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WARFARIN USE AND THE RISKS OF STROKE AND BLEEDING IN HEMODIALYSIS PATIENTS WITH ATRIAL FIBRILLATION: A META-ANALYSIS STUDY

[1]Dr. Ibn-e-Hassan, [2]Dr. Usama Saeed, [3]Dr. Mina Amer

[1]Nishtar Medical University, Multan, Pakistan, [2]Services Institute of Medical Sciences Lahore, [3]Quaid-e-Azam Medical College, Bahawalpur.

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Abstract:

Background: *risk and benefits of warfarin therapy in hemodialysis (HD) patients with fibrillation (AF) remains controversial. The aim of meta-analysis to evaluate risks of stroke and bleeding of warfarin treatment in these populations.*

Methods and results*: Relevant literatures were searched using the following electronic databases without any language restrictions: the Cochrane Library Database, PubMed, ISI, Ovid, and Chinese Biomedical Database from the building of the database to 2018. The studies were included if (a) studies described the risk of stroke or bleeding with or without warfarin in dialysis patients with AF, (b) studies provided information about hazard ratio (HR) and 95% confidence interval (CI) of stroke or bleeding, and (c) the study design should be a clinical cohort. Sensitivity analyses and publication bias were also performed. We identified 6 eligible studies with a total of 9816 patients. Combined HRs showed that warfarin cannot provide a prevention for strokes in HD patients with AF [HR = 1.23, 95% CI 0.80 - 1.87; P = 0.347], but associated with a higher risk of bleeding (HR = 1.20, 95% CI 1.03 - 1.39; P = 0.019).*

Conclusion: *This meta-analysis suggested that warfarin should not be recommended for the routine treatment of HD patients with AF.*

Keywords: *Hemodialysis, Atrial fibrillation, Warfarin, Stroke, Bleeding.*

Corresponding author:

Ibn-e-Hassan,

Nishtar Medical University, Multan, Pakistan.

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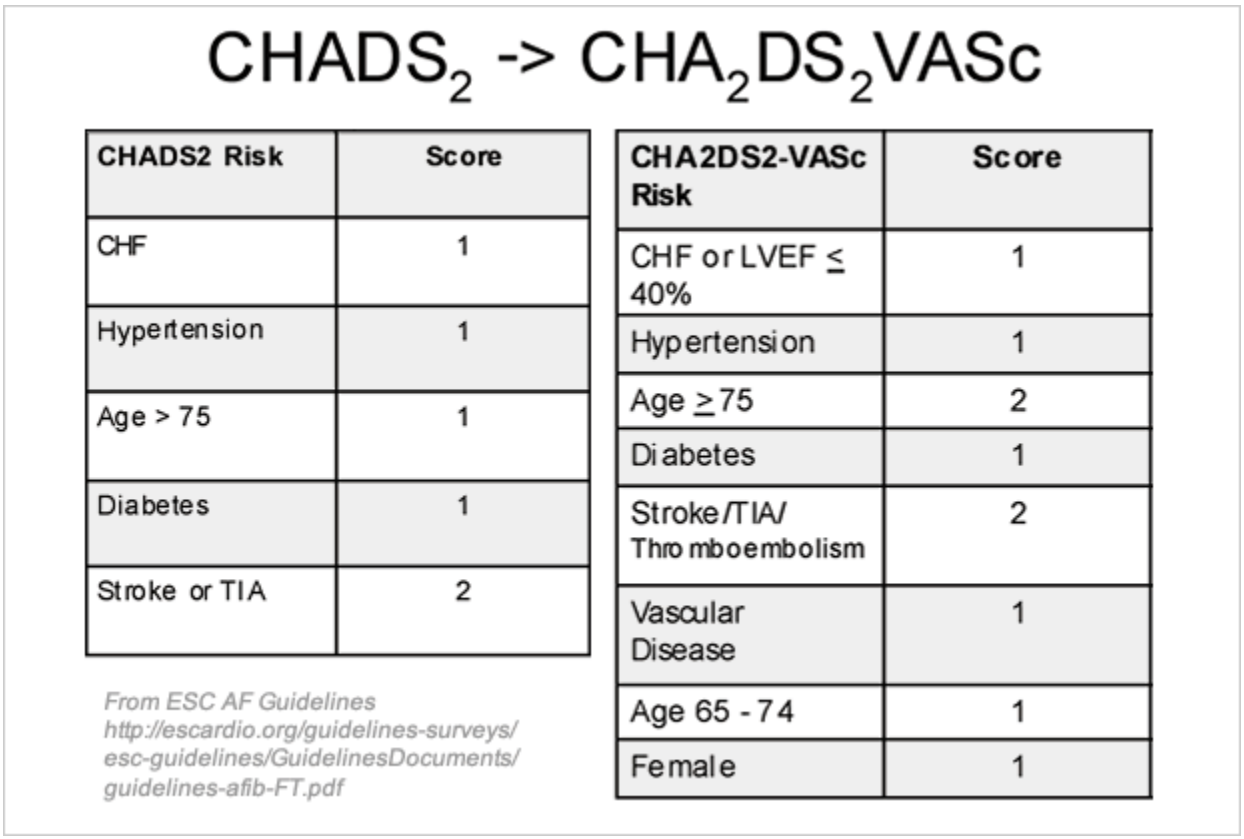
INTRODUCTION:

Atrial fibrillation (AF) is the most common arrhythmia in the general population and it's associated with an increased chances of stroke that can be predicted using the CHADS2 score [1]. (Fig 1) Compared with the general population, patients who receive maintenance dialysis have a 6-fold higher risk of atrial fibrillation, and a 5- to 10-fold higher risk of ischemic stroke. [2-4] The prevalence of atrial fibrillation (AF) in hemodialysis (HD) population is high, ranging from 7 to 27%. [5] Warfarin is indicated in patients with AF for prophylaxis of stroke, preventing approximately 60% of strokes. [6] The greatest accepted risk with warfarin is bleeding, but there is also emerging evidence that warfarin may contribute to vascular calcification and precipitate calcific uremic arteriolopathy in patients with end-stage renal disease (ESRD).[7]

Although warfarin is widely used in the dialysis patients for a numbers of indications, the exclusion of chronic dialysis recipients from randomized controlled trials of warfarin in patients with atrial fibrillation has led to uncertainty concerning its role in ischemic stroke prevention in this population. Many cohort studies [8] also stated that warfarin increased risk of stroke in HD patients with AF. HD patients with AF used warfarin if the CHA2DS2-VASc score > 2 (fig 1) was recommended by AHA/ACC 2014 guidelines. In contrast Olesen et al. [9] found that warfarin was correlated with a significantly decreased risk of stroke.

Because of the uncertainty in this area, recent guidelines have expressed appropriate caution regarding the use of warfarin anticoagulation in patients with atrial fibrillation who receive dialysis. To comprehensively synthesize information in this controversial area, this meta-analysis is conducted to evaluate the safety and efficacy of warfarin in chronic dialysis patients with atrial fibrillation.

Fig: 1 CHADS2 score and CHA2DS2-VASc score



METHOD:

Search strategy:

Selected articles were searched using the following electronic databases without Cochrane Library Database, PubMed, ISI, Ovid, and, Medline, Chinese Biomedical Database from the building of the database to 2018. By using mesh terms includes warfarin, hemodialysis/dialysis, and atrial fibrillation. The related research references were also reviewed.

Inclusion criteria:

The studies were included if (a) studies described the risk of stroke or bleeding with or without warfarin in dialysis patients with AF, (b) studies provided information about hazard ratio (HR) and 95% confidence interval (CI) of stroke or bleeding, and (c) the study design should be a clinical cohort.

Data extraction:

data was extracted from the following selected each article: first author's last name, year of publication, number of patients, follow-up period, dialysis types, HR for stroke, HR for bleeding. Discrepancies were settled by a meeting consensus.

Assessment of study quality:

The study quality was checked by using the Newcastle– Ottawa Scale (NOS) for cohort studies in meta-analysis [10], the star evaluates three main categories: selection, comparability, and outcome. A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. A total score of seven or more stars was considered as a high-quality study.

Statistical analysis:

A combined hazard ratio (HR), with 95% confidence interval (CI) was calculated by STATA statistical software (Version 12.0). Heterogeneity among studies was estimated by Cochrane's *Q*-statistic and I^2 tests. A random-effect model was used when *Q*-test exhibits a $P < 0.05$ or I^2 test shows > 50%; otherwise, the fixed-effect model was selected. To explore the sources of heterogeneity, subgroup analysis was performed. Subgroup meta-analyses were based on dialysis types. Sensitivity analyses were conducted in the meta-analysis to inspect the influence of an individual study. Publication bias was assessed by constructing a funnel plot and using Egger's and Begg's tests. A significant two-way *P* value for comparison was defined as $P < 0.05$.

RESULTS:

Literature selection:

Six clinical cohort studies met the inclusion criteria. The study selection process was outlined in Figure 2. The six cohort studies were published between 2009 and 2014, and enrolling a total of 9816 participants. The mean age of patient is 66.8, 68.1, and 68.9 years, respectively. [9] Chan et al [12] defined stroke outcome as hospitalization, death from ischemic or hemorrhagic stroke, or transient ischemic attack (TIA). Wizemann et al. defined stroke outcome as hospitalization, death from stroke or cerebrovascular events. Winkelmayer et al. defined stroke outcome as ischemic or hemorrhagic stroke. Olesen et al. Defined stroke outcome as hospitalization, death from stroke or systemic thromboembolism (ischemic stroke, peripheral artery embolism, or TIA). Wakasugi et al. defined stroke outcome as new ischemic stroke. Shah et al. defined stroke as the first hospital admission or emergency department visiting for ischemic cerebrovascular disease, TIA, or retinal infarct at any point during the follow-up period.

Chan et al. [11] did not describe the bleeding definition. Wizemann et al. [12] had no data about hazard ratio of bleeding. Winkelmayer et al defined bleeding outcome as gastrointestinal bleeding. Olesen et al.defined bleeding outcome as hospitalization or death from gastrointestinal, intracranial, urinary tract, or air-way bleeding. Wakasugi et al. defined bleeding outcome as fatal bleeding or bleeding that required hospitalization. Shah et al.defined bleeding outcome as the first hospital admission or emergency department visiting for intracerebral bleeding, gastrointestinal bleeding, intraocular bleeding, hematuria, or unspecified location of bleeding at any point during the follow-up period. The details of the articles were summarized in Table 1. According to NOS, all studies were of high quality.

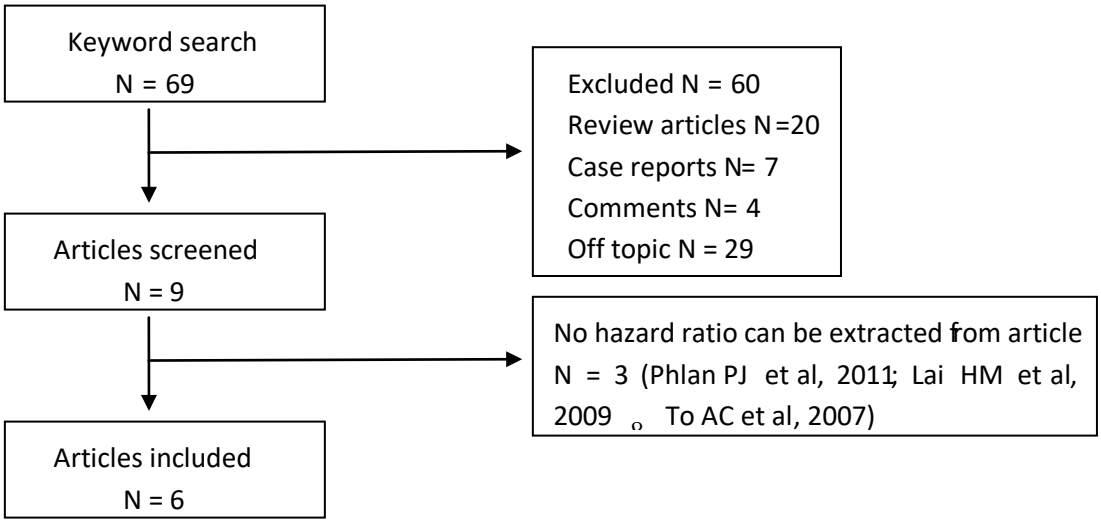


Figure 2: Selection of the studies included in the meta-analysis.

Table 1: The risks of stroke and bleeding in HD patients with AF under warfarin therapy

Studies	Number of patients	Periods	Dialysis types	HR for total stroke (95% CI)	HR for bleeding (95% CI)
Chan et al.[15] 2009	1671	1.6yrs	HD	Ischemic stroke 1.81 (1.12-2.92) Hemorrhagic stroke 2.22 (1.01-4.91) Total strokes 1.93 (1.29-2.90)	1.04 (0.73-1.46)
Wizemann et al. [14] 2010	1001 (age ≤ 65) 1137 (age 66-75) 1107 (age > 75)	8yrs	HD	1.29 (0.45-3.68) 1.35 (0.69-2.63) 2.17 (1.04-4.53)	no data
Winkelmayer et al. [13] 2011	2313	12yrs	HD	Ischemic stroke 0.92 (0.61-1.37) Hemorrhagic stroke 2.38 (1.15-4.96) Total strokes 1.08 (0.76-1.55)	0.96 (0.70-1.31)
Olesen et al. [16] 2012		12yrs	HD and PD	Warfarin 0.44 (0.26-0.74, $P = 0.002$)	1.27 (0.91-1.77, $P = 0.15$)
Wakasugi et al. [22] 2013	60	3yrs	HD	Ischemic stroke 1.94 (0.63-5.93)[a] Ischemic stroke 3.36 (0.94-11.23)[b]	0.85 (0.19-3.64)[a]
Shah et al. [23] 2014	1626	9yrs	HD and PD	1.14 (0.78-1.67)	1.44 (1.13-1.85)

HD, hemodialysis; PD, peritoneal dialysis; a Unadjusted, b Adjusted for CHADS2 score; HR, hazard ratio; CI, confidence interval

Warfarin use with the stroke risk:

2466 out of 9816 participants in six studies were received warfarin. There was statistically heterogeneity among the results of the included studies (I^2= 79.2%, P = 0.000, Figure 3), thus the random-effects model was selected. Meta-analysis showed that warfarin and the risk of stroke provided no statistically significant (HR = 1.23, 95% CI 0.80 - 1.87; P = 0.347). Subgroup meta-analyses were based on dialysis types. In HD patients, there was statistically heterogeneity among the results of the included studies (I^2= 53.5%, P = 0.092, Figure 3). Meta-analysis presented that warfarin increased the risk of stroke (HR = 1.57, 95% CI 1.09 - 2.25; P = 0.015, 4 trials). In HD and PD patients, there was statistically heterogeneity among the results of the included studies (I^2= 88.0%, P = 0.004, Figure 4). Meta-analysis showed that warfarin and the risk of stroke provided no statistically significant (HR = 0.72, 95% CI 0.28 - 1.83; P = 0.492, 2 trials)

Fig 3:

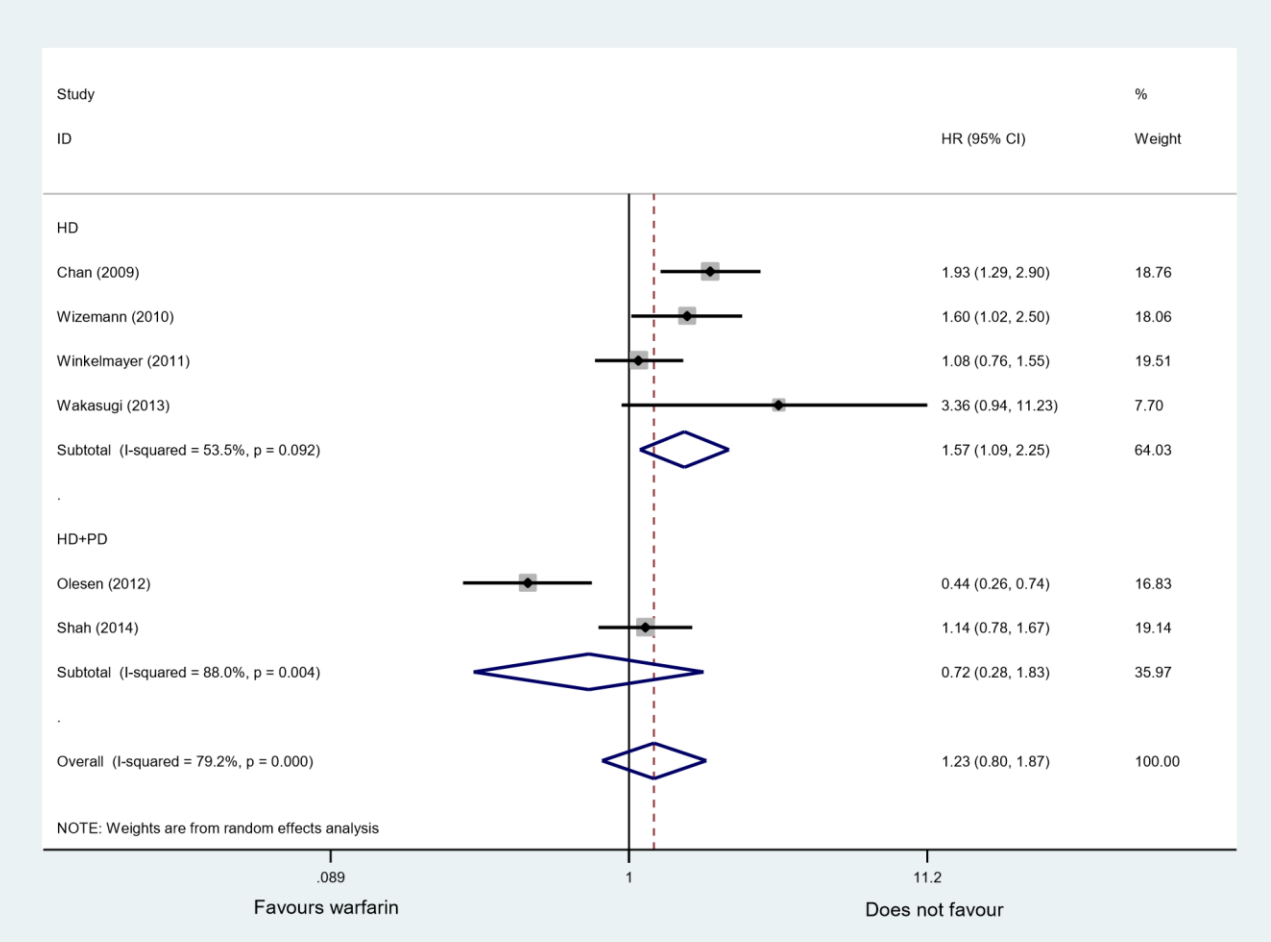


Figure 4: Subgroup analysis about warfarin use and the risk of stroke in hemodialysis patients with atrial fibrillation. HD, hemodialysis; PD, peritoneal dialysis.

Warfarin use with the bleeding risk

1957 out of 6571 participants in five studies were received warfarin. There were no statistical heterogeneity in the related six studies (I^2 = 20.4%, P = 0.285, Figure 4), thus the fixed-effects model was selected. Meta-analysis presented that warfarin increased the risk of bleeding (HR =

1.20, 95% CI 1.03 - 1.39; P = 0.019).

Sensitivity analyses and Publication bias

Sensitivity analyses were carried out in accordance with the stroke. There was significantly effect on the result of the HR and 95% CI when Olesen et al.study was excluded (Figure 5). It was showed that this study had high sensitivity and poor stability. The Egger's test and Begg's funnel plot were used to detect publication bias (Figure 6). The Egger's linear regression test (P = 0.807) and Begg's rank correlation test (Pr >|z| = 0.707) provided no evidence of substantial publication
bias.

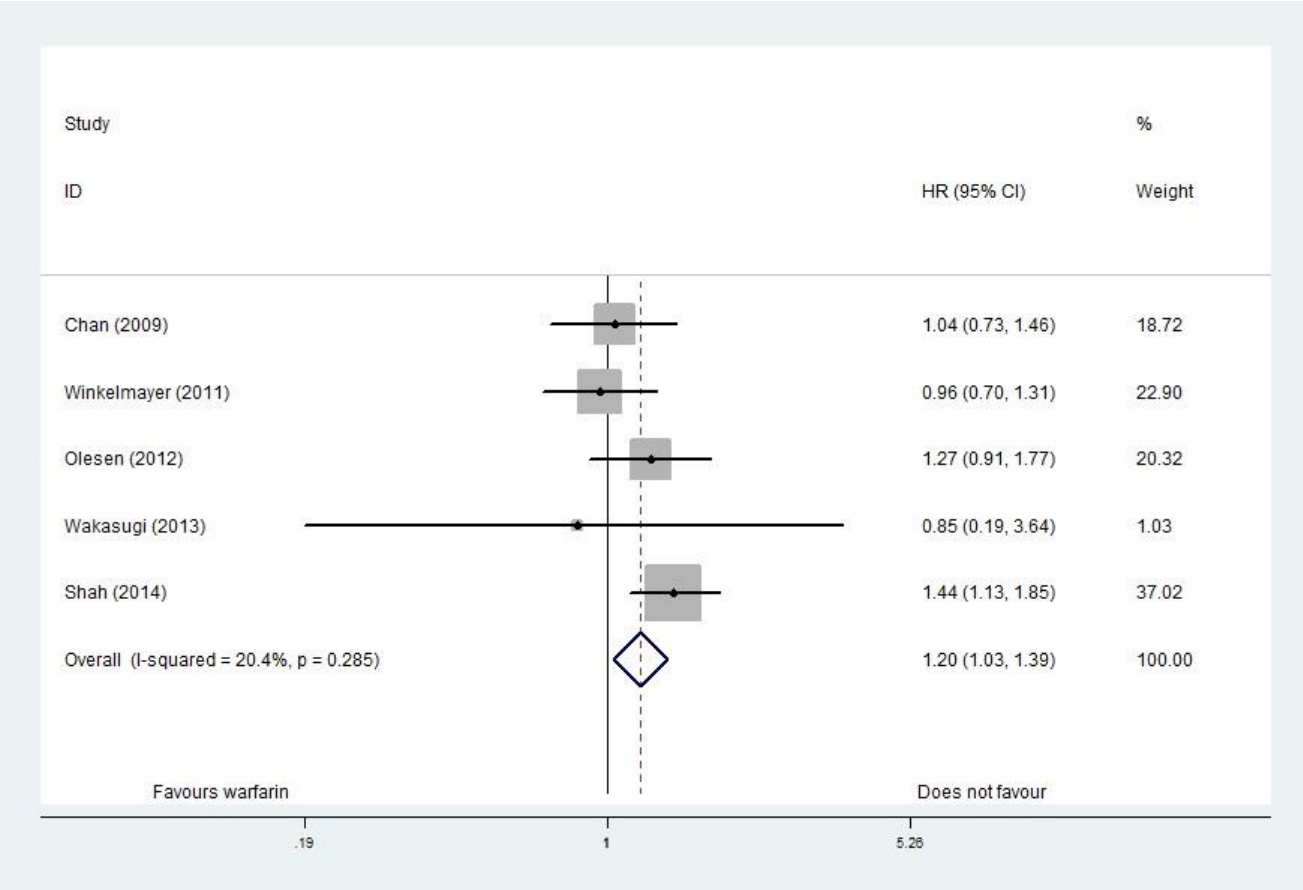


Figure 4: Warfarin use and the risk of bleeding in hemodialysis patients with atrial fibrillation.

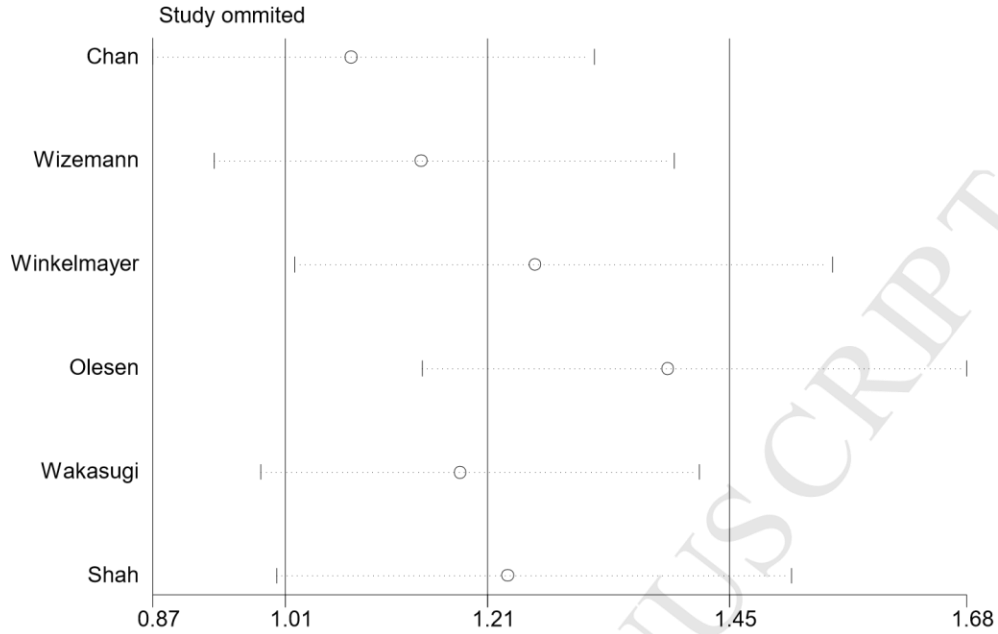


Figure 6: Sensitivity analyses about warfarin use and the risk of stroke in hemodialysis patients with atrial fibrillation.

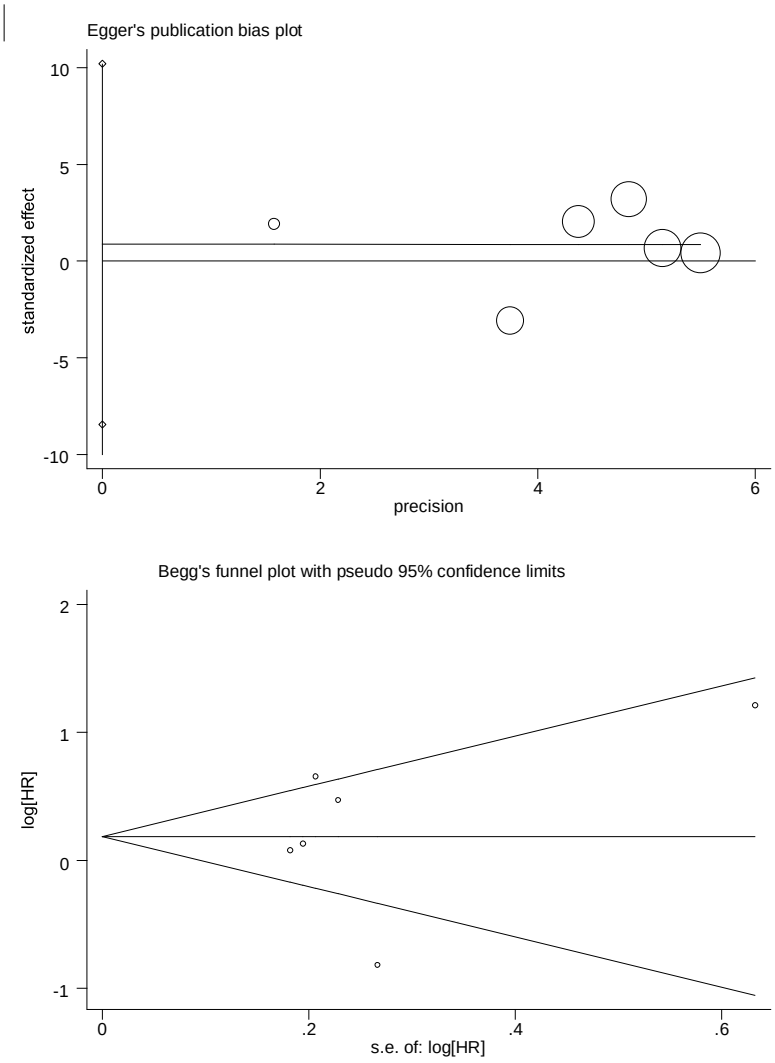


Figure 7: Egger's test and Begg's funnel plot (publication bias).

DISCUSSION:

Up to date, there is not any randomized controlled clinical trial has been done to evaluate the efficacy of warfarin in HD patients with AF. It is mainly due to the disease has a low incidence. The meta-analysis showed that warfarin treatment and the risk of stroke provided no statistically significant (HR = 1.23, 95% CI 0.80 - 1.87; *P* = 0.347, Figures 3). Warfarin is indicated in patients with AF for prophylaxis of stroke, preventing approximately 60% of strokes. However, HD patients have a higher risk of clotting. Arterio-venous graft and tunneled central venous catheter render an increased risk of local or systemic thromboembolism in HD patients. Although the balance of risks and benefits of warfarin perform favorable in mild to moderate CKD patients with AF, as lack of evidence from randomized controlled trials in these populations, current and previous observational studies on warfarin therapy failed to offer recommendations regarding warfarin management. Therefore, the Canadian Cardiovascular Society atrial fibrillation guidelines published in 2012 no longer recommend warfarin for AF patients undergoing dialysis for the primary prevention of stroke.

We performed subgroup analysis according to the dialysis type. The results showed that dialysis type has impact on the heterogeneity. Moreover, from the sensitivity analyses, we infer that Olesen et al.is one of the main sources of heterogeneity.

Bleeding is one of the major risks of warfarin therapy in AF patients, and the INR should be closely monitored. Our results believed that warfarin was associated with a higher risk of bleeding (HR = 1.20, 95% CI 1.03 - 1.39; *P* = 0.019). Platelet dysfunction, regular exposure to heparins during HD, frequent antibiotic use, dietary restrictions, impaired nutritional status, and drug-drug interactions render anticoagulation unpredictable. Hemorrhagic complications may be minimized with frequent INR monitoring Warfarin administration at the end of the dialysis session is related to prominent INR stability, which finally reduces the risk of bleeding according to precise dose adaptation and optimum therapeutic observance.

In a recent study, Praehause et al. analysed the quality of oral phenprocoumon treatment control in ESRD patients, suggested that phenprocoumon is not inferior to warfarin. The phenprocoumon therapeutic effect in HD patients with AF required to further verification. HD patients with AF generally suffer complications such as heart failure, hypertension, previous stroke and diabetes mellitus. These are factors that affect OAT administration and the CHADS2 scoring, therefore the risk of stroke cannot be evaluated properly. Yang et al. suggested an individualized risk stratification that includes bleeding diathesis consideration, CHADS2 scoring system and the consideration of antiplatelet therapy if oral anticoagulation is not used. Thet et al. also recommended an individualized approach to optimize all potential risk factors of bleeding and stroke.

CONCLUSION:

In conclusion, results suggested that warfarin should not be recommended for the routine treatment in HD patients with AF. Large scale, multi-centered, randomized controlled clinical trials should be performed to investigate the efficacy of warfarin treatment in HD and AF patients.

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