Am J Transl Res 2022;14(12):8416-8428
www.ajtr.org /ISSN:1943-8141/AJTR0146931

Review Article

Therapeutic effect of antithrombotic drug combinations in patients with atrial fibrillation undergoing percutaneous coronary intervention for coronary heart disease: a meta-analysis

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Received October 10, 2022; Accepted November 25, 2022; Epub December 15, 2022; Published December 30, 2022

Abstract: Objective: To explore suitable treatment strategies for patients with coronary heart disease and atrial fibrillation after percutaneous coronary intervention (PCI) via systematically analyzing and comparing the clinical efficacy of dual antithrombotic therapy (DAT) and triple antithrombotic therapy (TAT). Methods: Pubmed, Embase and Cochrane Library databases were searched. The literature from the database establishment to August 2022 was reviewed by 2 researchers separately according to the inclusion and exclusion criteria and the method recommended by the Cochrane Collaboration. The data was extracted for quality assessment. The primary endpoints of the study were safety endpoints and efficacy endpoints, the former includes major bleeding events and the latter includes mortality, myocardial infarction, stent thrombosis and stroke. RevMan5.4 software was used for meta-analysis. Results: There were 11 studies were included for the meta-analysis, 5 observational studies and 6 randomized controlled trials. The number of patients included was 2,4032, of which 13818 (57.5%) received DAT and 9483 (39.5%) received TAT. Our analyses indicated that compared with TAT treatment, DAT significantly reduced the incidence of major bleeding (OR=0.71, 95% CI [0.61, 0.83], P<0.0001) and the incidence of minor bleeding (OR=0.61, 95% CI [0.50, 0.75], P<0.00001). Subgroup analysis showed that DAT with novel oral anticoagulants (NOACs) reduced major bleeding (OR=0.64, 95% CI [0.54, 0.76], P<0.00001) and the incidence of minor bleeding (OR=0.56, 95% CI [0.45, 0.69], P<0.00001), but DAT with vitamin K antagonists (VKAs) was not significantly different from TAT in major bleeding (OR=1.20, 95% CI [0.82, 1.75], P=0.35) and minor bleeding (OR=1.15, 95% CI [0.64, 2.05], P=0.64). Conclusions: DAT with NOACs has a higher safety profile against bleeding in patients with atrial fibrillation after PCI. DAT with VKAs was similar to TAT in terms of antithrombotic effect and incidence of bleeding.

Keywords: Percutaneous coronary intervention, atrial fibrillation, antithrombotic, new oral anticoagulants, anticoagulation

Introduction

The total prevalence of atrial fibrillation (AF) in Chinese adults age 45 years old or more is about 2%, and the prevalence increases with aging, especially in people over 75 years old, the prevalence is as high as 5% [1]. A study has reported that about 38.2% of the global coronary heart disease (CHD) deaths from 1990 to 2017 were in China [2]. According to the China Health Statistical Yearbook published in 2021, the mortality of CHD in China is 127/100 000 [3]. The prevalence of AF in CHD patients is 4 times higher than that in non-CHD patients [4]. Dual antiplatelet therapy with aspirin (ASA) and P2Y12i inhibitor is the key to preventing stent thrombosis in patients with CHD after percutaneous coronary intervention (PCI), and oral anticoagulants (OACs) play an important role in preventing AF-related stroke. The combination of ASA, P2Y12i inhibitor and OACs, namely triple anticoagulant therapy (TAT), is presently the main means to prevent stent thrombosis [5]. Although TAT can reduce the incidence of major adverse cardiovascular events (MACE), discontinuation or non-use of OACs will increase the

risk of stroke, and discontinuation of any antiplatelet drug will increase the probability of stent thrombosis and myocardial infarction (MI) [6, 7].

Novel oral anticoagulants (NOACs) are new agents for the prevention and treatment of thromboembolism, whereas previously the only agent available was the vitamin K antagonist (VKA), warfarin. Compared with VKA, NOACs perform better efficacy and safety. Therefore, P2Y12i inhibitor combined with OACs (VKA or NOAC) was proposed as a new dual antithrombotic therapy (DAT) regimen. NOACs include the factor Xa inhibitors apixaban [8, 9], rivaroxaban [10-12], edoxaban [13] and the direct IIa inhibitor dabigatran [14]. Studies [15-17] showed that DAT was effective and may reduce the incidence of bleeding events compared with TAT. However, the validity and safety of the above drugs for CHD patients with AF after PCI is still unclear. Therefore, a meta-analysis was performed to evaluate the clinical efficacy, safety and prognosis of DAT and TAT in patients with CHD and AF after PCI.

Methods

Study selection and eligibility criteria

To obtain accurate meta-analysis results, we included patients with AF after PCI. Inclusion criteria: (1) The trial design was randomized controlled or observational, and compared DAT and TAT; (2) The DAT regimen was a combination of P2Y12i inhibitor and OACs (VKA or NOACs); (3) TAT regimen was a combination of P2Y12i inhibitor plus ASA and OAC (VKA or NOACs); (4) The efficacy endpoint was MACE, including death, MI, stent thrombosis and stroke; (5) The safety endpoints for clinical trials of thrombolytic therapy were International Society on Thrombosis and Hemostasis (ISTH) major bleeding events (MBE) and Thrombolysis In Myocardial Infarction (TIMI) bleeding, including fatal bleeding, bleeding of vital organs, intracranial bleeding, retroperitoneal bleeding, and TIMI major or minor bleeding, etc. Exclusion criteria: (1) MACE and ISTH major bleeding events were not designated as primary endpoints; (2) Incomplete data.

Searching strategy

Key terms including "percutaneous coronary intervention", "atrial fibrillation", "oral anticoagulants", "vitamin K antagonists", "novel oral anticoagulants", "bleeding", "stent thrombosis" and "myocardial infarction" were searched in Pubmed, Embase and Cochrane Library databases. The search formula was as follows: (1) "percutaneous coronary intervention" + "atrial fibrillation" + ("oral anticoagulants" or "vitamin K antagonists" or "novel oral anticoagulants"), (2) "percutaneous coronary intervention" + "atrial fibrillation" + ("bleeding" or "stent thrombosis" or "myocardial infarction"). The literature was limited to English language and publication time from the database establishment to August 2022.

Data extraction

Basic data about the included literature were summarized, including author name, publication date, study design, primary outcomes and follow-up time. Clinical data were extracted on several aspects, including the incidence of major and minor bleeding, mortality, stent thrombosis, MI and stroke. These data were extracted from each article by one author (Huabin He) and verified by the second author (Jianhai Chen). Disagreement was adjudicated with the third party (Xifeng Xiao) after consultation and discussion.

Assessment of risk of bias

The risk of bias of RCTs was performed based on the criteria recommended in the Cochrane Handbook for Systematic Reviews of Interventions 6.3.0, which included random sequence, allocation, blindness, objective evaluation of outcome indicators, an adequate description of outcome indicators and other biases. Each criterion was assessed as 'high risk', 'unclear risk' or 'low risk'. Observational studies were assessed for risk of bias according to the NOS scale. The funnel plot showed the risk of bias.

Statistical analysis

All analyses were performed using RevMan 5.4 software. Categorical variables were presented as pooled odds ratios (OR) and 95% confidence intervals (CI). Continuous variables were expressed as means and their 95% CIs. We performed a heterogeneity test and the I^2 statistic to show the percentage of the overall

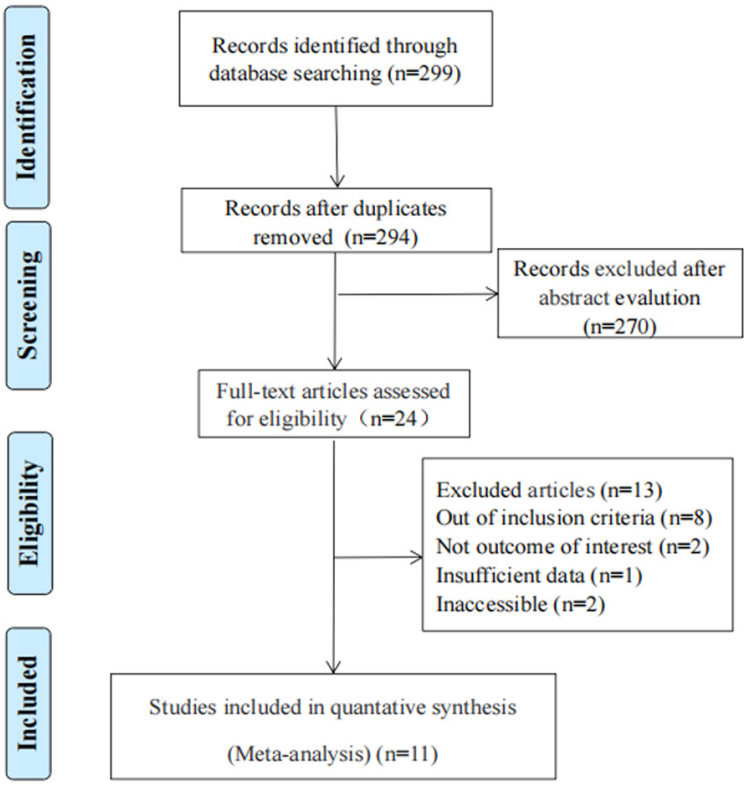

Figure 1. PRISMA flow diagram of literature searching and screening.

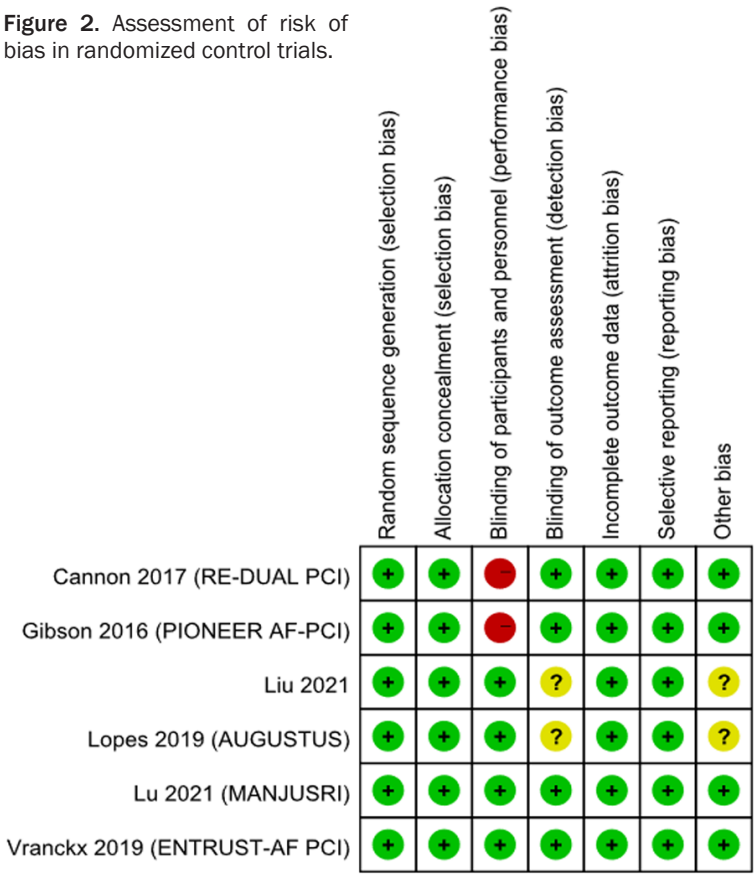

Figure 2. Assessment of risk of bias in randomized control trials.

difference between the included studies due to heterogeneity (non-randomness). Statistical tests for heterogeneity were performed using the Cochrane-Q test, with $P<0.01$ as a significant level. Random effects or fixed effects were selected according to the value of I^2 for pooled analysis. Statistical results of effect sizes were combined using forest plots.

Results

Retrieving results and assessment of risk of bias

A total of 299 papers were obtained from preliminary screening. The PRISMA flow chart is shown in **Figure 1**. Most studies (N=270) were excluded due to literature type or by reading the title or abstract. Two studies were not available for full text. After obtaining the full text of 24 studies, 13 studies were excluded because 8 studies did not meet the inclusion criteria, 2 studies had no results of interest and 1 study had incomplete results. In the end, 11 studies were contained for the meta-analysis. Six of them [10, 11, 13, 14, 16, 18] were RCTs, and 5 [12, 19-22] were observational studies. The quality evaluation of RCTs is shown in **Figure 2**. Observational studies were evaluated for quality according to the NOS scale, and the results are displayed in **Table 1**. Two articles did not mention the blinding of subjects and researchers, and two studies had incomplete descriptions of blinding of outcome assessments. There is implementation bias and measurement bias.

Study and patient characteristics

Our meta-analysis involved 24,032 participants with AF

Table 1. Risk of bias assessment in observational studies

Study	Selection				Comparability control for important factor	Exposure			Scores
	Adequate definition of cases	Represent-activeness of the cases	Selection of controls	Definition of controls		Ascertai-nment of exposure	Same method of ascertain-nment for cases and controls	Non-Response rate	
Gao 2010	*	-	-	*	*	*	*	*	6
Lamberts 2013	*	*	*	*	**	*	*	*	8
Park 2022	-	-	*	-	*	*	*	*	5
Rubboli 2014	*	-	-	*	*	*	*	*	6
De Vecchis 2016	*	*	*	*	*	*	*	*	8

after PCI. **Table 2** provides the main characteristics of these studies, including the design, baseline characteristics and outcome measures. All studies included a comparison between DAT and TAT. The NOACs used in the included studies were dabigatran [13], rivaroxa [9, 11, 14, 16], and edoxaban [12]. The shortest follow-up time was 3 months, the longest was 18 months, and the average was 10.7 months.

Safety meta-analysis of DAT and TAT

The forest plot for the combined analysis of major bleeding events is shown in **Figure 3**. The incidence of major bleeding was 2.46% (339/13801) in patients receiving DAT and 4.44% (419/9435) in those receiving TAT. Compared with TAT, DAT significantly lowered the risk of major bleeding (OR=0.71, 95% CI [0.61, 0.83], P<0.0001). Subgroup analysis by OAC types illustrated that compared with TAT, the use of DAT with NOACs reduced the occurrence of major bleeding (OR=0.64, 95% CI [0.54, 0.76], P<0.00001). There was no significant difference in the incidence of major bleeding between DAT with VKA and TAT in patients with CHD and AF after PCI (OR=1.20, 95% CI [0.82, 1.75], P=0.35). Cochran Q test showed that there was no significant heterogeneity among the study results (P=0.13).

The analysis of minor bleeding events of all studies is shown in **Figure 4**. Of the 5114 patients receiving DAT, 168 had minor bleeding, and of the 4901 patients receiving TAT, 272 had minor bleeding. DAT showed a significant advantage in preventing minor bleeding (OR=0.61, 95% CI [0.50, 0.75], P<0.00001). Subgroup analysis by OAC types showed that DAT with NOACs reduced the incidence of minor bleeding (OR=0.56, 95% CI [0.45, 0.69], P< 0.00001). However, no difference was found in the risk of minor bleeding between patients receiving DAT with VKA and TAT (OR=1.15, 95% CI [0.64, 2.05], P=0.64). There was no significant heterogeneity in the results (P=0.18).

Meta-analysis of the effectiveness of DAT and TAT

The forest plot of mortality analysis is shown in **Figure 5**. The mortality rates of DAT and TAT were 3.69% (481/13048) and 4.28% (371/8678), respectively, with no statistical significance (OR=0.98, 95% CI [0.84, 1.14], P=0.79). Subgroup analysis by OAC types demonstrated that mortality was comparable between DAT and TAT regardless of whether the drug used in DAT was NOACs or VKA. There was no significant heterogeneity in the results (P=0.76).

The forest plot of the risk of MI is shown in **Figure 6**. The incidence of MI in patients receiving DAT and TAT were 3.80% (496/13064) and 4.26% (372/8727), respectively. Pooled effect (OR=1.03, 95% CI [0.88, 1.21], P=0.71) showed no significant difference between DAT and TAT. Subgroup analysis by OAC types showed that DAT with NOACs and TAT resulted comparable risk of MI (OR=1.09, 95% CI [0.91, 1.30], P=0.35). Similar result was also obtained in the comparison of DAT with VKA and TAT (OR=0.84, 95% CI [0.59, 1.19], P=0.32). There was no significant heterogeneity in the results (P=0.50).

The forest plot of the pooled analysis of stent thrombosis incidence is shown in **Figure 7**. The results showed that stent thrombosis occurred in 46 of the 5058 patients who received DAT. Of the 4847 patients who received TAT, 41

Table 2. Characteristics of the included studies

Study	Participants (N)			Interventions		Primary Outcome	Follow up (months)
	Total	DAT	TAT	DAT	TAT		
Cannon 2017 (RE-DUAL PCI)	2725	1744	981	Dabigatran + P2Y12i	VKA + ASA + P2Y12i	ISTH major bleeding	14
Gao 2010*	257	121	136	Rivaroxaban + P2Y12i	VKA + ASA + P2Y12i	TIMI major or minor bleeding	12
Gibson 2016 (PIONEER AF-PCI)	2124	696	697	Rivaroxaban + P2Y12i	Rivaroxaban or VKA + ASA + P2Y12i	TIMI major or minor bleeding	12
Lamberts 2013*	2444	548	1896	VKA + P2Y12i	VKA + ASA + P2Y12i	TIMI major or minor bleeding	12
Liu 2021	106	54	52	Rivaroxaban + P2Y12i	VKA + ASA + P2Y12i	Major bleeding	12
Lopes 2019 (AUGUSTUS)	4614	2307	2307	Apixaban + P2Y12i	VKA + ASA + P2Y12i	ISTH major bleeding	6
Lu 2021 (MANJUSRI)	294	148	146	VKA + P2Y12i	VKA + ASA + P2Y12i	TIMI major bleeding	18
Park 2022*	9042	7256	1786	NOAC + P2Y12i	VKA + ASA + P2Y12i	MACE, major bleeding	3
Rubboli 2014*	841	162	679	VKA + P2Y12i	VKA + ASA + P2Y12i	MACE, major bleeding	12
De Vecchis 2016*	79	31	48	VKA + P2Y12i	VKA + ASA + P2Y12i	MACE, major bleeding	24
Vranckx 2019 (ENTRUST-AF PCI)	1506	751	755	Edoxaban + P2Y12i	VKA + ASA + P2Y12i	ISTH major bleeding	12

Note: *represents observational studies. VKA: Vitamin K antagonist. ASA: Aspirin. ISTH: International Society on Thrombosis and Hemostasis. TIMI: Thrombolysis In Myocardial Infarction. MACE: Major adverse cardiovascular events. DAT: Dual antithrombotic therapy. TAT: Triple antithrombotic therapy.

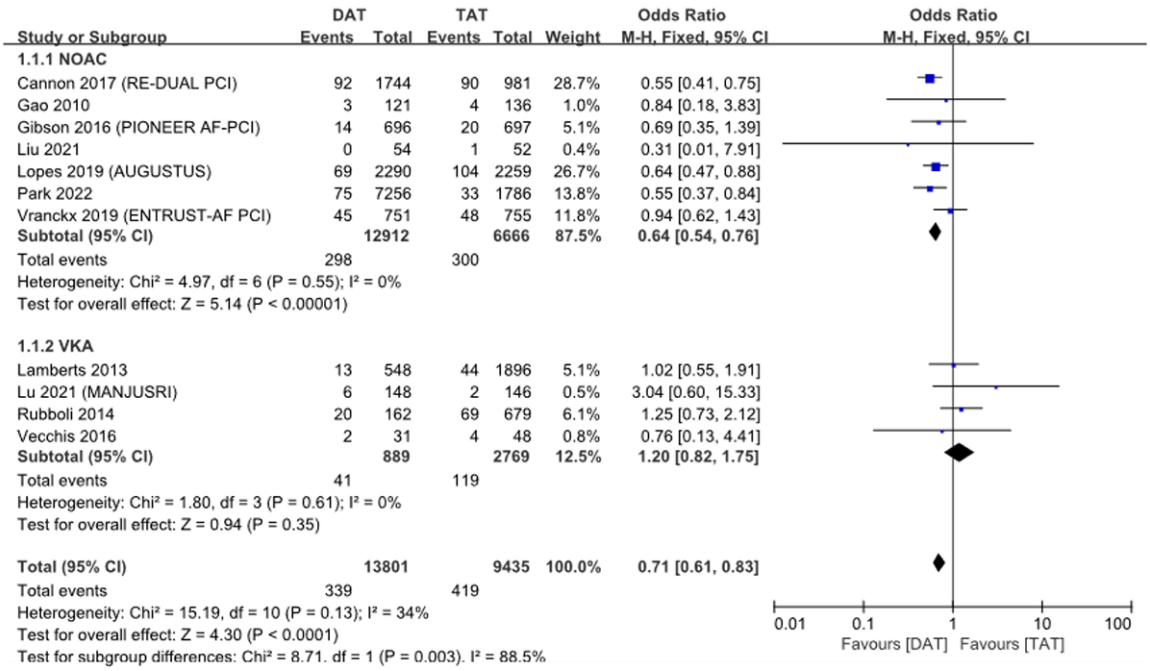

Figure 3. Forest plot for meta-analysis of major bleeding.

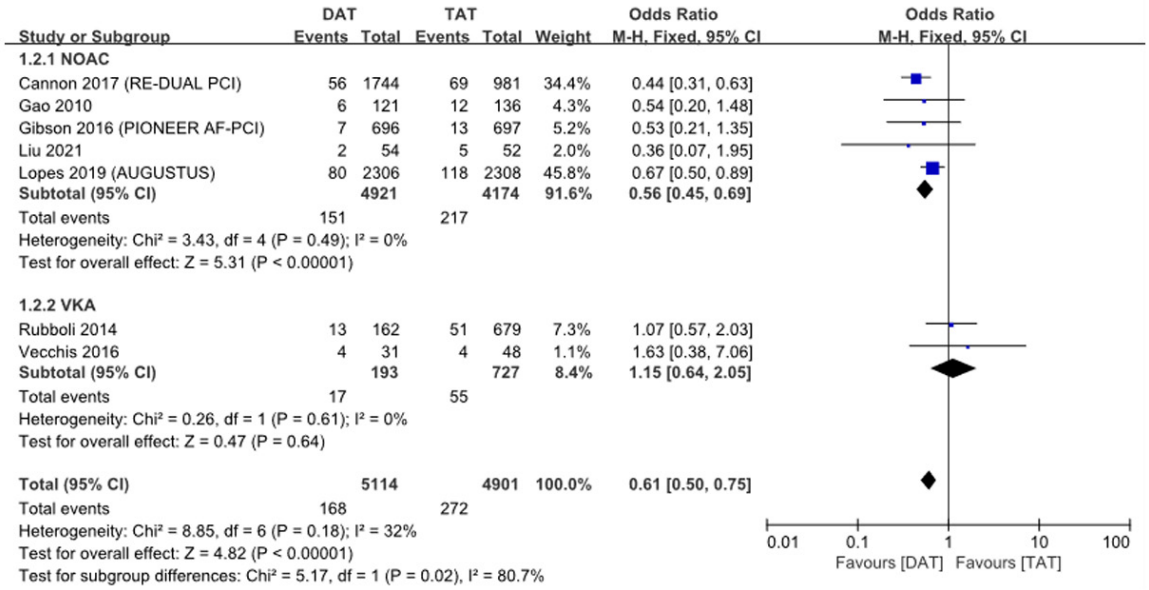

Figure 4. Forest plot for meta-analysis of minor bleeding.

developed stent thrombosis. The total OR indicated that DAT and TAT resulted comparable risk of stent thrombosis (OR=1.12, 95% CI [0.70, 1.74], P=0.61). Subgroup analysis showed that the risk from NOACs (OR=1.12, 95% CI [0.70, 1.79], P=0.65) and VKA (OR=1.17, 95% CI [0.35, 3.98], P=0.80) were similar to that of TAT. There was no significant heterogeneity in the results (P=0.80).

The analysis of stroke incidence is shown in **Figure 8**. The incidence of stroke after DAT and TAT was 0.99% (127/12885) and 1.56% (133/8533), respectively. There was a signifi-

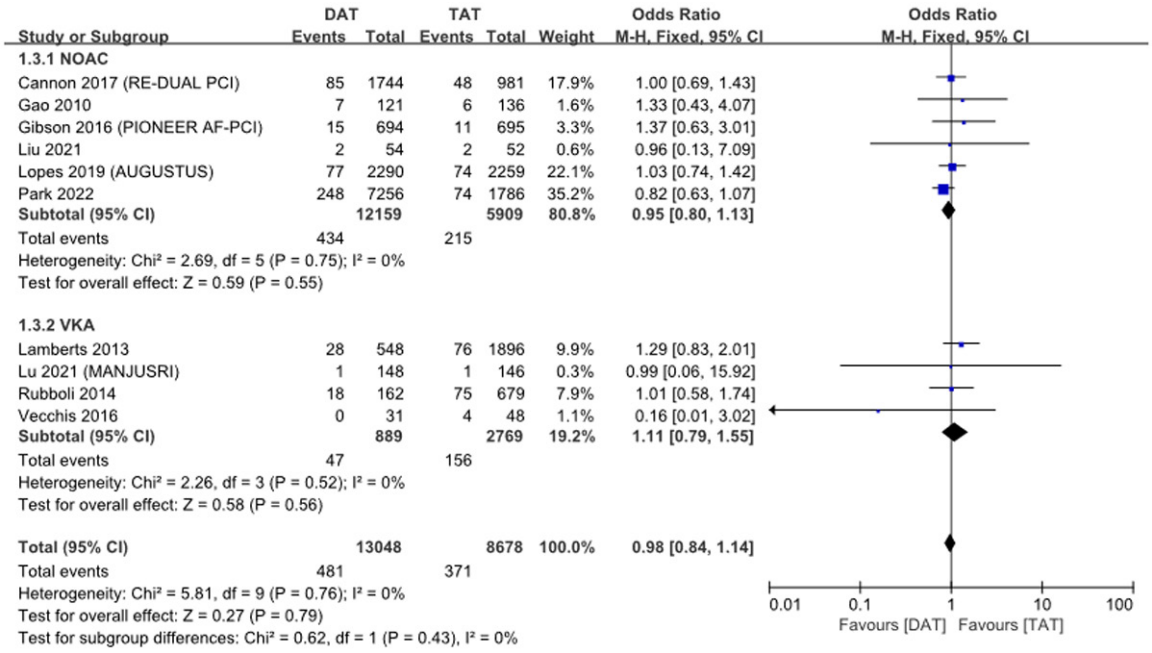

Figure 5. Forest plot for meta-analysis of mortality.

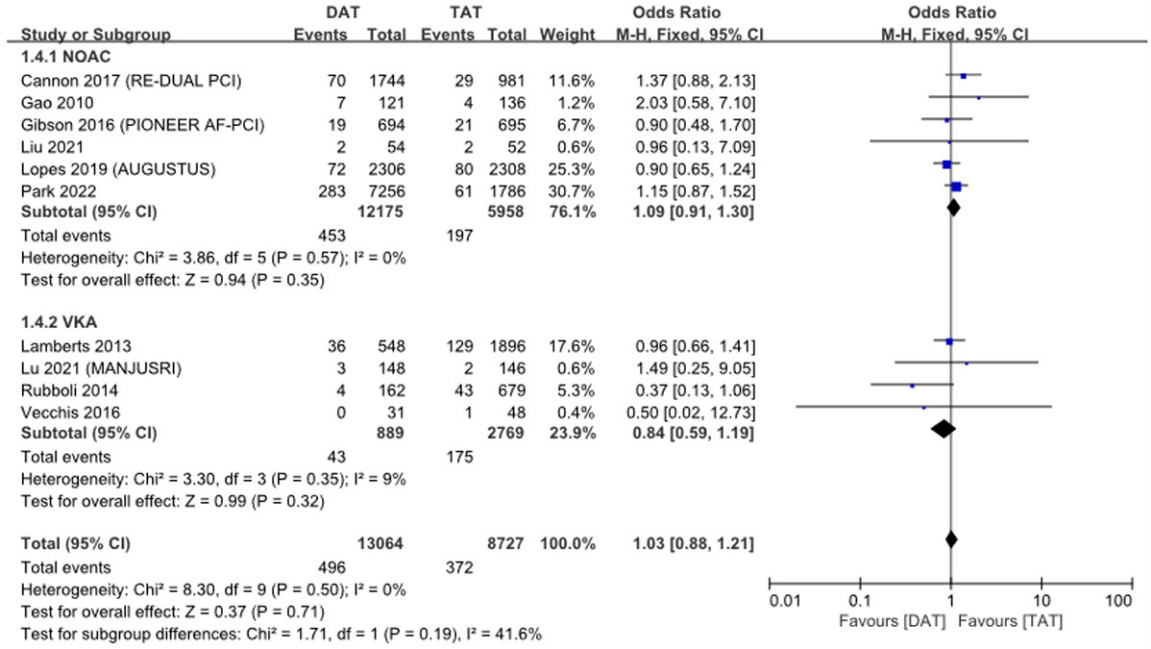

Figure 6. Forest plot for meta-analysis of myocardial infarction.

cant heterogeneity among the studies included when analyzing the risk of stroke (I^2=55%, P=0.02). Subgroup analysis by OAC types showed no significant heterogeneity in TAT and DAT involved in NOACs (I^2=45%, P=0.11), and no significant heterogeneity in TAT and DAT involved in VKA (I^2=0%, P=0.45). There was no significant heterogeneity between DAT with VKA and TAT. It indicates that OAC types may be one of the sources of heterogeneity.

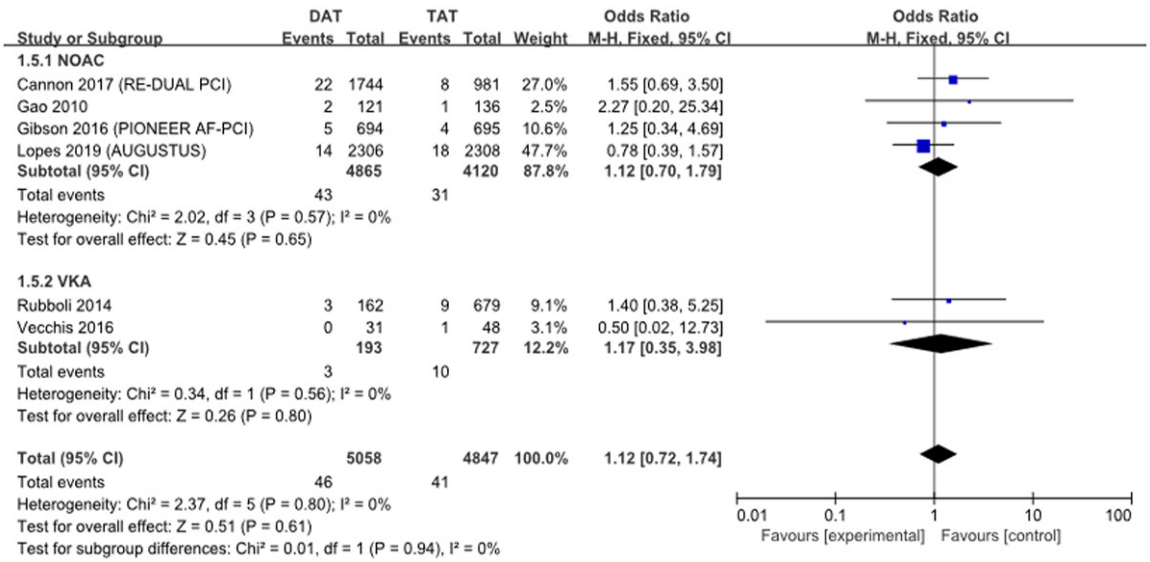

Figure 7. Forest plot for meta-analysis of stent thrombosis.

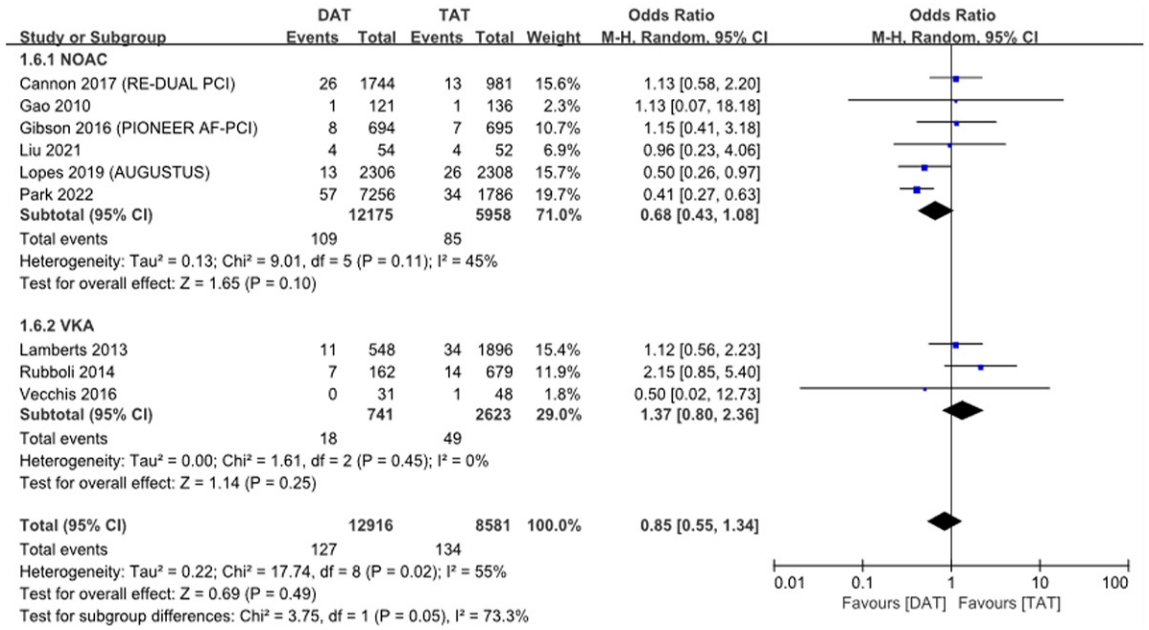

Figure 8. Forest plot for meta-analysis of stroke.

It is generally recommended to make a funnel plot when the number of meta-analysis studies is more than 10. In this study, a funnel plot was made for 11 studies with major bleeding as an indicator. **Figure 9** indicates that there was no publication bias in the included studies.

Sensitivity analysis

According to the assessment of the risk of bias, we excluded the studies with a higher risk of bias and re-conducted the meta-analysis, and found a similar outcome, with a higher safety profile from DAT with NOACs concerning bleeding risk after PCI in patients with AF (**Figure 10**). In DAT, the schemes using VKA and NOACs had similar effectiveness (**Figures 11-13**), and in TAT, the effectiveness was also similar. We found that DAT performed better than TAT in terms of safety, but only when NOACs were used. When VKA was used, its safety was con-

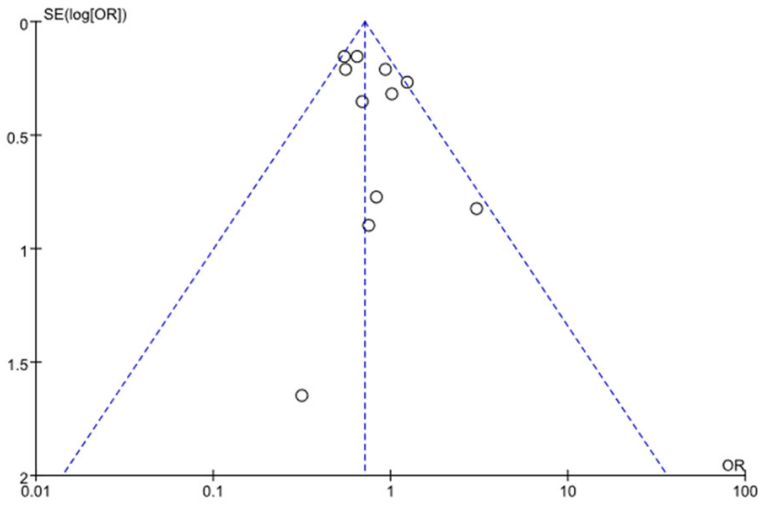

Figure 9. Funnel plot of the included studies.

sistent with TAT. There was no significant difference in effectiveness between the two groups. This is consistent with the main results of our previous analysis.

Discussion

We performed a meta-analysis of combined antithrombotic therapy (DAT and TAT) in patients with CHD and AF after PCI. Our results revealed that in terms of safety, patients receiving DAT with NOACs had significantly lower rates of major and minor bleeding. The safety of DAT with VKA was not significantly different from that of TAT. In terms of efficacy, it was comparable between DAT and TAT in the outcomes of mortality, MI and stent thrombosis.

A previous meta-analysis [7] about the efficacy of VKA pointed out that TAT (ASA + P2Y12i + VKA) significantly reduced the incidence of all-cause mortality, stent thrombosis and stroke in contrast to DAT (ASA + P2Y12i). However, the risk of major bleeding was significantly increased. Subsequent studies [15, 23] performed meta-analyses of P2Y12i combined with OACs and found that the occurrences of major or minor bleeding were significantly declined, but the incidence of mortality, MI, stent thrombosis and stroke were similar, which is consistent with our analysis. We used major bleeding as an outcome measure, including ISTH-defined major bleeding or clinically relevant nonmajor bleeding, intracranial bleeding and TIMI major bleeding. This may overestimate the incidence of bleeding events after receiving different combination regimens. However, our results suggest that DAT has a positive impact on reducing the incidence of major bleeding. These studies have clarified the safety of DAT in antithrombotic therapy for patients with AF after PCI. The reduction in bleeding complications was associated with no use of ASA [24], and this regimen did not increase the incidence of stent thrombosis.

We performed a subgroup analysis to further explore the impact of NOACs versus VKA on outcomes. The results implied that NOACs had a significant effect on reducing the incidence of major and minor bleeding events compared with TAT, while VKA had comparable effects to those of TAT. WOEST trial [25] compared VKA plus clopidogrel with VKA plus clopidogrel and ASA in patients undergoing PCI and suggested that the former significantly reduced the incidence of bleeding events. PIONEER AF-PCI trial [10] also compared rivaroxaban combined with triple therapy and VKA triple therapy. Their results showed that the former had obvious advantages in clinical bleeding, and its effectiveness was comparable to that of VKA triple therapy. Park et al. [21] compared VKA combined with dual antiplatelet therapy (DAPT) and NOAC combined with DAPT triple therapy, and the results of a three-month follow-up inferred that the risk of bleeding was similar between DAT and TAT. However, the long-term prognosis of the treatment cannot be determined due to the short follow-up time. Both the WOEST trial and the PIONEER AF-PCI trial confirmed that NOACs had a significant effect on long-term clinical bleeding. This indicated that NOACs are more suitable than VKA for patients with AF after PCI. However, there is also a review [17] which indicated that although dual therapy was equivalent to triple therapy in terms of mortality, MI, and stroke, it increased the risk of stent thrombosis. Further exploration explained that this may be due to the different criteria for stent thrombosis among the included studies. Therefore, in future trial

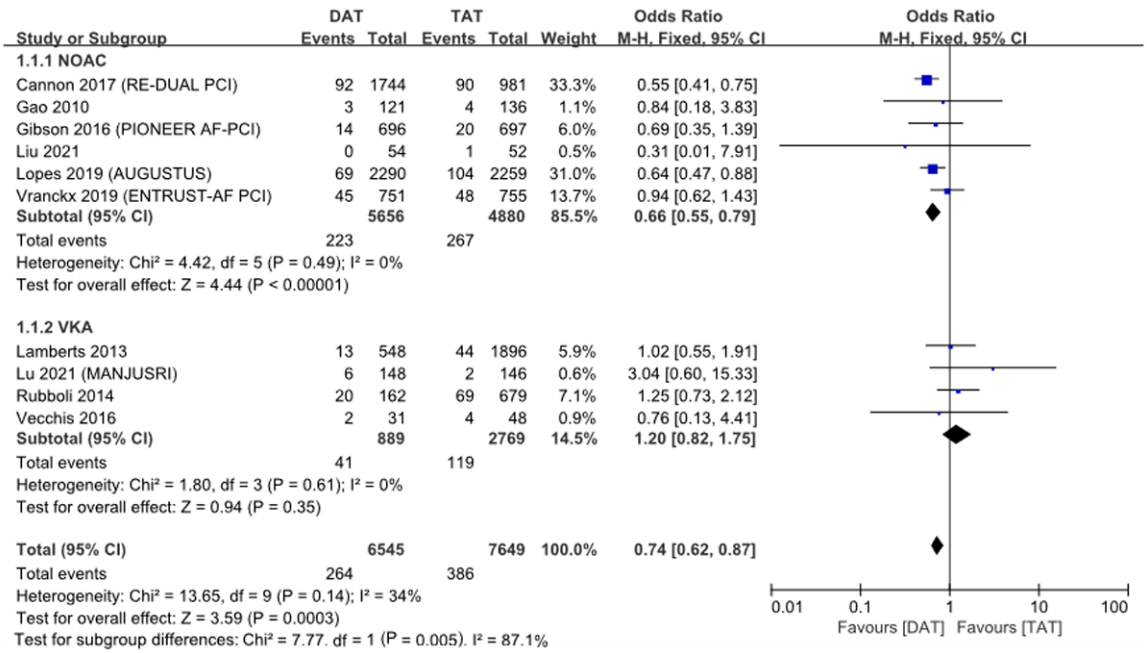

Figure 10. Forest plot for meta-analysis of major bleeding events after excluding studies with high risk of bias.

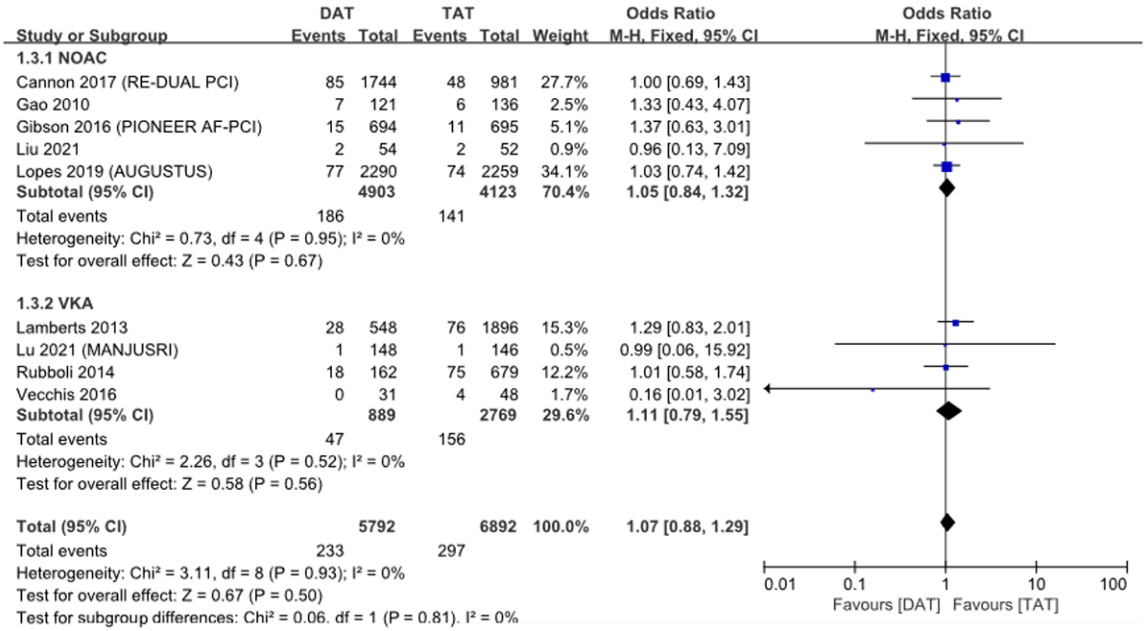

Figure 11. Forest plot for meta-analysis of mortality after excluding studies with high risk of bias.

design, each outcome endpoint event should be clearly defined and the test criteria should be unified according to relevant guidelines. In addition, we did not have data on the duration of drug treatment. The drug use and the duration of use should be determined based on the patient's risk of bleeding, MI and stent thrombosis [26]. In patients at particularly high risk for ischemia, ASA as a primary agent may be needed to prevent atherosclerotic thrombotic events, but this requires a better study design and further investigation. Additional analyses

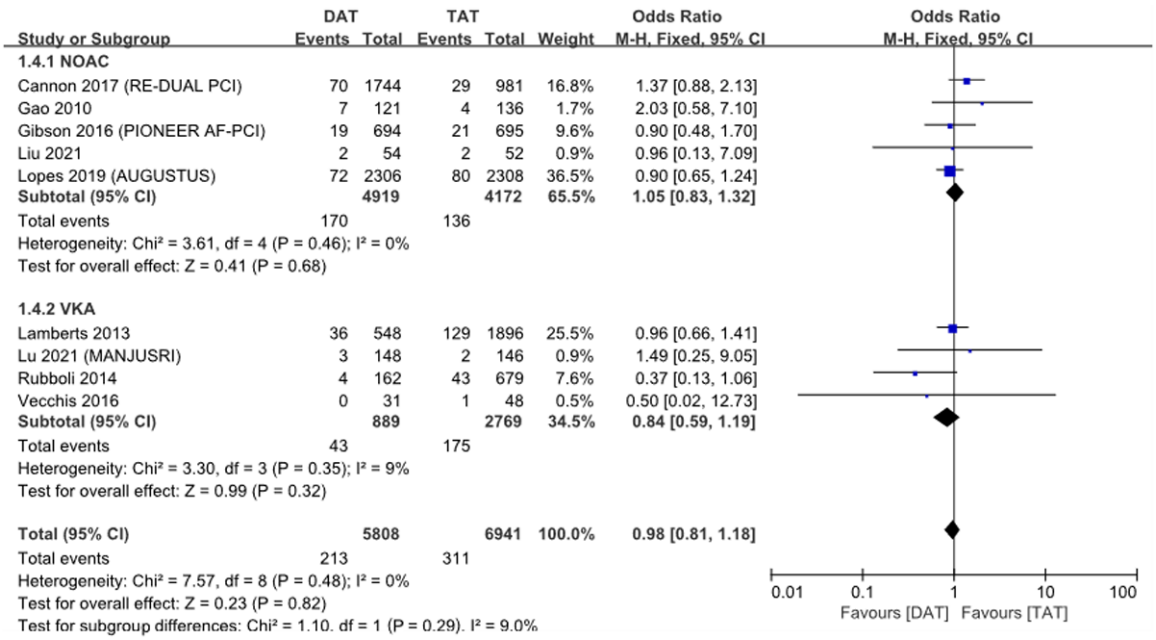

Figure 12. Forest plot for meta-analysis of myocardial infarction after excluding studies with high risk of bias.

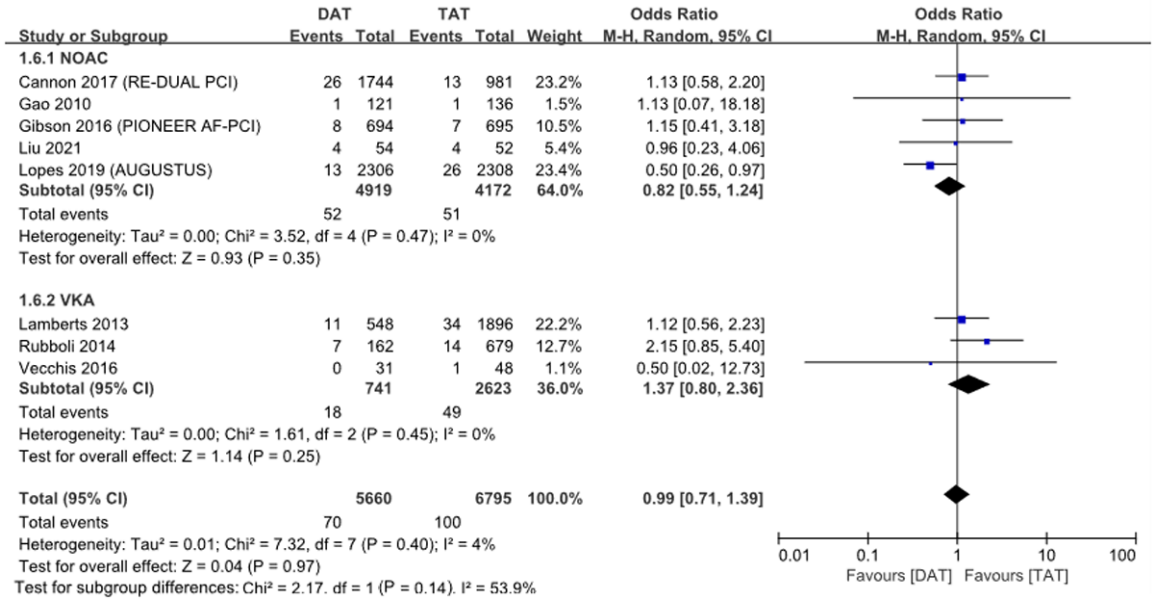

Figure 13. Forest plot for meta-analysis of stroke after excluding studies with high risk of bias.

based on drug use should be conducted in the future analyses to clarify the effect of treatment duration on MACE and bleeding events.

There are some limitations in this study. Firstly, the sample sizes of the included studies vary greatly, and there is an inevitable bias when combining statistics. Secondly, the included studies have different definitions of stroke, which may affect the reliability of the conclusions. Thirdly, the follow-up time and target international normalized ratio varied among studies, which may affect the reliability of the analysis results. Fourthly, our meta-analysis included RCTs and observational studies, which may pose additional risks of bias. Lastly, we

combined two groups of dual therapy with different NOAC dose levels from the RE-DUAL PCI trial into one group for the comparison with TAT. This may lead to biased analysis results. Therefore, more RCTs are needed for further analysis.

In respect to death, MI, stent thrombosis and stroke, DAT resembled TAT, but the risk of bleeding after DAT was lower than that after TAT. In subgroup analysis by OAC types, DAT with NOACs significantly reduced risk of bleeding, but VKA did not. In existing studies, DAT with NOACs has an advantage in reducing the risk of bleeding, but it is not significantly different from TAT in terms of efficacy outcomes. These conclusions proved that DAT with NOAC is a good choice for the patients with CHD and AF. However, large-scale, multicenter, randomized, double-blind and longer follow-up studies are still needed for further validation.

Disclosure of conflict of interest

None.

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