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Original Article

Effectiveness and safety of warfarin and anti-platelet drugs for the primary prevention of stroke in patients with non-valvular atrial fibrillation: a meta-analysis

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Abstract: Objective: To evaluate the effectiveness and safety of warfarin and anti-platelet drugs as the primary approach to the prevention of stroke in patients with non-valvular atrial fibrillation (NVAF). Methods: Three English databases (the Cochrane library, Embase, and Medline), and three Chinese databases (the Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, and Chinese Periodical Full-text Database of Science and Technology) were searched to select potentially eligible studies published before May, 2014. The studies were randomized controlled trials (RCTs) that investigated the effectiveness and safety of using warfarin and anti-platelet drugs in preventing stroke in NVAF patients; The statistical analysis was performed using the Review Manager 5.2 software provided by the Cochrane Collaboration. Results: nine articles were finally included. Compared with antiplatelet drugs, warfarin treatment significantly reduced the risk of stroke (OR = 0.62, 95% CI 0.50-05.77), systemic embolism events (OR = 0.49, 95% CI 0.31-0.77), ischemic stroke events (OR = 0.46, 95% CI 0.36-0.59), stroke-related disability or death events (OR = 0.66, 95% CI 0.52-0.84). Warfarin did not increase the incidence of All-cause death events (OR = 0.92, 95% CI 0.78-1.08), intracranial hemorrhage events (OR = 1.28, 95% CI 0.85-1.93), major hemorrhage events (OR = 1.01, 95% CI 0.79-1.29). Conclusions: This meta-analysis found that compared with antiplatelet drugs, warfarin treatment significantly reduced the risk of stroke, systemic embolism events, ischemic stroke events, stroke-related disability or death events. And warfarin did not increase the incidence of All-cause death events, intracranial hemorrhage events, major hemorrhage events.

Keywords: Atrial fibrillation, stroke, warfarin, anti-platelet drugs

Introduction

Atrial fibrillation (AF), which is a common arrhythmia affecting more than 1% of the population, increases the risk of stroke and other vascular events [1, 2]. According to different classification methods, AF can be divided into different types such as valvular atrial fibrillation (VAF) and non-valvular atrial fibrillation (NVAF); paroxysmal, persistent, and permanent AF; independent AF and AF accompanied by other heart disease. AF has been acknowledged as a risk factor for ischemic stroke, the high disability and mortality rates of which represent a tremendous burden on families and society in general; therefore, preventing stroke in AF patients is very important. Drugs currently used for the prevention of thromboembolism in AF patients include anti-coagulants and anti-platelet drugs. Warfarin, which is similar to the naturally occurring anti-coagulant, dicoumarol, is the most commonly used anti-coagulant drug in clinical practice. Numerous studies have demonstrated the effectiveness of warfarin in treating and preventing stroke; however, the clinical application of warfarin is restricted by several factors including the increased risk of hemorrhage, requirement for close monitoring of the international normalized ratio (INR), and tendency to be affected by multiple drugs and foods. Several novel anti-coagulants have also been developed, although the use of these drugs is also limited by their relatively high prices.

The present meta-analysis of several randomized clinical trials was conducted to systematically investigate the effectiveness and safety of warfarin and anti-platelet drugs as the primary approach to the prevention of stroke in patients with NVAF, and to provide evidence-based information that can be used to determine the most appropriate use of warfarin and anti-platelet drugs in clinical practice.

Materials and methods

Study searches

Three English databases (the Cochrane library, Embase, and Medline), and three Chinese databases (the Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, and Chinese Periodical Full-text Database of Science and Technology) were searched to select potentially eligible studies published before May, 2014. Additional studies were also selected in manual searches. The abstracts of the articles were reviewed carefully to determine compliance with the eligibility criteria. The full-texts of the potentially eligible studies were then further evaluated for compliance with the inclusion and exclusion criteria of the present study.

Inclusion and exclusion criteria

The inclusion criteria of the present study were as follows: 1) the study was a randomized controlled trial that investigated the effectiveness and safety of using warfarin and anti-platelet drugs in preventing stroke in NVAF patients; 2) the subjects in the studies were AF patients (paroxysmal, persistent, or permanent AF) confirmed by electrocardiography (ECG) and with no history of stroke or transient ischemic attack (TIA); and 3) the subjects were treated with anti-coagulant drugs (adjusted dose, INR: 2.0-4.5) and any dose of anti-platelet drugs for > 4 weeks, with a follow-up time was > 1 year.

The exclusion criteria were as follows: 1) not a randomized clinical trial; 2) subjects were with other types of AF, valve disorder-induced AF, or with a defined history of stroke or TIA; 3) fixed-dose of anti-coagulant drugs were used in the study; and 4) warfarin and anti-platelet drugs were used in combination.

Methodological quality appraisal

The full-texts of the eligible articles were reviewed by two investigators independently, and the quality of the articles was then evaluated according to the criteria recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Edition 5.1). In brief, the quality of the articles was appraised for the following aspects: 1) appropriate randomization method; 2) correct allocation concealment; 3) appropriate blinding; 4) completeness of the data; 5) selective reporting of results; and 6) other sources of bias. All six aspects were evaluated as “yes”, “no”, or “unknown”; the risk of bias was evaluated as low, unknown, and high risk.

Endpoints

Effectiveness endpoints: 1) The primary endpoint was stroke events (including ischemic stroke and hemorrhagic stroke) diagnosed according to the clinical presentation and imaging findings (cranial CT or MRI), while cases with only imaging findings but without clinical presentation were not considered as stroke.

2) The secondary endpoints were: a) systemic embolism events, defined as arterial embolism outside nerve system caused by cardiogenic embolus; b) ischemic stroke events, diagnosed according to the clinical presentation and imaging findings (cranial CT or MRI). Ischemic stroke with secondary hemorrhage was also classified as an ischemic stroke event; c) stroke-related disability or death (including ischemic and hemorrhagic stroke). Stroke-related death was defined as death occurring within 30 days of the stroke, with other causes excluded; stroke-related disability was defined as disability caused by stroke, which severely affected the daily lives and caused neurological dysfunction lasting for more than 3 months; and d) all-cause death, defined as death caused by both vascular and non-vascular events.

Safety endpoints: 1) Intracranial hemorrhage events: cranial CT confirmed subdural hematoma, epidural hematoma, intracerebral hemorrhage, and subarachnoid hemorrhage.

2) Major hemorrhage events: see **Table 1**.

Statistical analysis

The statistical analysis was performed using the Review Manager 5.2 software provided by the Cochrane Collaboration. Odds ratios (ORs) and corresponding 95% confidence intervals (Cis) were estimated for the binary variables. I^2

Table 1. The general characteristics of the included studies

Study	Years of follow-up	Interventions	Outcome measures	Definition of major bleeding
AFASKI trial	2	Aspirin 75 mg/d	① Primary outcomes: thromboembolic complication (stroke, TIA, or embolic complications to the viscera and extremities)	Need medical interventions
		Warfarin target INR: 2.8~4.2	② Secondary outcomes: death	
SPAF-II trial	3.1	Aspirin 75 mg/d	① Primary outcomes: ischaemic stroke and systemic embolism	Fatal or life-threatening or requiring surgery or serious blood loss
		Warfarin target INR: 2~4.5	② Secondary outcomes: all strokes with residual functional deficit, vascular death	
AFASAK II trial	3.5	Aspirin 300 mg/d	① Primary outcomes: ischaemic stroke and systemic embolism	Fatal, life-threatening or potentially life-threatening, requiring surgical treatment or blood transfusion
		Warfarin target INR: 2~3.0	② Secondary outcomes: TIA, AMI and death	
PATAF trial	2.7	Aspirin 150 mg/d	① Primary outcomes: stroke,systemic embolism, major bleeding, vascular death	Requiring hospital admission and blood transfusion or causing fall in haemoglobin concentration ≥ 2.0 mmol/L
		Warfarin target INR: 2.5~3.5	② Secondary outcomes: non-fatal myocardial infarction, retinal infarction, TIA, minor bleeding complication, or non-vascular death	
ACTIVE-W trial	1.3	Aspirin 100 mg/d+ clopidogrel 75 mg/d	① Primary outcomes: stroke,non-CNS systemic embolism, myocardial infarction, or vascular death	Any bleeding requiring transfusion of at least two units of red blood cells or equivalent of whole blood, or which was severe (death, drop in haemoglobin of at least 50 g/L, requiring drugs or surgical intervention, or requiring a transfusion of a least 4 units of blood)
		Warfarin target INR: 2~3	② Secondary outcomes: major bleeding events	
BAFTA trial	2.7	Aspirin 75 mg/d	① Primary outcomes: fatal or non-fatal disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage and other clinically significant arterial embolism	A fatal haemorrhage or requiring transfusion or requiring surgery
		Warfarin target INR: 2~3	② Secondary outcomes: major haemorrhage, other vascular events, and all-cause mortality	
Hu Dayi trial	1.6	Aspirin 150~160 mg/d	① Primary outcomes: ischaemic stroke or all-cause death	Fatal ,life-threatening or fatal haemorrhage or requiring transfusion or requiring surgery
		Warfarin target INR: 2~3 (age ≥75 years INR 1.6~2.5)	② Secondary outcomes: systemic embolism, TIA, non-syndrome stroke, AMI, serious bleeding	
WASPO trial	1.0	Aspirin 300 mg/d	① Primary outcomes: death, embolism (stroke, TIA, systemic embolism), serious bleeding	Intracranial haemorrhage, fall in haemoglobin by > 2 g/dl, need for blood transfusion
		warfarin target INR: 2~3.0	② Secondary outcomes: complications, minor bleeding	
CHEN Ke-ping	2	Aspirin 200 mg/d	① Primary outcomes: embolism (ischaemic stroke, TIA or systemic embolism)	Intracranial haemorrhage, fatal bleeding or bleeding requiring a transfusion of a least 4 units of blood
		Warfarin target INR: 2.1~2.5	② Secondary outcomes: all-cause death and bleeding complications	

Table 2. The general characteristics of the included studies

	AFASAK I trial		SPAF IIa trial		SPAF IIb trial		AFASAK II trial		PATAF trial	
	1989 [3]		1994 [4]		1994 [4]		1998 [5]		1999 [6]	
	Warfarin	Aspirin	Warfarin	Aspirin	Warfarin	Aspirin	Warfarin	Aspirin	Warfarin	Aspirin
Number of patients	335	336	358	357	197	188	170	169	131	141
Age (years), average (SD)	72.8 (-)	75.1 (-)	64 (8)		80 (3)		73.2 (7.0)	73.1 (7.2)	70	70.8
Age >75, number (%)	/	/	0 (0)		385 (100)		/	/	/	/
Male, number (%)	176 (53)	184 (55)	543 (76)		227 (59)		97 (57)	110 (65)	58 (44)	67 (48)
hypertension, number (%)	108 (32)	112 (33)	379 (53)		200 (52)		80 (47)	73 (43)	46 (35.1)	53 (37.6)
systolic, average (SD)	/	/	/		/		149.2 (18.3)	147.2 (20.3)	149 (17)	147 (19)
Diabetes melitus, number (%)	25 (7)	26 (8)	122 (17)		50 (13)		23 (14)	17 (10)	25 (19.0)	10 (7.1)
Weight, average (SD), kg	/	/	/		/		/	/	/	/
BMI, average (SD)	/	/	/		/		/	/	78	86
Coronary artery disease, number (%)	/	/	/				/	/	/	/
Myocardial infarction, number (%)	27 (8)	23 (7)	64 (9)		46 (12)		14 (8)	12 (7)	9 (6.9)	15 (10.6)
History of stroke or TIA, number(%)	20 (6)	17 (5)	/		/		14 (8)	14 (8)	/	/
systemic embolism, number (%)	/	/	/		/		/	/	/	/
Atrial fibrillation type, number(%)										
Paroxysmal	/	/	/		/		/	/	35 (26.7)	33 (23.4)
Persistent	/	/	/		/		/	/	/	/
Permanant	/	/	/		/		/	/	/	/
Heart failure, number (%)	168 (50)	183 (54)	122 (17)		100 (26)		119 (70)	119 (70)	/	/
CHADS2 scores, average (SD)	/	/	/		/		/	/	/	/
CHADS2 scores, number (%)	/	/	/		/		/	/	/	/
1-2	/	/	/		/		/	/	/	/
2	/	/	/		/		/	/	/	/
>2	/	/	/		/		/	/	/	/
Drug therapy before, number (%)										
Oral anticoagulants	/	/	/		/		/	/	/	/
Aspirin	/	/	/		/		/	/	/	/
Statins	/	/	/		/		/	/	/	/
Trial quality, Jadad score	5		3		3		3		4	

	ACTIVE-W trial		BAFTA trial		Hu Dayi trial		WASPO trial		CHEN Ke-ping	
	2006 [7]		2007 [8]		2006 [9]		2007 [10]		2012 [11]	
	Warfarin	Aspirin +clopidogrel	Warfarin	Aspirin	Warfarin	Aspirin	Warfarin	Aspirin	Warfarin	Aspirin
Number of patients	3371	3335	488	485	335	369	36	39	239	201
Age (years), average (SD)	70.2 (9.5)	70.2 (9.4)	81.5 (4.3)	81.5 (4.2)	62.6 (10.3)	63.8 (9.7)	83.5	82.6	66.8 (6.9)	67.6 (7.2)

Age >75, number (%)	/	/	488 (100)	485 (100)	/	/	36 (100)	39 (100)	22 (9.2)	2 (14.4)
Male, number (%)	2211 (66)	2219 (67)	267 (55)	264 (54)	/	/	14 (39)	21 (54)	151 (63.2)	119 (59.2)
hypertension, number (%)	2767 (82)	2755 (83)	259 (53)	268 (55)	/	/	17 (49)	18 (46)	141 (59.0)	133 (66.2)
systolic, average (SD)	133 (18.8)	133 (19.1)	139.9 (19.2)	141.3 (19.9)	/	/	/	/	/	/
Diabetes melitus, number (%)	717 (21)	712 (21)	68 (14)	61 (13)	/	/	1 (3)	2 (5)	29 (12.1)	30 (14.9)
Weight, average (SD), kg	/	/	/	/	/	/	/	/	/	/
BMI, average (SD)	28.7 (5.0)	28.9 (4.9)	/	/	/	/	/	/	/	/
Coronary artery disease, number (%)	1259 (38)	1207 (36)	/	/	/	/	4 (11)	11 (28)	/	/
Myocardial infarction, number (%)	591 (18)	573 (17)	47 (10)	56 (12)	/	/	/	/	13 (5.4)	6 (3.0)
History of stroke or TIA, number (%)	510 (15)	510 (15)	64 (13)	60 (12)	/	/	/	/	50 (20.9)	31 (15.4)
systemic embolism, number (%)	/	/	/	/	/	/	/	/	4 (1.7)	0 (0)
Atrial fibrillation type, number (%)										
Paroxysmal	594 (18)	605 (18)	/	/	0	0	/	/	/	/
Persistent	468 (14)	426 (13)	/	/	335	369	/	/	/	/
Permanent	2305 (68)	2300 (69)	/	/	0	0	36	39	167 (71.7)	181 (72.2)
Heart failure, number (%)	1040 (31)	991 (30)	96 (20)	94 (19)	/	/	/	/	147 (62.6)	132 (67.0)
CHADS2 scores, average (SD)	2.0 (1.1)	2.0 (1.1)	/	/	/	/		/	/	/
CHADS2 scores, number (%)			/	/						
1-2	/	/	349 (72)	349 (72)	/	/	/	/	/	/
2	/	/	/	/	/	/	/	/	/	/
>2	/	/	139 (28)	136 (28)	/	/	/	/	/	/
Drug therapy before, number (%)										
Oral anticoagulants	2627 (78)	2526 (76)	194 (40)	187 (39)	/	/	/	/	/	/
Aspirin	884 (26)	1005 (30)	203 (42)	204 (42)	/	/	/	/	/	/
Statins	1254 (37)	1281 (38)	/	/	/		/	/	/	/
Trial quality, Jadad score	3		3		2		5		3	3

Table 3. The methodological quality of the included studies

	Randomization method	Allocation concealment	Blinding	Data completeness	Selective data reporting	Other sources of bias	Grade
AFASKI trial	Computer generated randomization	Perfect	Double-blind	Complete	No	Unclear	Low bias risk
SPAF-II trial	Computer generated randomization	Unclear	Unclear	Complete	No	Unclear	Unclear bias risk
AFASAK II trial	Computer generated randomization	Not mentioned	No blinding	Complete	No	Yes	Unclear bias risk
PATAF trial	Computer generated randomization	Perfect	Double-blind	Complete	No	No	Low bias risk
ACTIVE-W trial	Not mentioned	Not mentioned	Single-blind	Complete	No	Yes	Unclear bias risk
BAFTA trial	Computer generated randomization	Perfect	Single-blind	Complete	No	No	Low bias risk
Hu Dayi trial	Blocked randomization	Not mentioned	Not mentioned	Complete	No	No	Unclear bias risk
WASPO trial	Computer generated randomization	Perfect	Open	Complete	No	No	Unclear bias risk
CHEN Ke-ping	Stratified block randomization	Not mentioned	Not mentioned	Complete	No	No	Unclear bias risk

was calculated to evaluate the heterogeneity among studies. In the case of studies without statistical heterogeneity ($P > 0.05$, $I^2 < 50\%$), the ORs and 95% CIs were estimated using the fixed-effect model; otherwise ($P < 0.05$, $I^2 > 50\%$), the ORs were obtained using the random-effect model. Forest plots were also drawn. As the risk of bias in the included articles was uncertain, sensitivity analysis was also performed.

Sensitivity analysis

Sensitivity analysis was performed by switching the meta-analysis with the fixed-effect model and random-effect model.

Publication bias analysis

Funnel plots were drawn for each endpoint to evaluate the publication bias.

Results

General characteristics of the studies

In total, 1,168 articles were retrieved through literature searches. The titles and abstracts of these articles were reviewed independently by two investigators to exclude the unrelated articles, leaving 19 articles. After further evaluating the articles according to the inclusion and exclusion criteria, nine articles (8 in English and 1 in Chinese) were finally included. Aspirin was the anti-platelet drug used in all but one study, which use a combination of aspirin and clopidogrel. The general characteristics of the included studies (AFASKI trial [3], SPAF-II trial [4], AFASAK II trial [5], PATAF trial [6], ACTIVE-W trial [7], BAFTA trial [8], Hu Dayi trial [9], WASPO trial [10], CHEN Ke-ping [11]) are shown in **Tables 1** and **2**.

Methodological quality appraisal of the included studies: see **Table 3**.

Effectiveness evaluation

Primary endpoint: stroke events (including ischemic and hemorrhagic stroke): Among the 10 clinical trials included, seven reported the data for stroke events. The pooled OR was 0.62 (95% CI: 0.50-05.77), heterogeneity analysis showed that the I^2 was 0% ($P = 0.47$), it meant this study without statistical heterogeneity. It was estimated using the fixed-effect model; And the pooled effects analysis showed that the Z-value was 4.32 ($P < 0.0001$), suggesting that warfarin treatment significantly reduced the risk of stroke in NVAF patients. Among the 5,009 patients treated with warfarin, 137 developed stroke events (incidence, 2.73%), while among the 5,012 patients treated with anti-platelet drugs, 218 developed stroke events (incidence, 4.34%). These data suggested that, compared with anti-platelet drug treatment, warfarin prevented stroke events in an additional 1.6% of patients with NVAF (**Figure 1**).

Secondary endpoints: 1) Systemic embolism events: A total of 83 cases of systemic embolism events were reported in the 11,280 subjects, including embolisms in the arteries of the extremities, and the mesenteric, renal artery, and retinal arteries. The pooled OR was 0.49 (95% CI: 0.31-0.77), heterogeneity analysis showed that the I^2 was 0% ($P = 0.56$), it meant this study without statistical heterogeneity. It was estimated using the fixed-effect model. And the pooled effects analysis showed that the Z-value was 3.11 ($P = 0.002$), suggesting that there was a significant difference between the two groups. In addition, 26 cases of sys-

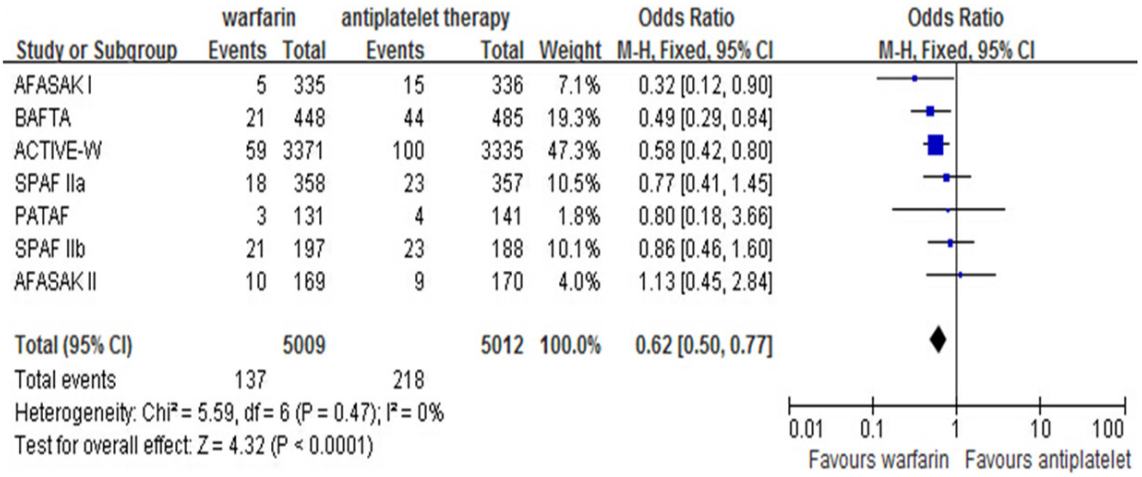

Figure 1. The primary endpoint: stroke events (including ischemic and hemorrhagic stroke).

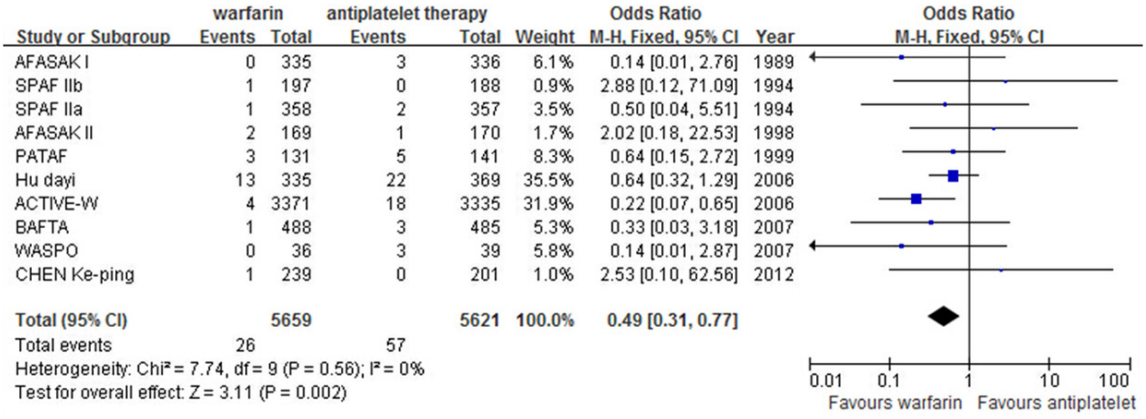

Figure 2. Secondary endpoint: systemic embolism events.

temic embolism events occurred in the 5,659 patients treated with warfarin (incidence, 0.45%), and 57 cases of systemic embolism events occurred in the 5621 patients treated with anti-platelet drugs (incidence, 1.01%). These data suggested that, compared with anti-platelet drug treatment, warfarin prevented systemic embolism events in an additional five patients in every 1,000 with NVAF (**Figure 2**).

2) Ischemic stroke events: The pooled OR for ischemic stroke events was 0.46 (95% CI: 0.36-0.59), heterogeneity analysis showed that the I^2 was 0% (P = 0.61), it meant this study without statistical heterogeneity. It was estimated using the fixed-effect model. And the pooled effects analysis showed that the Z-value was 6.13 (P < 0.00001), suggesting that there was a significant difference between the two groups. Among the 5,659 patients treated with warfarin, there were 95 cases of ischemic stroke events (incidence, 1.68%), and 200 cases of ischemic stroke events among the 5,621 patients treated with anti-platelet drugs (incidence, 3.56%). These data suggested that, compared with anti-platelet drug treatment, warfarin prevented ischemic stroke events in an additional 19 patients in every 1,000 with NVAF (**Figure 3**).

3) Stroke-related disability or death events: The pooled results showed that, compared with the NVAF patients treated with anti-platelet drugs, the incidence of stroke-related disability/death events was significantly lower in those treated

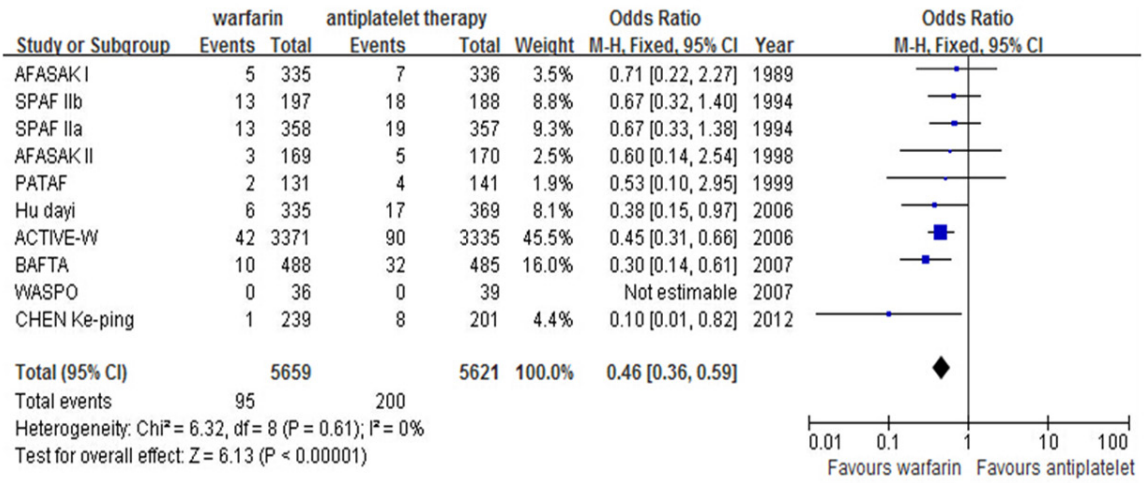

Figure 3. Secondary endpoint: ischemic stroke events.

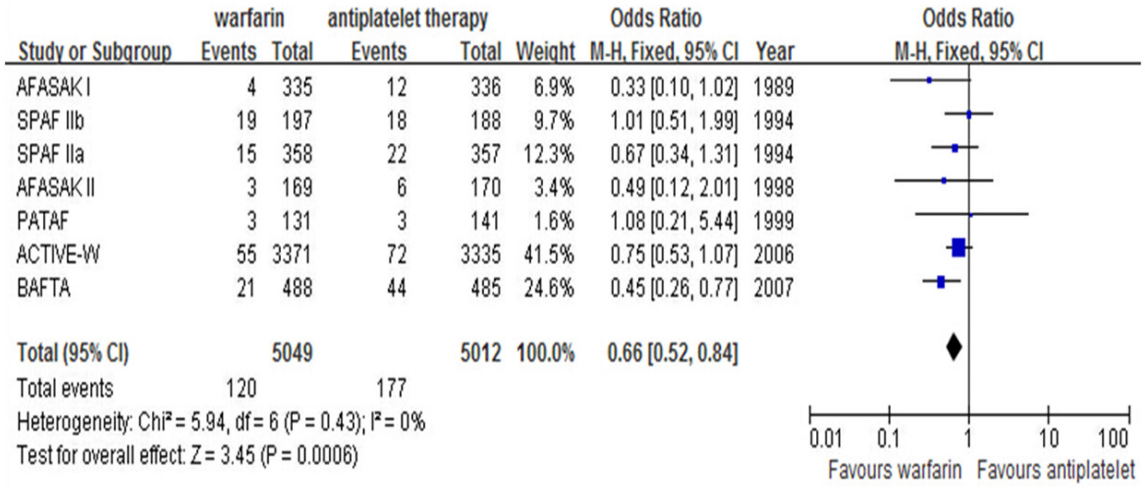

Figure 4. Secondary endpoint: stroke-related disability or death events.

with warfarin. The pooled OR was 0.66 (95% CI: 0.52-0.84); heterogeneity analysis showed that the I^2 was 0% (P = 0.43), it meant this study without statistical heterogeneity. It was estimated using the fixed-effect model. And the pooled effects analysis showed that the Z-value was 3.45 (P = 0.0006). The results showed that 120 cases of stroke-related disability or death events occurred in the 5,049 patients treated with warfarin (incidence, 2.38%), and 177 cases of ischemic stroke events occurred in the 5,012 patients treated with anti-platelet drugs (incidence, 3.53%). These data suggested that, compared with the with anti-platelet drug treatment, warfarin prevented stroke-related disability or death events in an additional 11 patients in every 1,000 with NVAF (**Figure 4**).

4) All-cause death events: Of the 10,609 cases treated, a total of 643 patients died. Of these, 310 deaths were among the 5,324 patients treated with warfarin (incidence, 5.82%), while 333 were among the 5,282 patients treated with anti-platelet drugs (incidence, 6.3%); the difference between these two groups was not statistically significant. The pooled OR was 0.92 (95% CI: 0.78-1.08), heterogeneity analysis showed that I^2 was 0% (P = 0.97), it meant this study without statistical heterogeneity. It was estimated using the fixed-effect model.

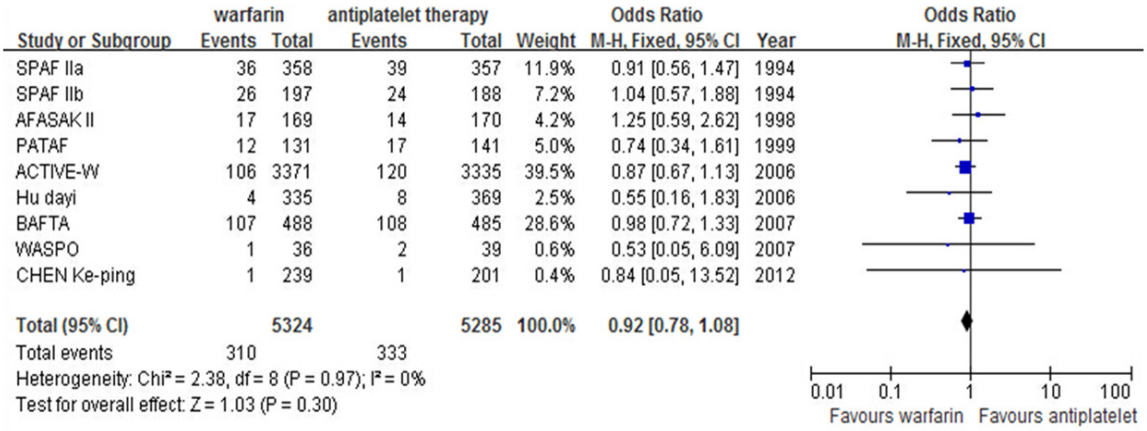

Figure 5. Secondary endpoint: All-cause death events.

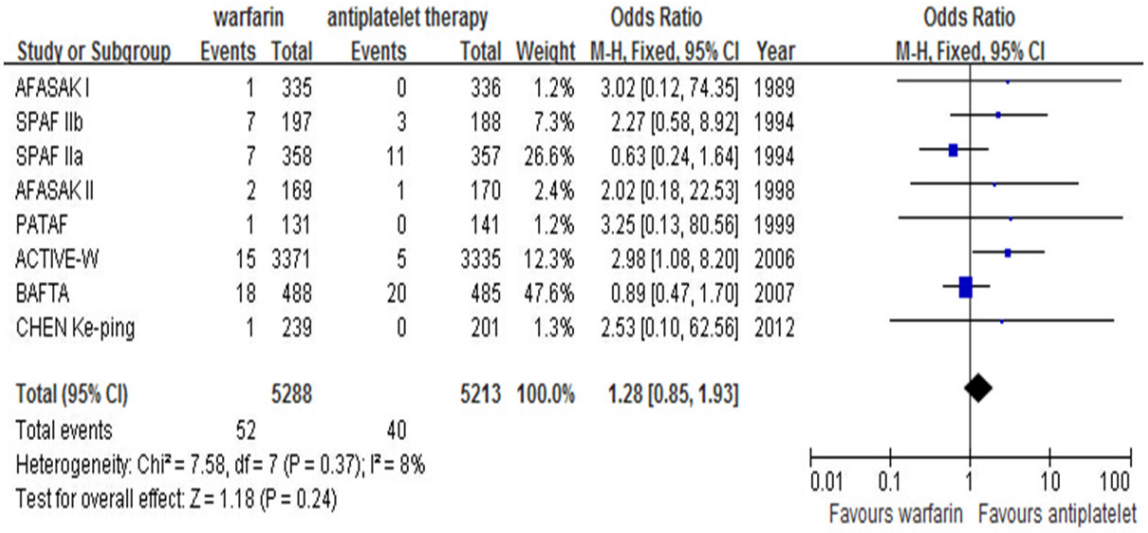

Figure 6. Safety evaluation: intracranial hemorrhage events.

And the pooled effects analysis showed that the Z-value was 1.03 (P = 0.30) (**Figure 5**).

Safety evaluation

Intracranial hemorrhage events: Intracranial hemorrhage events included cranial CT confirmed subdural hematoma, epidural hematoma, intracerebral hemorrhage, and subarachnoid hemorrhage. In the pooled analysis, the OR was 1.28 (95% CI: 0.85-1.93), heterogeneity analysis showed that the I^2 was 8% (P = 0.37), it meant this study without statistical heterogeneity. It was estimated using the fixed-effect model. And the pooled effects analysis showed that the Z-value was 1.18 (P = 0.24); the difference between the two groups was not statistically significant. These data indicated that, compared with anti-platelet drug treatment, warfarin did not increase the incidence of intracranial hemorrhage events (**Figure 6**).

Major hemorrhage events: The pooled OR for major hemorrhage events was 1.01 (95% CI: 0.79-1.29), heterogeneity analysis showed that the I^2 was 26% (P = 0.24), it meant this study without statistical heterogeneity. It was estimated using the fixed-effect model. And the pooled effects analysis showed that the Z-value was 0.09 (P = 0.93); the difference between the two groups was not statistically significant. These data suggested that, compared with anti-platelet drug treatment, warfarin did not

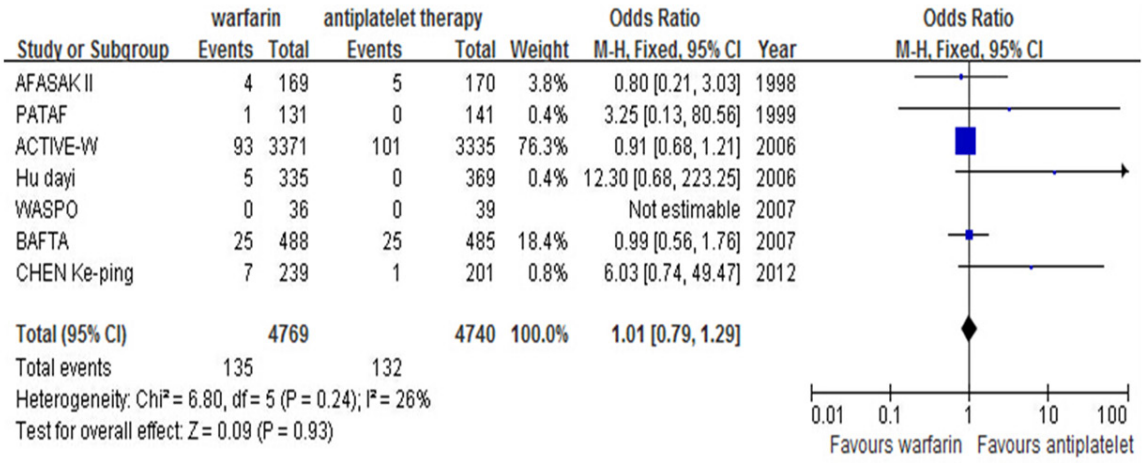

Figure 7. Safety evaluation: major hemorrhage events.

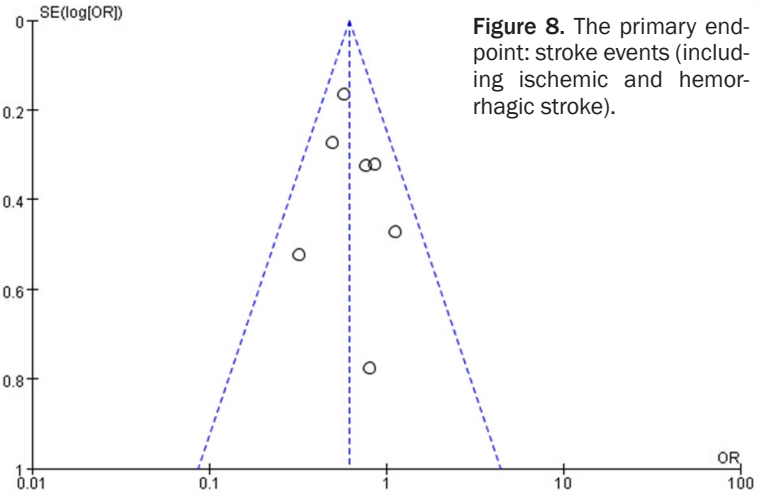

Figure 8. The primary endpoint: stroke events (including ischemic and hemorrhagic stroke).

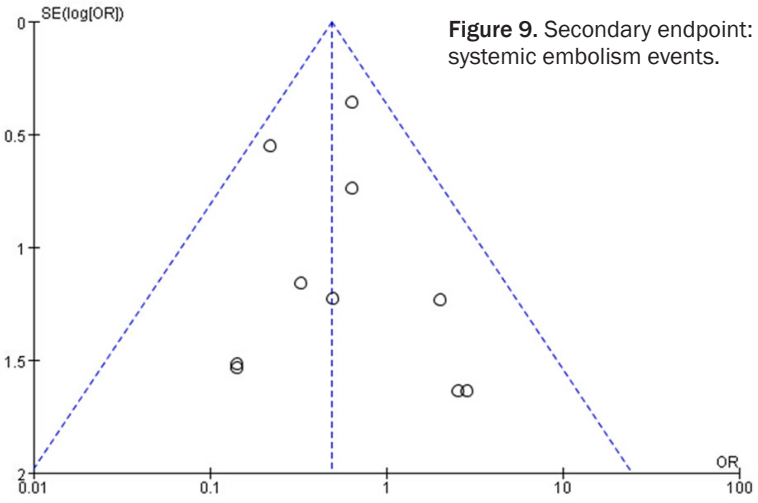

Figure 9. Secondary endpoint: systemic embolism events.

increase the incidence of major hemorrhage events (**Figure 7**).

Sensitivity analysis

Results of the analysis of the parameters using the random-effect model were in accordance with those using fixed-effect model, suggesting that the results were stable.

Publication bias analysis

The funnel plots for each of the parameters were symmetric, suggesting no sign of publication bias (**Figures 8-14**).

Discussion

Oral anti-coagulants are still the drugs of choice for treating patients at high risk of stroke [12], with a 45% decrease in the risk of stroke in AF patients compared with those treated with aspirin [13]. Previous studies have shown that there is no significant difference in the risk of ischemic stroke among patients with the three types of AF (paroxysmal, persistent, and permanent) [14]. In recent years, the incidence of NVAF has increased substantially and ischemic stroke induced by NVAF accounts for 15%-20% of all ischemic strokes. Anti-coagulant drugs are also

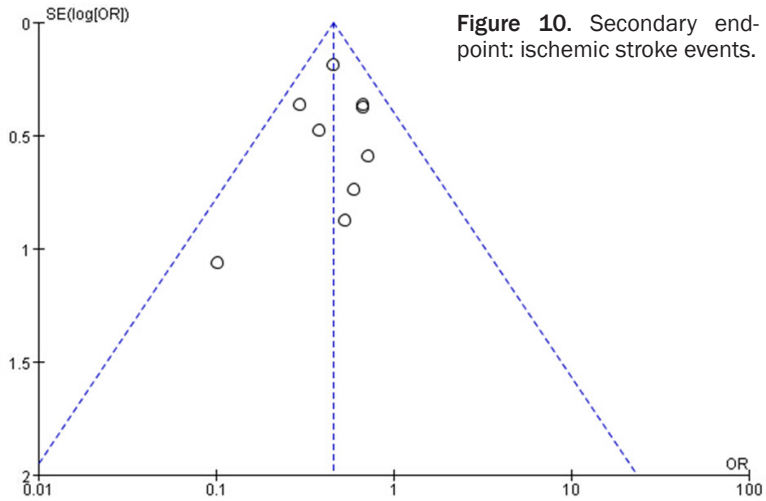

Figure 10. Secondary endpoint: ischemic stroke events.

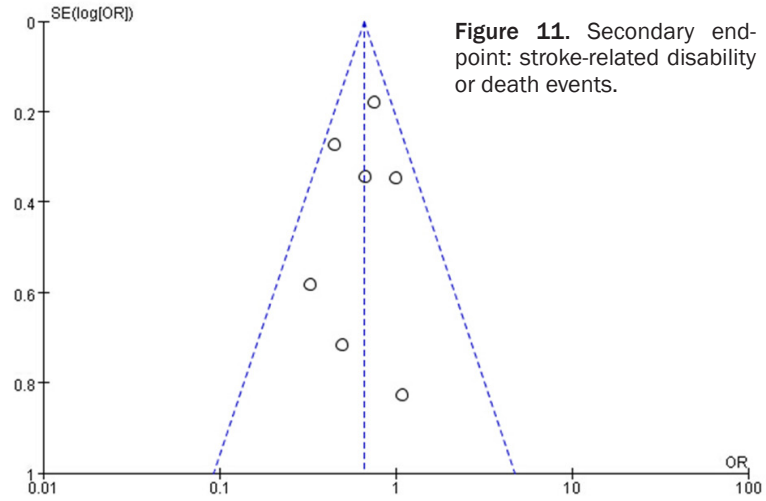

Figure 11. Secondary endpoint: stroke-related disability or death events.

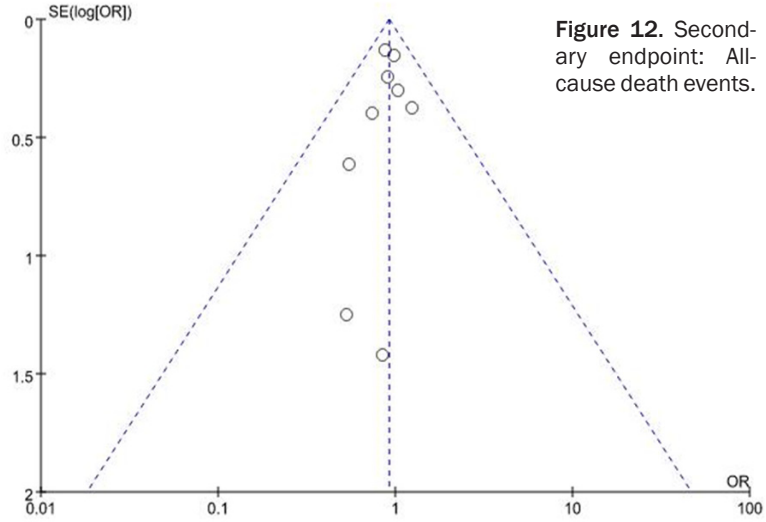

Figure 12. Secondary endpoint: All-cause death events.

effective for the prevention of stroke in patients with NVAF; however, only a small proportion of NVAF patients have rheumatic heart disease, and there are also several difficulties with regard to the methodological aspects; therefore, only patients with NVAF (AF patients with no rheumatic heart disease, artificial valve replacement, or history of valve repair) were included in the present study.

In the effectiveness evaluation, the analyses of the primary endpoint (stroke events) and the secondary endpoints (systemic embolism events, ischemic stroke events, and stroke-related disability or death events) revealed significantly lower risk in the warfarin treatment group than that in the anti-platelet drug treatment group. Current opinion suggests that stroke and non-central nervous system embolism events in AF patients are caused predominantly by cardiac thrombosis, while platelet activation is not a major pathway in the pathogenesis of stroke in AF patients. This indicates that treatment with oral anti-coagulant drugs that target left atrial thrombosis could be more effective. In the PATAF study, the investigators compared the effectiveness of standard doses of anti-coagulant drugs and aspirin in the general population and found no benefits in terms of stroke, systematic embolism, and vascular deaths. It can be speculated that this is associated with the relatively small sample size and the fact that the majority of patients included had advanced disease. Hart found that anti-platelet drugs reduced the incidence of stroke in AF patients without a history of stroke or TIA, while oral anti-coagulant drugs conferred relatively fewer benefits due to more

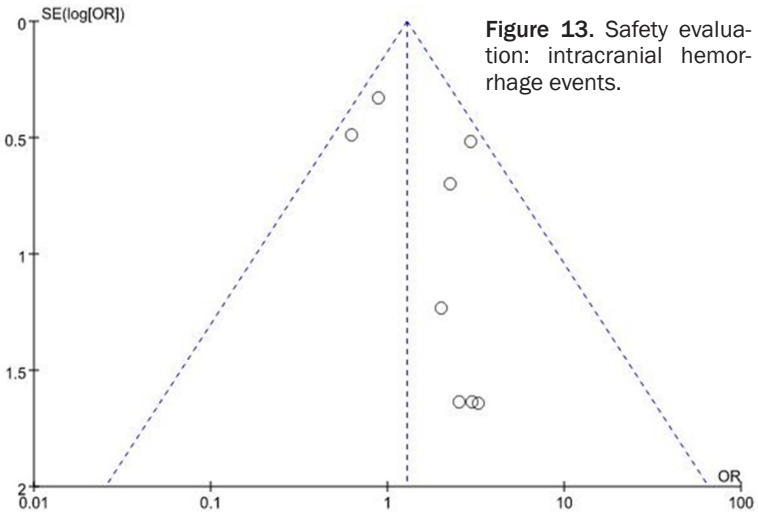

Figure 13. Safety evaluation: intracranial hemorrhage events.

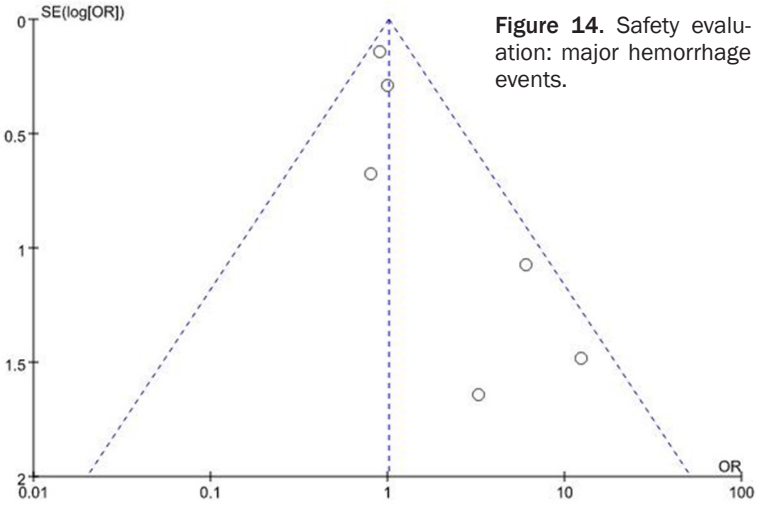

Figure 14. Safety evaluation: major hemorrhage events.

frequent complications [15]. These studies revealed a significant difference in the risk of stroke among individual AF patients, and therefore, differences in the benefits of antithrombotic therapies for such patients. Consequently, AF patients are generally stratified according to the risk of stroke in clinical practice. The most commonly used classification method is the CHA2DS2-VASc scoring system defined by the ACC/AHA/ESC in 2011, which recommends the use of anti-platelet drugs for patients at low risk of stroke (score = 0), anti-coagulant drugs for the patients at high risk (score ≥ 2), and anti-platelet or anti-coagulant drugs for patients with moderate risks (score = 1) [16]. The findings of the present study showed that, compared with anti-platelet drugs, warfarin significantly reduced the incidence of stroke and systematic embolism events; however, the mortality rate in these two groups was comparable. The ACTIVE-W study suggested that this result could be caused by the use of warfarin mainly to reduce the incidence of minor stroke, while warfarin had less effect on the incidence of more severe stroke or death events.

A meta-analysis performed by Aguilar in 2006 [17] showed that anti-coagulants were more effective in the prevention of stroke in NVAF patients than anti-platelet drugs; however, the pooled analysis for safety evaluation was not performed due to substantial heterogeneity among the included studies. In the present study, the results of the safety evaluation showed no significant differences with regard to intracranial or major hemorrhage events between the two groups. Hemorrhagic complications are relatively common during anti-coagulation therapy. Warfarin-induced hemorrhagic complications are associated with many factors including the regularity of drug intake, sensitivity to warfarin, severity of hypertension, comorbidities, and combined drug use. In particular, the anti-coagulation intensity is a highly important factor that can affect the risk of hemorrhagic complications. Previous studies have shown a substantially increased risk of intracranial hemorrhage in the patients with INR > 4 [18]. Hu [19] found that the incidence of severe hemorrhage was significantly higher in the warfarin treatment group than that in the aspirin treatment group (5 cases vs. 0 cases, $P < 0.05$); however, the INR exceeded 3.0 in all five cases with severe hemorrhage in the warfarin treatment group (including INR of 3.85, 4.89, and 5.76 in 3 cases). Furthermore, the overall incidence of hemorrhage was only 1.5%, which was in accordance with other studies [19]. In contrast, the SPAF-II study showed that, even

for patients with similar anti-coagulation intensity, the risk of major hemorrhage among patients treated with warfarin was significantly higher in the SPAF IIb group (age > 75 years) than that in the SPAF IIa group (age ≤ 75 years) (P = 0.008). The risk of thromboembolism was also higher in the SPAF IIb group (4.8% per year) than that in the SPAF IIa group and the results also showed that warfarin treatment was more effective in preventing ischemic stroke in older patients. Therefore, safety issues should be considered when performing anti-coagulation therapy in elderly people. The results of the BAFTA study conducted exclusively NVAF patients aged > 75 years showed that the risk of major hemorrhage was similar among those treated with warfarin or aspirin, which could be associated with the fact that 40% of the patients in the warfarin treatment group had been treated with warfarin prior to enrollment. The warfarin-related risk was actually higher for warfarin-naive patients than that for the patients who had been treated with warfarin previously. The investigators speculated that this could be due to better patient compliance, leading to improved INR control, among those treated with warfarin previously compared with the warfarin-naive patients. Similarly, 77% of the patients included in the ACTIVE-W trial had previously received warfarin treatment prior to enrollment. The annual risk of major hemorrhage was 2.0% in these patients after they had been randomly assigned into the warfarin treatment group, while for the warfarin-naive patients assigned to the warfarin treatment group, the risk of major hemorrhage was 2.9%.

Novel oral anti-coagulant drugs associated with several advantages including the absence of a requirement for INR monitoring and fewer interactions with food or other drugs are increasingly being used in clinical practice; however, these drugs are generally expensive, and no standardized monitoring method is currently available. Furthermore, since these drugs have been marketed for a relatively short period, continued monitoring is required to accumulate sufficient clinical safety evidence. Consequently, warfarin remains the most commonly used oral anti-coagulant drug to date. The present study involved a meta-analysis including the latest relevant studies to investigate the effectiveness and safety of using warfarin and antiplatelet treatments in preventing stroke in NVAF patients and to provide evidence to improve guidance for clinical drug use.

Disclosure of conflict of interest

None.

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