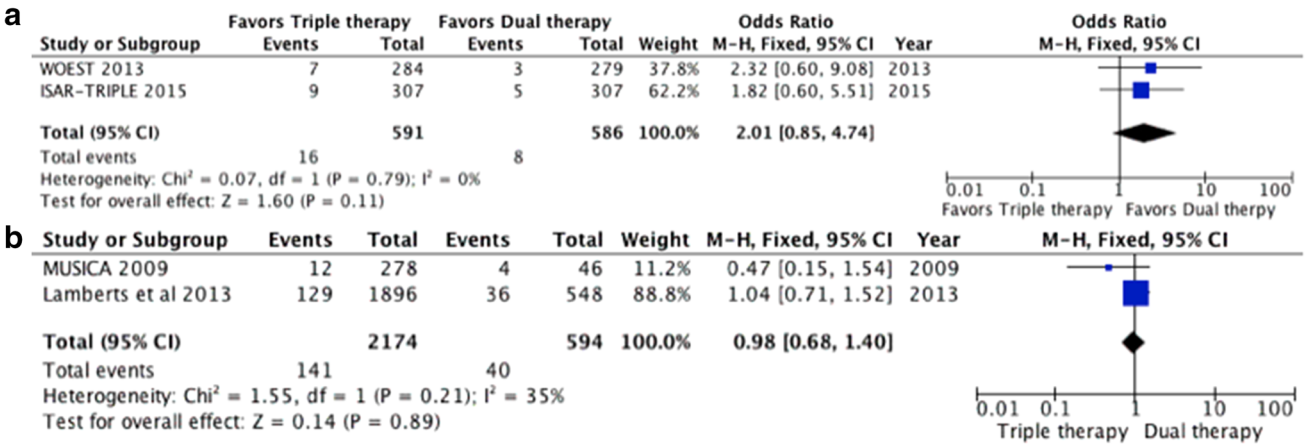

Fig. 2 Fixed-effect meta-analysis for cardiovascular death. *CI* confidence interval, *M–H* Mantel–Haenszel

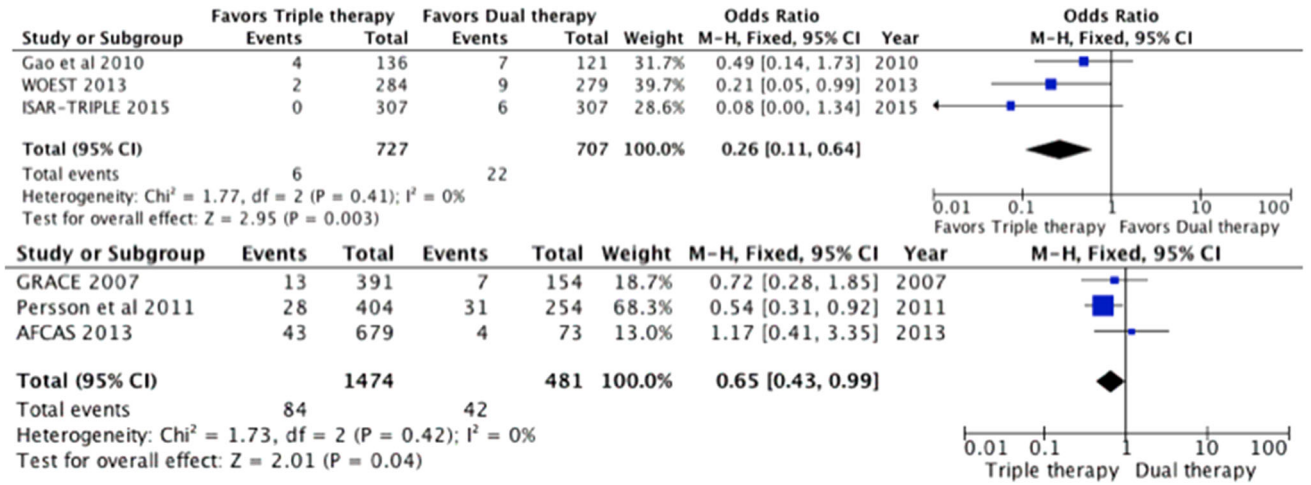

Fig. 3 Fixed-effect meta-analysis for myocardial infarction. *CI* confidence interval, *M–H* Mantel–Haenszel

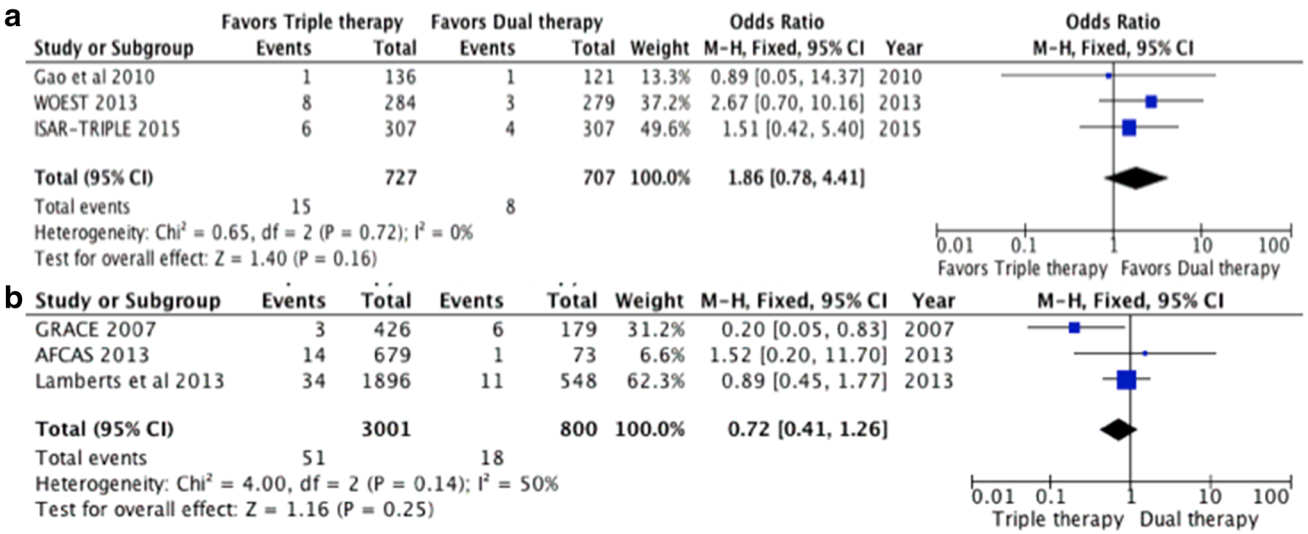

Fig. 4 Fixed-effect meta-analysis for rates of stroke. *CI* confidence interval, *M–H* Mantel–Haenszel

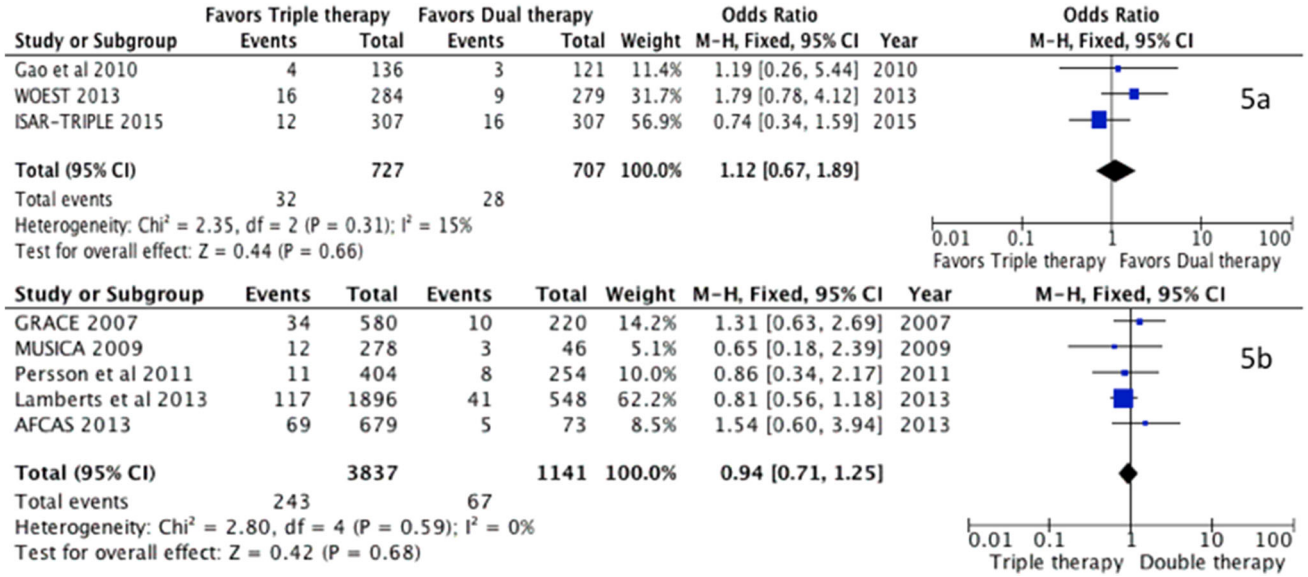

Fig. 5 Fixed-effect meta-analysis for rates of major bleeding. *CI* confidence interval, *M–H* Mantel–Haenszel

heterogeneity between trials (Figs. 2a, b, 6). However, MI rates were significantly lower in the TT group in both groups (OR 0.26, p = 0.003 for prospective controlled studies, and OR 0.65, $p = 0.04$ for cohort studies), without significant heterogeneity between trials (Figs. 3a, b, 6). Target vessel revascularization was reported in two prospective controlled studies and one cohort study. No significant differences between groups were found ($p = 0.78$). Similarly, stroke rates were not significantly different between TT and DT without significant heterogeneity between trials (Figs. 4a, b, 6). Finally, TT and DT did not differ significantly in major bleeding rates (prospective studies OR 1.12; 95 % CI 0.67–1.89; $p = 0.66$; Fig. 5a; and cohort studies OR 0.94; 95 % CI 0.74–1.25; $P = 0.68$; Figs. 5b, 6).

The funnel plot did not show asymmetry consistent with publication bias, and the Egger's test was not significant for the outcomes studied.

4 Discussion

The main conclusion of our meta-analysis is that TT is associated with similar rates of all-cause mortality, stroke, and major bleeding but significantly lower rates of MI than DT (mainly OAC plus clopidogrel). A previous meta-

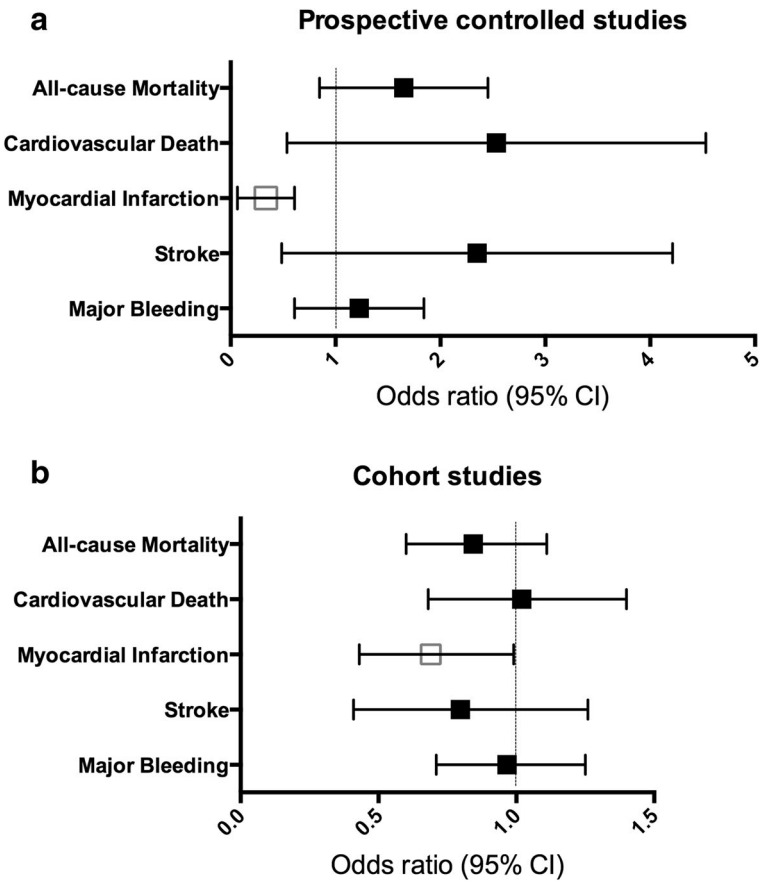

Fig. 6 Forest plot of the main outcomes. *CI* confidence interval

analysis suggested that TT was associated with lower stroke rates but higher bleeding risk than DAPT and similar safety and efficacy compared with the combination of OAC plus clopidogrel [12]. Our analysis focused on the effects of TT compared with OAC and mainly clopidogrel combination. We included four more studies than the prior analysis and we also analyzed prospective controlled and cohort studies separately. Although we did not find any significant differences in all-cause mortality, stroke, target vessel revascularization, and major bleeding, the MI rates were significantly lower in the TT group. Whether stent thrombosis is the cause for the increased MI rates is unclear, as the majority of the studies were not powered and did not report stent thrombosis rates. Nevertheless, increased MI rates with DT did not translate into higher rates of cardiovascular or all-cause death.

Prior cardiovascular studies have suggested that mortality, cardiovascular events, and stroke rates were higher in patients with an indication for OAC who underwent coronary stenting and were discharged on DAPT without anticoagulant [13–15]. However, the WOEST study [3] indicated that aspirin may not be necessary, as patients receiving OAC plus clopidogrel had lower all-cause mortality and major bleeding than those receiving TT. OAC plus single antiplatelet therapy has been compared with TT in cohort studies. The largest registry of over 12,000 patients with atrial fibrillation who underwent percutaneous intervention [7] showed that all-cause death, stroke, and major bleeding were similar in TT and DT.

Risk of bleeding complications is the main concern with TT. Different duration, indication, dose, and target of anticoagulation complicate the estimation of major bleeding from the existing randomized and cohort studies. Additionally, definitions of major bleeding vary across the studies. Heterogeneity in duration of treatment and type of stents used may affect the interpretation of our results. The main cardiovascular and bleeding complications reported in six of eight studies of our analysis occurred while the patients were receiving treatment. In the ISAR-TRIPLE study, no excess bleeding or ischemic events were noted in a 3-month period after treatment discontinuation. However, in the AFCAS study, about 50 % of major bleeding events occurred after the discontinuation of clopidogrel while patients were treated with VKAs (with or without aspirin). Conversely, all major bleeding events occurred while patients were receiving treatment in the dual antiplatelet arm of the AFCAS trial.

An earlier Danish cohort study of more than 82,000 patients hospitalized with atrial fibrillation showed that TT and OAC plus clopidogrel carried a more than threefold

higher risk of fatal and non-fatal bleeding compared with warfarin or single antiplatelet monotherapy [16]. Therefore, low-dose aspirin and warfarin should be used in patients receiving TT to achieve international normalized ratio (INR) of 2–2.5 to decrease bleeding risk. These measures are supported by a previous prospective study [17] that showed similar bleeding risk in patients receiving TT and INR of 2–2.5 compared with those receiving DAPT. Shorter duration of TT in patients who underwent DES implantation may be associated with similar clinical outcomes and bleeding risk compared with longer TT as suggested by the ISAR-TRIPLE study. The length of anticoagulation is largely dependent on the type of stent. After DES implantation ACS, DAPT is recommended for at least 12 months. However, a recent prospective controlled study showed that second-generation DES implantation combined with abbreviated DAPT duration resulted in lower rates of major cardiovascular events and stent thrombosis compared with bare metal stent (BMS) implantation in patients at higher risk of bleeding [18].

Newer $P2Y_{12}$ inhibitors are associated with more effective platelet inhibition but higher bleeding risk compared with clopidogrel. In a study of 377 patients with an indication for anticoagulation after coronary stenting, use of prasugrel was associated with significantly higher bleeding rates than clopidogrel [19]. However, newer anticoagulants, such as factor Xa inhibitors, may be associated with similar or lower bleeding risk compared with VKAs and thus present a reasonable alternative to warfarin in patients with atrial fibrillation or venous thromboembolism who require DAPT.

5 Conclusions

Any meta-analysis based on pooling of data from studies with different doses and types of antithrombotic regimens presents challenges. In our analysis, most of the patients were enrolled in cohort studies, which probably better represent real-world clinical practice but are affected by confounding and selection bias due to baseline heterogeneity. In addition, the ability of the analysis to detect differences between regimens would have been diminished by incomplete adherence to assigned treatments. Furthermore, outcomes evaluated here were not available as prespecified criteria or primary outcomes in all eligible trials. Taking into consideration the limitations a meta-analysis carries, we demonstrated that TT is associated with similar mortality and bleeding rates but fewer MIs than OACs and single antiplatelet therapy. The results of future clinical trials will help to clarify the impact of different treatment strategies on long-term outcomes. Currently, individualized treatment may represent the most reasonable approach, especially in specific coronary artery disease subpopulations.

Compliance with Ethical Standards

Ethical approval No ethical approval was required for this study.

Conflict of interest The authors declare they have no conflicts of interest relevant to this work. The authors are solely responsible for the design and conduct of this study: all study analyses, the drafting and editing of the paper and its final contents.

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