ORIGINAL ARTICLE

Safety of anticoagulant therapy for patients with atrial fibrillation: a systematic review and meta-analysis

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Background. **Anticoagulants are recommended in patients with atrial fibrillation (AF). However, many patients chose antiplatelet therapy or did not take any therapy owing to bleeding risk. Major bleeding events (MBE) can be the origin of poor prognosis. *Objectives.* We sought to explore the safety of anticoagulants by analyzing the differences of the incidence of MBE and vascular death events (VDE) in patients with AF. Methods. Three databases were searched from inception to November 30, 2017. Fifteen randomized controlled trials (RCTs) were included in this study. *Results.* Compared with placebo (risk ratio [RR] 1.95, 95% confidence interval [CI] 0.87-4.38, p = 0.11), although warfarin increased the risk of bleeding events (warfarin vs aspirin: RR 1.86, 95% CI 1.30-2.65, p = 0.0006), the risk was not higher with greater treatment intensity. In addition, warfarin did not increase the risks in MBE (warfarin vs aspirin: RR 1.08, 95% CI 0.71-1.64, p = 0.72; warfarin vs placebo RR 2.27, 95% CI 0.84-6.15, p = 0.11). Moreover, a significantly decreased risks of VDE were shown in the standard plus high intensity warfarin group (warfarin vs aspirin: RR 0.44, 95% CI 0.25-0.76, p = 0.004; warfarin vs placebo: RR 0.30, 95% CI 0.13-0.71, p = 0.005). Only one study demonstrated that compared with aspirin, apixaban did not rise the incidence of MBE (p=0.57) and it had a decreased mortality trend (P=0.07). *Conclusions.* It is safe to use anticoagulants in patients with AF. In addition, the warfarin dose should not be too conservative.**

Key words: **Aspirin; Hemorrhage; Meta-Analysis; Mortality; Oral anticoagulation; Warfarin.**

Antecedentes. **Los anticoagulantes se recomiendan en pacientes con fibrilación auricular. Sin embargo, muchos pacientes prefieren perapia antiplaquetaria o ninguna debido al riesfo de sangrado mayor. Los eventos de sangrado mayor (SM) pueden ser el origen de un mal pronóstico. *Objetivos.* Buscamos explorar la seguridad de los anticoagulantes analizando las diferencias en la incidencia de SM y eventos vasculares mortales (EVM) en pacientes con FA. *Métodos.* Tres bases de datos fueron investigadas desde el inicio hasta Noviembre 30, 2017. Quince estudios controlados randomizados se incluyerin en este estudio. *Resultados.* Comparada con placebo, (risk ratio [RR] 1.95, 95% intervalo de confianza [IC] 0.87-4.38, p = 0.11), aunque la warfarina incrementó el riesgo de sangrado (warfarin vs aspirin: RR 1.86, 95% CI 1.30-2.65, p = 0.0006), el riesgo no aumentó con el aumento en la intensidad del tratamiento. Además, la warfarina no incrementó el riesgo de SM (warfarin vs aspirin: RR 1.08, 95% IC 0.71-1.64, p = 0.72; warfarin vs placebo RR 2.27, 95% IC 0.84-6.15, p = 0.11). Además, una importante reducción en el riesgo de EVM fue observado grupo de warfarina a altas dosis ((warfarin vs aspirin: RR 0.44, 95% IC 0.25-0.76, p = 0.004; warfarin vs placebo: RR 0.30, 95% IC 0.13-0.71, p = 0.005). Solamente un estudio demostró que comparado con aspirina, el apixabán no aumentó la incidencia de SM (p = 0.57), y tuvo una tendencia hacia una menor mortalidad. (p = 0.07). Conclusiones. El uso de anticoagulantes orales es seguro en pacientes con FA. Además, la dosis de warfarina no debería ser tan conservadora.**

Palabras clave: Aspirina; Hemorragia; Meta-análisis; Mortalidad; Anticoagulantes orales; Warfarina.

Cir Card Mex 2019; 4(2): 35-47

Anticoagulants recommended by guidelines are considered effective for prevention and treatment of thrombotic cardiovascular events in patients with atrial fibrillation (AF) [1-2]. Warfarin, one of the vitamin K antagonists, is the most commonly used anticoagulant agent in patients with AF [3]. In addition, novel oral anticoagulants (NOACs) represented their more predictable effects and more favorable hemorrhagic risk profile in the past few years [4]. Despite the evidence of the superiority of anticoagulant

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over antiplatelet agents in preventing stroke, many patients with AF at high risk of thrombotic events prefer aspirin, even when this one was not recommended by current guidelines, either alone or in combination with clopidogrel [5]. Moreover, some patients did not even take any therapy, especially in China [6]. This fact might be due to the concern of bleeding risk [7]. Bleeding events can be divided into non-major bleeding events and major bleeding events [8]. The former might not cause severe clinical consequences, while the latter could be the primary origin of poor prognosis [9]. The WAPSO study[10] and Mant et al. [11] reported a little increased risk for major bleeding in the aspirin group, although there was no statistical difference when comparing with the warfarin group. In addition, vascular mortality, usually as a main outcome in many clinical trials for patients with AF [12-14], it was lower in the warfarin group than that in the control group (either taking aspirin or placebo) [15]. Although the well-designed AFASAK study [15] recommended warfarin for prevent thromboembolic complications in patients with non-rheumatic AF, and meta-analysis conducted by Segal et al. [16] and Zhang et al. [17] have confirmed that, they all did not conduct subgroup analysis about the intensity of warfarin for bleeding events. It is necessary to conduct a systematic review in analyzing the safety of anticoagulant therapy in patients with AF. This study aimed to compare the bleeding events, major bleeding events and vascular mortality in patients with AF between the recommended anticoagulants and aspirin or placebo.

MATERIAL AND METHODS

Electronic searches.

A computerized literature search of the PubMed, Embase, and the Cochrane Central Register of Clinical Trials was conducted. Terms and key words used included "atrial fibrillation or AF or nonvalvular atrial fibrillation or NVAF" and "warfarin or coumadin or dabigatran or rivaroxaban or apixaban or edoxaban or anticoagulation". Only primary research which were randomized controlled studies carried out from inception to November 30, 2017 were included in this review. Grey literature such as conference papers and the reference list of articles were also searched. The search was limited to English-language articles involving human subjects.

Inclusion and exclusion criteria

The included studies, for the purposes of full-text review, satisfied the following criteria according to PICO principle: P: patients with diagnosis of AF or NVAF; I: the patients took warfarin or NOACs; C: the patients took aspirin or placebo or no treatments; Outcomes: the bleeding events, the major bleeding events and the vascular death events and the thromboembolic events. We named all intensity of warfarin as the warfarin group and defined the INR range of 2.0 to 3.0 as the standard-intensity warfarin [18], 2.0 to 4.5 as standard plus high intensity warfarin [19] and 1.5 to 2.5 as low-intensity warfarin [20]. All bleeding events were recorded. Major bleeding events were defined as an intracranial hemorrhage (including hemorrhagic stroke) or extracranial bleeding that was fatal or required a transfusion, surgery, or hospital admission in these studies [21]. Vascular death was any death that was clearly not due to non-vascular cause such as trauma. Patient follow-up was carried out for at least 3 months. Exclusion criteria were as follows: i) patients with any repaired or replaced heart valve and with a clinically significant bleeding diathesis or other severe complication; ii) three or above domains with a high risk of bias in one trial; iii) non-English publications, letters, case reports, comments, and editorials were also excluded.

Data extraction and management

The data extraction process involved the use of a framework to extract the data separately by all the authors from the articles selected. All the extracting data included were reviewed and agreed by all the authors. For trials reported in more than one publication, we extracted data from the most complete publication. The proportion of time spent within the therapeutic INR range for each study group was expressed as an incidence density using a patient-years approach.

Assessment of risk of bias in included studies

The assessment tool used for evaluating the risk of bias was the Cochrane Handbook for Systematic Reviews of Interventions. The process involved the separate critical assessment of the various domains including the random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Recommendations for judging risk of bias are provided in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions [22]. Each item for included studies was evaluated as low, unclear, or high risk of bias. Discrepancies about the quality assessment of included studies were resolved by consensus.

Statistical analysis

The meta-analysis of data extracted was performed by RevMan 5.3. Data were combined to estimate the pooled risk ratio with 95% confidence intervals for the different outcomes of interest of the bleeding events and the major bleeding events, vascular mortality and thromboembolic events. Subgroup analysis was performed to determine the effects of treatments on patients with AF. A heterogeneity test, which was carried out to evaluate the evidence of variability of the intervention effects, was evaluated with I^2 statistics for each outcome, considering I^2 >50% as significant heterogeneity. The random-effects model was taken as measuring the outcomes with the presence of high heterogeneity. Otherwise, fixed-effects models were used. The funnel-shaped distribution was used to assess the publication bias. All the P values were 2-tailed, with statistical significance specified at $P < 0.05$ and the 95% confidence interval (95% CI).

RESULTS

Flowchart of selection process for the studies is shown in **Fig. 1.** The main characteristics of the included studies are described in **Table 1**. Fifteen articles meeting the inclusive and the exclusive criteria were included in the analysis. A total of

14197 patients were included. The width range of time for follow up was from 1.0 to 4.3 year. Only one article [23] explored the safety of NOAC (apixaban) versus aspirin for patients with AF. One study [12] compared the effects between coumarin and aspirin, which was annexed into the data of warfarin since the mechanism of both anticoagulant agents were similar. The remaining thirteen papers all used warfarin as intervention agent. The aspirin was used in thirteen included studies and the range of dosing varied from 75 mg to 325 mg/day. The placebo was taken as comparisons in four studies.

Assessment of risk of bias in included studies.

The graphs of biases existing in the included studies are shown in **Fig. 2**. With respect to the selection bias, 25% of the studies showed unclear risk of bias. In terms of the blinding of bias, 60-85% of studies had either unclear risk of bias or low risk of bias. About 85% of studied reported either unclear risk of bias or low risk of bias in the other risks of bias (selective reporting, incomplete outcome data and other potential sources of bias). Four trials showed the low risk of biases in all domains, while ten trials showed the high risk of bias in one domain.

Bleeding events

Eight articles [10,12,15,24-28] totally containing 6,814 patient-years in the warfarin group and 5,663 in the aspirin group, reported bleeding events. The result found there was a higher risk of bleeding events in the warfarin group (RR 1.86, 95% CI 1.30 to 2.65, p = 0.0006). Five articles [10,25-28] with 2,155 patient-years in the standard-intensity warfarin group

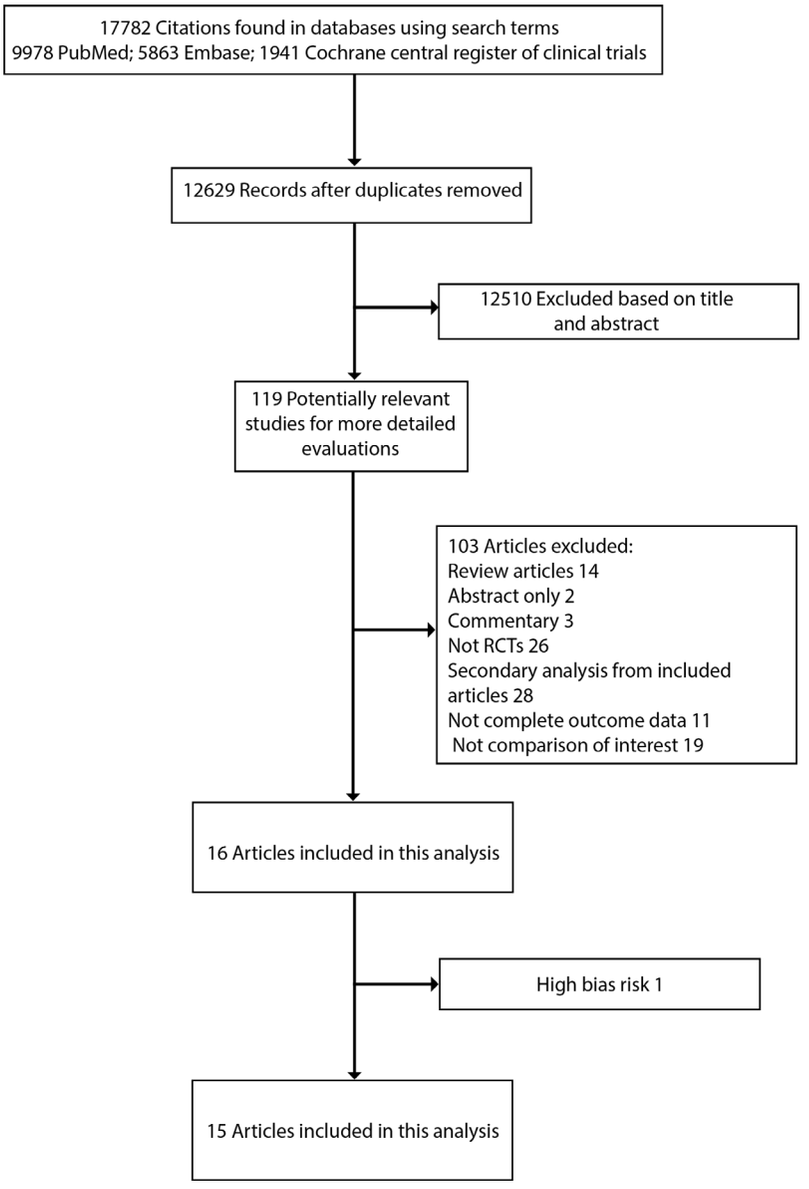
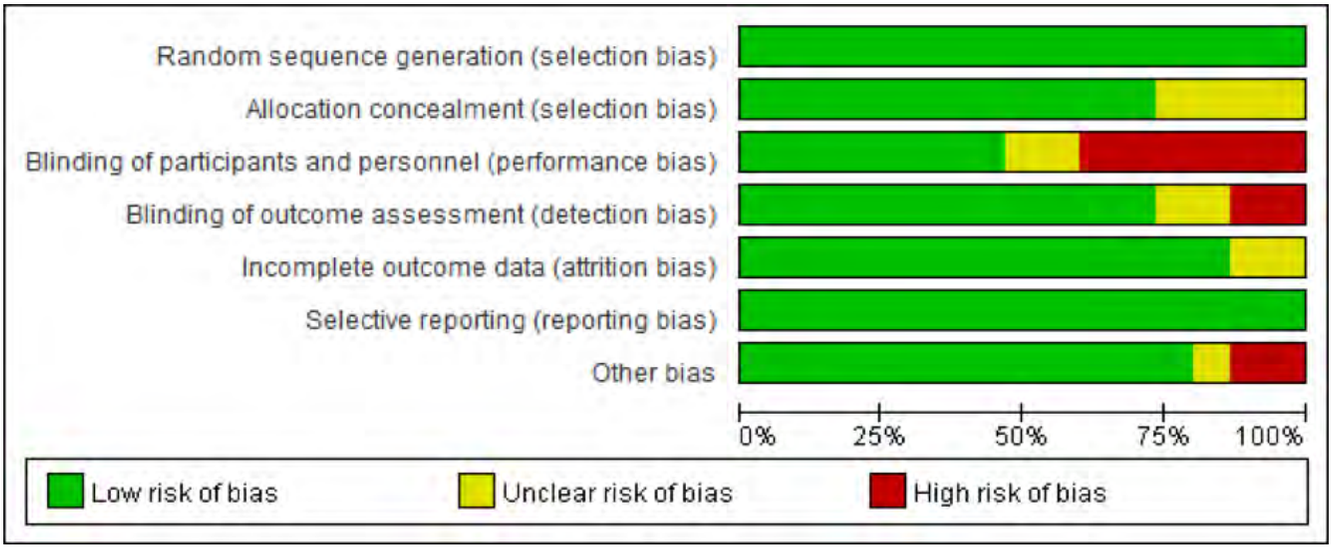


Figure 1. Flow chart of search results



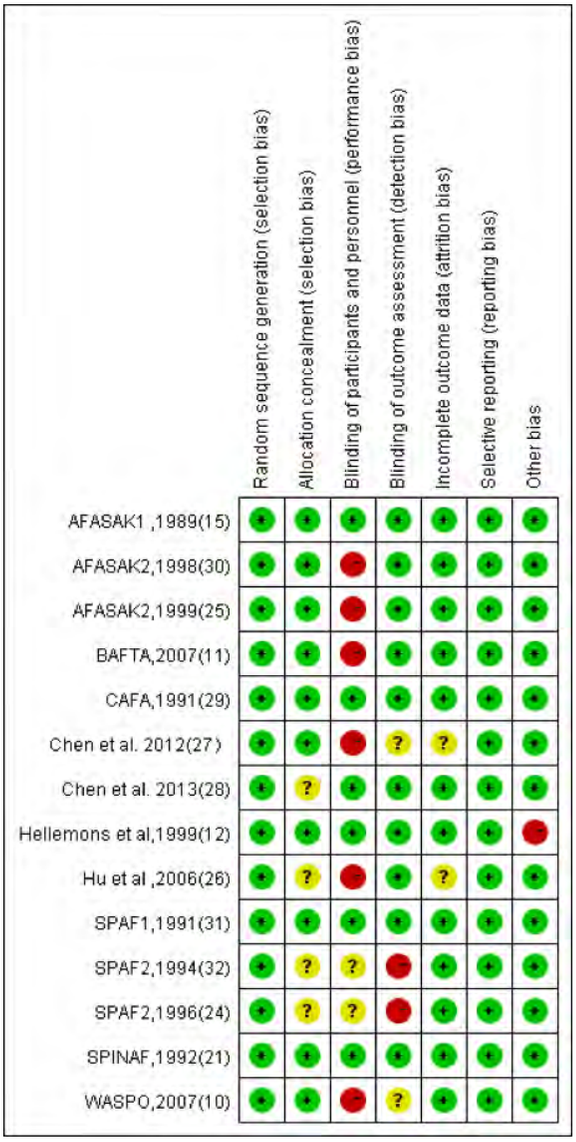


Figure 2. (A Top) Risk of bias graph of the included studies (B Bottom) Risk of bias summary of the included studies.

and 2,743 in the aspirin group, reported the comparison of bleeding events. Findings here showed higher risk of bleeding events in the warfarin group (RR 1.96, 95% CI 1.50 to 2.58, p < 0.0001) **(Fig. 3.1)**

There were three articles [15,21,29] reported the bleeding events of the warfarin group and the placebo group. There was no significant difference in bleeding events between the two groups (RR 1.95, 95% CI 0.87 to 4.38, p = 0.11). Only one paper [29] reported an increased bleeding risk in the standard-intensity warfarin group **(Fig. 3.2)**

Major bleeding events

Seven trials [10-12,15,25-27] containing 3,873 patient-years in the warfarin group and 4,003 in the aspirin group, reported major bleeding events. There did not show the differences for major bleeding events between the warfarin and the aspirin group (RR 1.08, 95% CI 0.71 to 1.64, p = 0.72). Similar results were shown between the standard-intensity warfarin group (RR 1.16, 95% CI 0.74 to 1.82, p = 0.51), even the standard plus high intensity warfarin group (RR 0.44, 95% CI 0.12 to 1.62, p = 0.22), comparing with the aspirin group. Comparing with placebo group, major bleeding events did not increase in the warfarin group (**Fig. 4.1**) (**Fig. 4.2**)

Vascular death events

Six trials [12,15,26-27,30-31] containing 2,779 patient-years in the warfarin group and 3,374 in the aspirin group, reported the events of the vascular death. The test of the overall effect for warfarin on the events of the vascular death was less than that in the aspirin group (RR 0.55, 95% CI 0.36 to 0.85, p = 0.008), while there was no difference between either in the standard-intensity warfarin group (RR 0.78, 95% CI 0.36 to 1.68, p = 0.53) or in the low-intensity warfarin group and the aspirin group. However, in the stan-

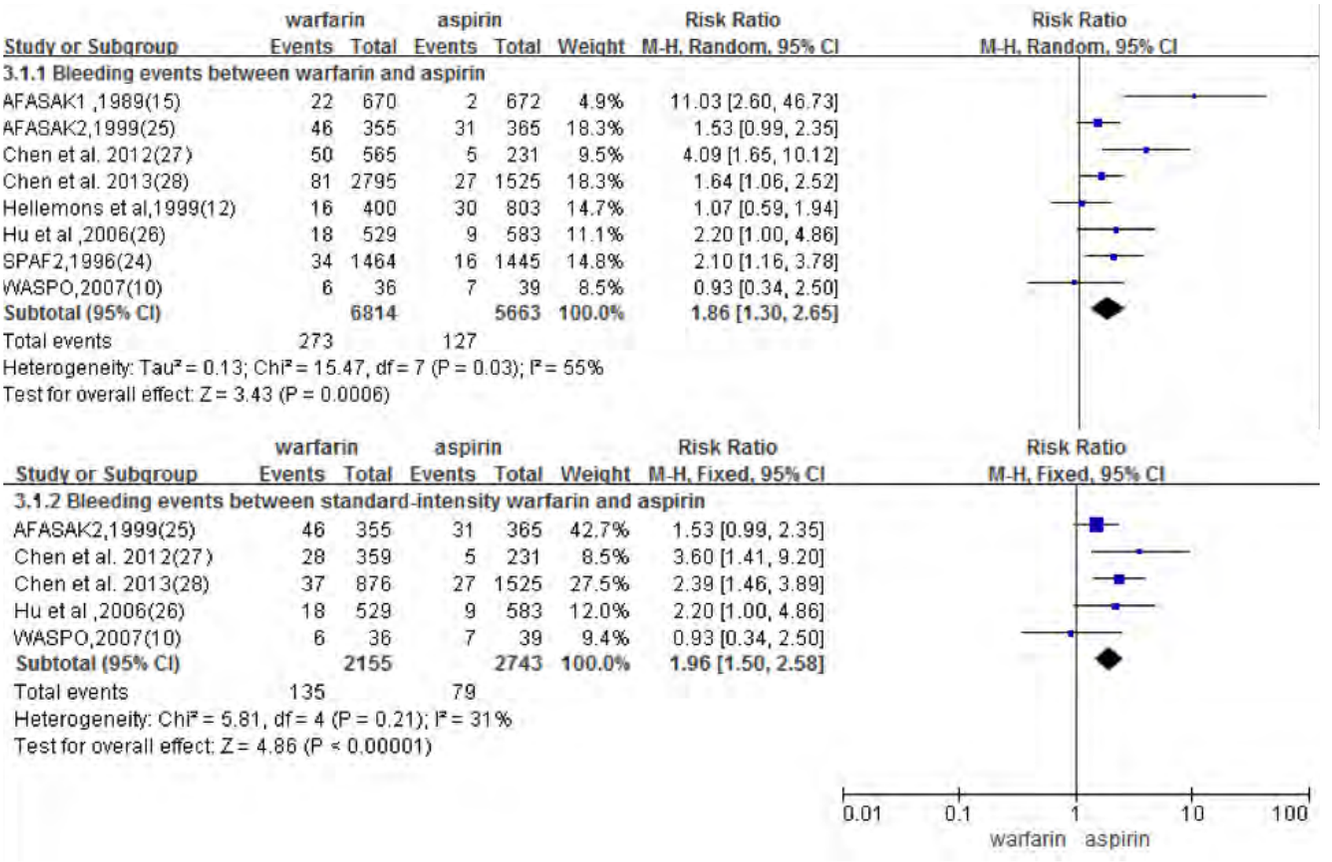


Figure 3.1 Risk of bleeding events in patients receiving warfarin or aspirin

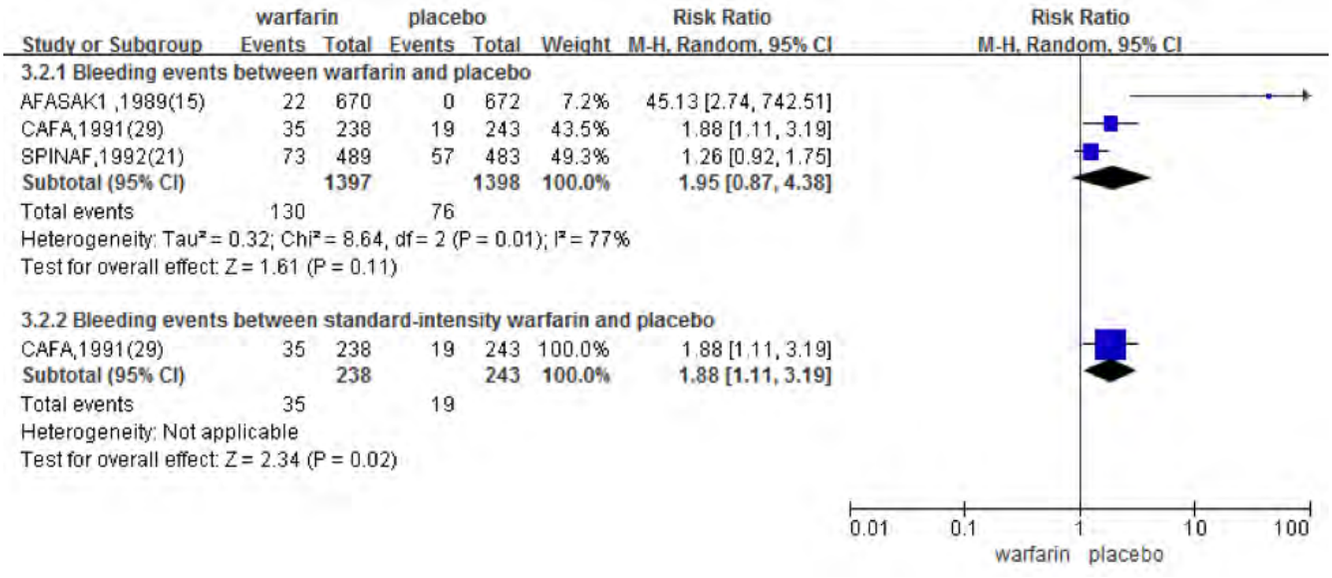


Figure 3.2 Risk of bleeding events in patients receiving warfarin or placebo

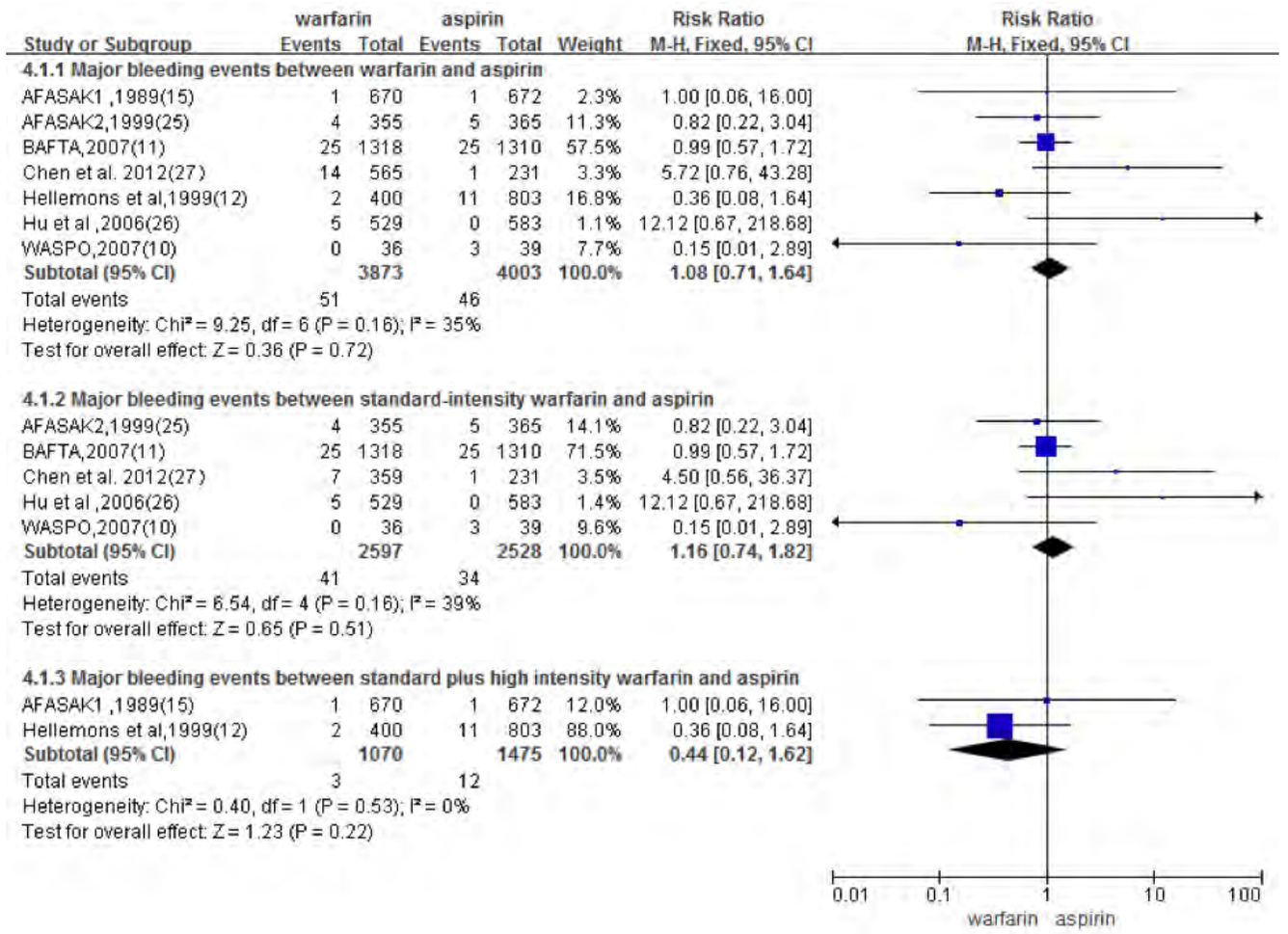


Figure 4.1 Risk of major bleeding events in patients receiving warfarin or aspirin

dard plus high intensity warfarin group, the vascular death events showed a lower risk, compared with both of the aspirin (RR 0.44, 95% CI 0.25 to 0.76, p = 0.004) group and the placebo group (RR 0.30, 95% CI 0.13 to 0.70, p = 0.005) (**Fig 5.1**) (**Fig. 5.2**).

Only one study [23] containing 2,808 patients in the apixaban group and 2,791 in the aspirin group, explored the safety of antithrombotic therapy for patients with AF. The final result demonstrated that the rate of major bleeding events in apixaban group did not show an increase (1.4% vs 1.2% per year, p=0.57), while the rate of death had a decreased trend (p = 0.07) compared with aspirin.

Risk for thromboembolsim in patients receiving warfarin or aspirin, or placebo are shown in **Fig 6.1** and **Fig. 6.2.**

DISCUSSION

Bleeding event is usually taken as a safety indicator in anticoagulant therapy for patients with AF [26-28]. It includes non-major bleeding event such as bleeding from the skin or mucous membranes, and major bleeding event such as intracranial hemorrhage [8]. Even though non-major bleeding event accounts for a large proportion of bleeding events, it would not affect prognosis or lead to poor clinical outcomes after it was properly treated [9]. According to the criteria of the International Society on Thrombosis and Haemostasis (ISTH), major bleeding [33] was defined as a fatal bleeding, and/or a symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or a bleeding causing a fall in hemoglobin level of 20 g/L(1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells. It is important that major bleeding was associated with substantially increased risk of ischemic stroke, myocardial infarction and death [9]. Although the severe bleeding, being included the major bleeding, could cause serious outcomes which had been applied to evaluate the safety of anticoagulant therapy [34-36] in many studies, it could not be adapted in this study due to difficulty of being extracted from the included studies. Therefore we took the major bleeding events to evaluate the safety of anticoagulant therapy in this study.

The result of this study showed that there is an obvious

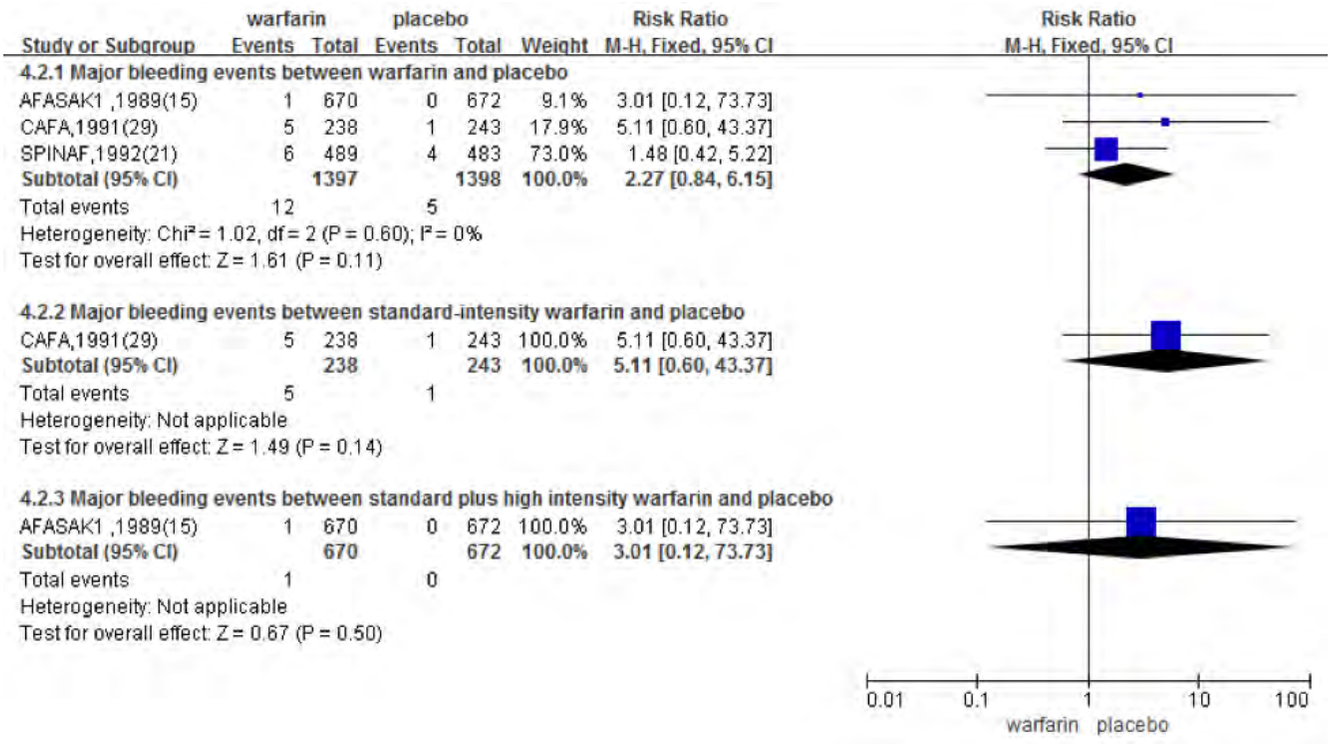


Figure 4.2. Risk of major bleeding events in patients receiving warfarin or placebo

increase of bleeding events in the warfarin group, comparing with that in the aspirin group, which is consistent with previous studies [26-28]. Interestingly, compared either with aspirin or placebo, warfarin did not rise the risk of major bleeding events in anticoagulant therapy for patients with AF. The possible reasons were as following: INR was being closely monitored during the process of taking warfarin. Once a minor bleeding event occurring at skin or mucous membranes, some interventions would be immediately taken in the clinic, and this could effectively prevent an occurrence of major bleeding event. Another reason might be that warfarin had a special antagonist. Once an occurring of minor bleeding event, vitamin K could be used to antagonize the effect of warfarin, which could effectively prevent further bleeding. Besides, for patients who were >80 years of age, the result of the WASPO study [10] indicated aspirin may be less safe than warfarin.

All-cause mortality, considered as an important indicator of prognosis in patients with AF [37] it could be combined by the non-vascular cause such as trauma [35] and the vascular mortality which was closely associated with the death due to vascular problems during the anticoagulant therapy. In this study the vascular mortality was taken as an essential appraisal of outcomes. For patients with AF, the vascular death might be induced by serious thromboembolic events and major bleeding events. In this analysis, compared with the aspirin group, there is a lower risk of vascular death in the warfarin group. Further analysis showed that high-intensity warfarin could prompt the reduction of the mortality in patients with AF, while the standard-intensity and low-intensity warfarin did not show the same results. Similar findings were found out while taking a placebo as control. Possible reason may be that the high-intensity warfarin significantly decreased severe thromboembolic events, thereby reducing a series of subsequent death events [9,38]. In order to explore more possible explanation, much more randomized control trials and studies should be conducted.

At present, according to ESC Guidelines for the management of atrial fibrillation [3], it is effective for preventing thromboembolic events if oral warfarin could be adjusted to maintain the target INR (2.0 3.0). Warfarin therapy is highly safe with the similar risk of major bleeding events between two groups. Based on this study, additionally the dose of warfarin should not be too conservative in clinical setting since a high-intensity warfarin could help to avoid an increase in mortality rate.

NOACs are also considered as effective anticoagulant agents in patients with AF. The AVERROES study [23] found out that apixaban did not increase the risk of major bleeding. This means apixaban is safer than aspirin in anticoagulant therapy. Moreover, after taking warfarin as a control group and comparing the effect of all NOACs on major bleeding and all-cause mortality in a meta-analysis. NOACs take the similar risks of major bleeding events and significant reduction in intracranial hemorrhage and mortality. This indicates that apixaban is also safer than warfarin [1].

Study limitations

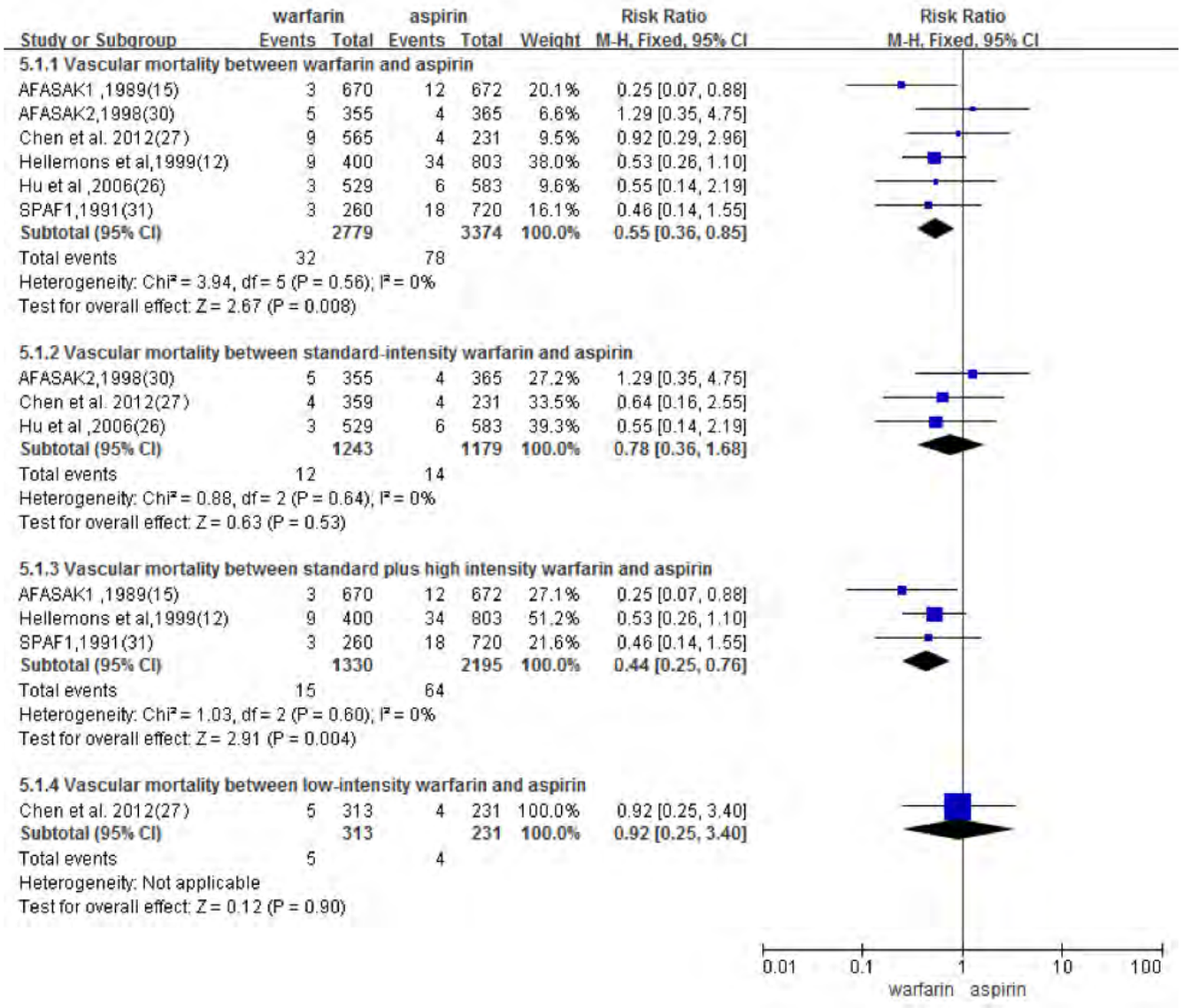


Figure 5.1. Risk of vascular mortality in patients receiving warfarin or aspirin

There are several limitations in this study. First, several studies included were conducted more than 20 years ago, which may exist differences in the management of patients who took warfarin. Second, two studies [12,23] included were terminated early before completion due to an increased risk of bleeding or clear benefit, which reduced the power to detect meaningful differences. Third, an asymmetric, funnel-shaped distribution in the bleeding events indicated the presence of publication bias **(Fig. 7)**. Finally, the number of included studies and the total sample were small in some subgroup analyses, which could influence the stability of the results.

By closing, as a conclusion, we can say that these data support that it is safe to use anticoagulant therapy in patients with AF. In addition, the warfarin dose should not be too conservative in clinical settings since high-intensity warfarin could prompt the reduction of the vascular mortality in patients with AF.

FUNDING: None

DISCLOSURE: The authors have no conflicts of interest to disclose.

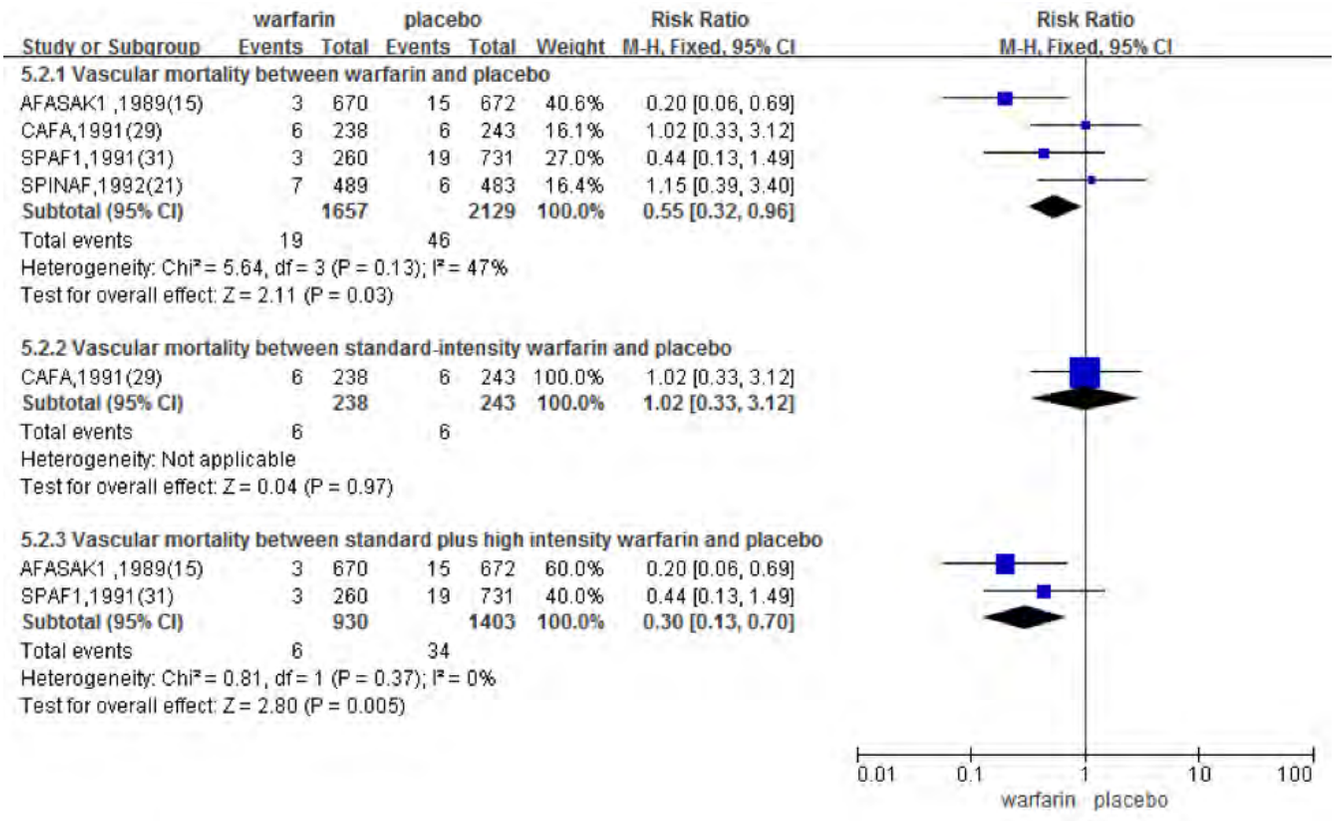


Figure 5.2. Risk of vascular mortality in patients receiving warfarin or placebo

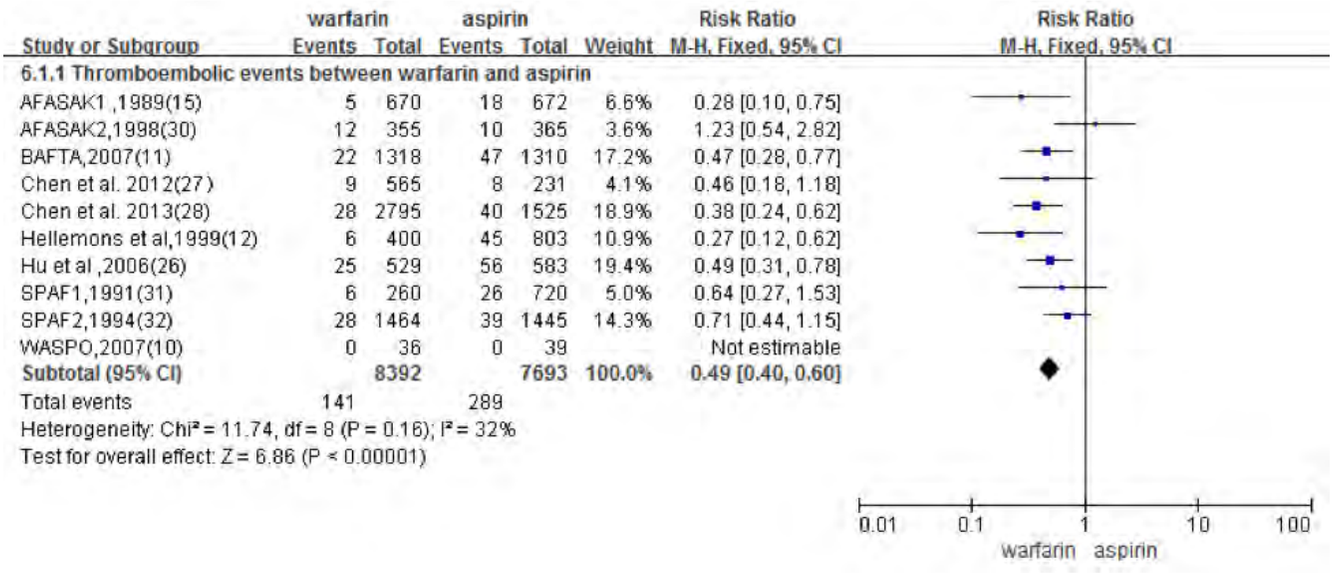


Figure 6.1 Risk of thromboembolic events in patients receiving warfarin or aspirin.

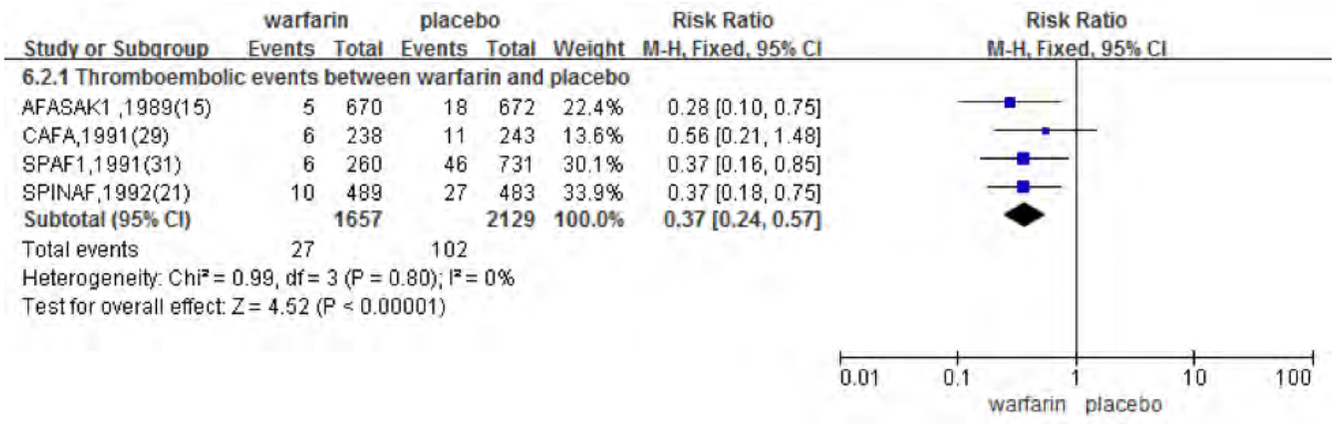
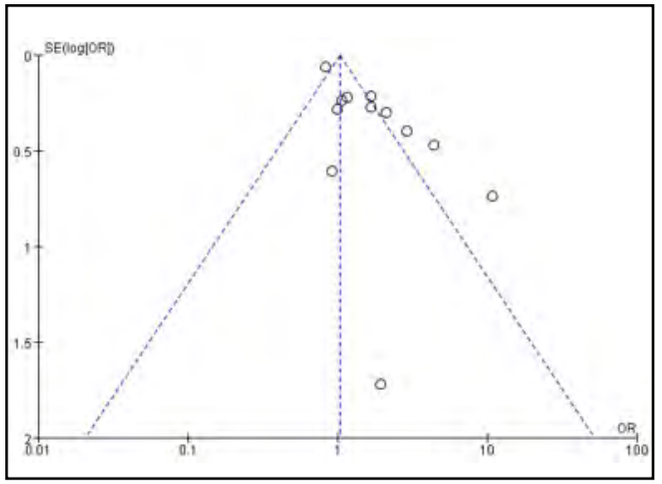
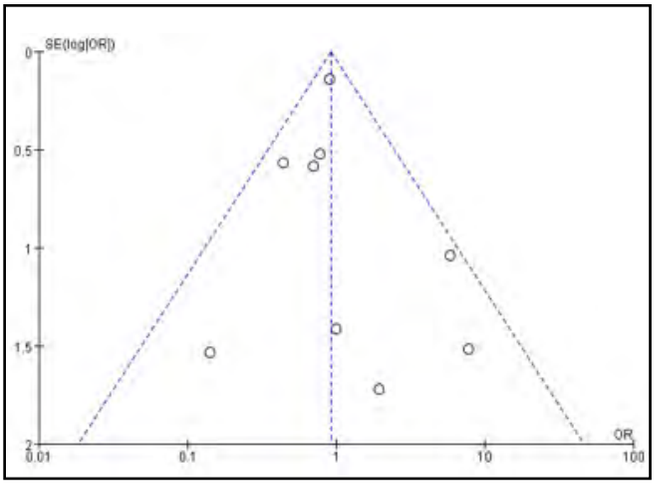


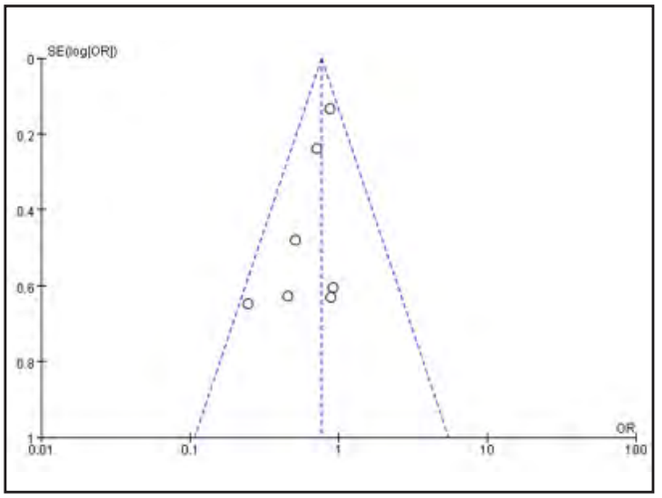
Figure 6.2. Risk of thromboembolic events in patients receiving warfarin or placebo



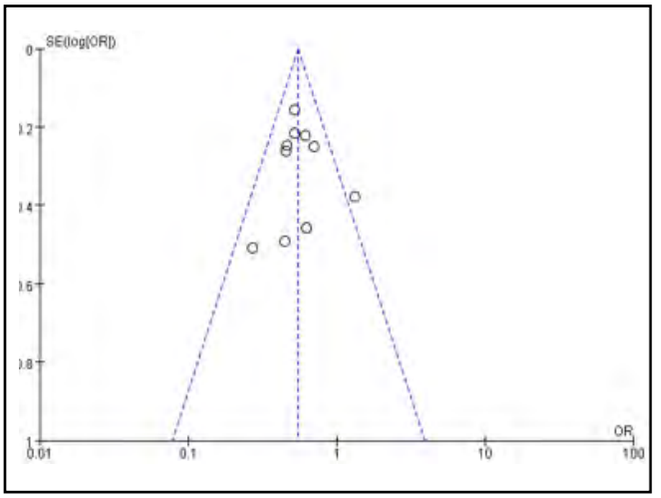
Bleeding events



Major bleeding events



Vascular mortality



Thromboembolic events

Figure 7. Funnel plots of the comparison between warfarin and aspirin

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SUPPLEMENTARY MATERIAL

TABLE 1. CHARACTERISTICS OF STUDY INCLUDED IN THE ANALYSIS

Study, Year	Country	Age (yr)*	Treatment	Participants (n)	HF (%)	HTN (%)	DM (%)	Prior TIA or Stroke (%)	CHADS2 Score	HAS-BLED Score	Follow-up (yr) †	Endpoint
AFASAK1, 1989 (15)	Denmark	38-91	Warfarin (INR 2.8-4.2); Aspirin 75 mg/d; Placebo	335 336 336	51.7	32.1	8.3	5.8	NA	NA	2.0	W vs As: ABCD W vs P ABCD
CAFA, 1991(29)	Canada	68.0±9.3 67.4±9.4	Warfarin (INR2-3); Placebo	187 191	22.2	38.6	11.9	3.7	NA	NA	1.3	ABCD
SPAF1, 1991(31)	USA	67	Warfarin (INR 2.0-4.5); Aspirin 325 mg/d; Placebo	210 552 568	19.0	52.0	16.7	7.0	NA	NA	1.3	W vs As: AD W vs P AD
SPINAF, 1992 (21)	USA	67±7 67±7	Warfarin (INR1.4-2.8); Placebo	281 290	30.5	58.1	18.5	NA	NA	NA	1.8	ABCD
SPAF2, 1994 (32)	USA	70	Warfarin (INR2.0-4.5); Aspirin 325 mg/d	555 545	NA	NA	NA	NA	NA	NA	2.6	A
SPAF2, 1996 (24)	USA	70	Warfarin (INR2.0-4.5); Aspirin 325 mg/d	555 545	NA	NA	NA	NA	NA	NA	2.6	B
AFASAK2, 1998 (30)	Denmark	73.2±7.0 73.1±7.2	Warfarin (INR2-3); Aspirin 300 mg/d	170 169	70.0	45.0	12.0	8.0	NA	NA	2.2	AD
Hellemons et al, 1999 (12)	Nether-lands	73.8	Coumarin (INR2.5-3.5); Aspirin(150mg/day);	131 319	NA	39.3	19.1	NA	NA	NA	2.7	ABCD
AFASAK2, 1999 (25)	Denmark	73.2±7.0 73.1±7.2	Warfarin (INR2-3); Aspirin 300 mg/d	170 169	70.0	45.0	12.0	8.0	NA	NA	2.2	BC
Hu et al , 2006 (26)	China	62.6±10.3 63.8±9.7	Warfarin (INR2-3); Aspirin150-160mg/d	335 369	NA	NA	NA	NA	NA	NA	1.6	ABCD

SUPPLEMENTARY MATERIAL

TABLE 1. CHARACTERISTICS OF STUDY INCLUDED IN THE ANALYSIS

Study, Year	Country	Age (yr)*	Treatment	Participants (n)	HF (%)	HTN (%)	DM (%)	Prior TIA or Stroke (%)	CHADS2 Score	HAS-BLED Score	Follow-up (yr) †	Endpoint
BAFTA, 2007 (11)	UK	81.5±4.3 81.5±4.2	Warfarin (INR2-3); Aspirin 75 mg/d	488 485	19.5	54.3	13.3	12.8	1-2 (72%); 3-6 (28%)	NA	2.7	AC
WASPO, 2007 (10) ‡	UK	83.9	Warfarin (INR2-3); Aspirin 300mg/d	36 39	NA	46.7	4.0	NA	≥ 2	≥ 1	1.0	ABC
AVERROES, 2011(23)	Worldwide	70±9 70±10	Apixaban (5mg/bid); Aspirin (81-324 mg/d)	2808 2791	38.8	86.4	19.6	13.6	2.0±1.1 2.1±1.1	NA	1.1	AB
Chen, et al. 2012 (27)	China	66.8±6.9 68.1±7.0 67.6±7.2	Warfarin (INR1.6-2.0); Warfarin (INR2.1-2.5); Aspirin 200mg/d	250 239 201	NA	61.3	13.3	20.3	NA	NA	1.3	ABCD
Chen, et al. 2013(28) §	China	72.4 72.2 72.6	Warfarin (INR1.7-2.5); Warfarin (INR2.6-3.0); Aspirin 150 mg/d;	445 205 361	NA	40.2	37.1	21.5	≥ 1	≥ 1	4.3	AB

** Reported as mean ± standard deviation or mean or the range of age.*
† Reported as mean or median.
‡ All patients were >80 and <90 years of age in the WASPO study.
§ All patients aged ≥65 years were included in the Chen 2013 study.
Abbreviation: AF = atrial fibrillation; INR = international normalized ratio; NA = Not available; W = warfarin; As = aspirin; P = placebo; A = thromboembolic events; B = bleeding events; C = major bleeding events; D = vascular mortality. AFASAK=Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation study; CAFA= Canadian Atrial Fibrillation Anticoagulation; SPAF=Stroke Prevention in Atrial Fibrillation study; SPINAF= Stroke Prevention in Nonrheumatic Atrial Fibrillation; BAFTA=Birmingham Atrial Fibrillation Treatment of the Aged study; WASPO= Warfarin vs Aspirin for Stroke Prevention in Octogenarians study; AVERROES= Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are unsuitable for Vitamin K Antagonist Treatment.