Systematic Review and Meta-Analysis

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Effect of anticoagulation therapy in older patients with chronic kidney disease and atrial fibrillation

A meta-analysis

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Abstract

Background: The role of anticoagulation therapy for stroke prevention in older atrial fibrillation (AF) patients with chronic kidney disease (CKD) remains unclear. Therefore, we conducted a meta-analysis to explore the efficacy and safety of anticoagulation therapy in this population.

Methods: The Cochrane Library, PubMed, and Embase databases were systematically searched for studies reporting the effect of anticoagulation therapy in older patients with AF and CKD. The risk ratios (RRs) and 95% confidence intervals (CIs) were regarded as the risk estimates. A random-effects model selected was to evaluate the treatment outcomes. The presentations were based on the Preferred Reporting Items for reporting systematic reviews and meta-analyses statement.

Results: A total of 7 studies with 24,794 older patients with AF and CKD were included. The follow-up of the included studies ranged from 0.9 to 9.0 years. In older patients with no dialysis, compared with nonanticoagulants, anticoagulants reduced the risk of all-cause death (RR 0.66, 95% CI 0.54–0.79), but had comparable risks of ischemic stroke/transient ischemic attack (TIA, RR 0.91, 95% CI 0.46–1.79) and bleeding (RR 1.17, 95% CI 0.86–1.60). In older patients with dialysis, compared with nonanticoagulants, anticoagulants increased the risk of bleeding (RR 1.37, 95% CI 1.09–1.74), but had similar risks of ischemic stroke/TIA (RR 1.18, 95% CI 0.88–1.58) and death (RR 0.87, 95% CI 0.60–1.27).

Conclusion: Compared with nonanticoagulation, anticoagulation therapy is associated with a reduced risk of death in older AF patients with nondialysis, but an increased risk of bleeding in older patients with dialysis.

Abbreviations: AF = atrial fibrillation, CI = confidence interval, CKD = chronic kidney disease, NOAC = nonvitamin K antagonist oral anticoagulant, NOS = Newcastle–Ottawa Scale, RR = risk ratio, TIA = transient ischemic attack, VKA = vitamin K antagonist.

Keywords: anticoagulation therapy, atrial fibrillation, chronic kidney disease, dialysis, older

1. Introduction

Atrial fibrillation (AF) and chronic kidney disease (CKD) are increasingly common conditions, affecting millions of people worldwide and leading to substantial morbidity and health-care expenditure.[1,2] The prevalence of AF is high in patients with CKD: approximately 18% to 20% in CKD with nondialysis[3,4] and 15% to 40% in patients with dialysis.[5,6] AF and CKD often coexist, cause, and exacerbate each other.[7,8] CKD patients with concomitant AF suffer from a worse prognosis.[9,10] In addition, a meta-analysis has shown that AF with increased mortality, allograft loss, and stroke after kidney transplantation.[11] Among patients with coexisting AF and CKD, the rates of stroke and bleeding events increase when the kidney function decreases.[12,13] A previous study[14] has shown that patients with AF and nonend-stage CKD had a 49% increased risk of stroke or systemic thromboembolism compared with AF patients without CKD; and the highest risk was observed in AF patients with end-stage CKD on dialysis. Moreover, AF patients on dialysis need routine heparin anticoagulant therapy during dialysis, which may increase the risk of bleeding. Hence, balancing the risks of thromboembolic and bleeding is a key consideration in AF patients with CKD. Recently, several studies have found that warfarin shows benefits in patients with AF and CKD.[14–16]

Older patients (aged ≥65 years) with CKD are at a high risk of AF.[5] The proportion of older patients accounts for 60% to 80% of the entire patients with AF and CKD.[14] The incidence of stroke and bleeding may increase with age in AF patients.[17,18]

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However, whether anticoagulation therapy is effective and safe in patients with coexisting AF and CKD is still unclear. More recently, several studies[19–25] have investigated the efficacy and safety of anticoagulation therapy in patients with AF and CKD, but these studies yield conflicting results. Therefore, we performed a meta-analysis to elucidate the efficacy and safety of anticoagulation therapy in patients with AF and CKD.

2. Methods

In this meta-analysis, the presentations were based on the Preferred Reporting Items for reporting systematic reviews and meta-analyses statement.[26] There was no need to provide the ethical approval because this meta-analysis was performed based on the published studies.

2.1. Literature search

Using electronic retrieval methods, we systematically searched the Cochrane Library, PubMed, and Embase databases until April 2019 for studies reporting the anticoagulation therapy in older patients with AF and CKD. No language restrictions were imposed during the searches. Non-English articles were translated into English using Google's automatic-translation software. To identify studies involving relevant participants, we performed the search with the following terms: atrial fibrillation, chronic kidney disease, renal insufficiency, renal failure, end-stage renal disease, renal replacement therapy, dialysis, hemodialysis, and peritoneal dialysis. To identify studies involving intervention, we performed the search with the following terms: *oral anticoagulation*, *anticoagulation*, *warfarin*, *phenprocoumon*, *low molecular weight heparin*, *unfractionated weight heparin*, *dabigatran*, *rivaroxaban*, *apixaban*, *edoxaban*, *darexaban*, *betrixaban*, *ximelagatran*, *otamixaban*, and *argatroban*. These 2 items were combined using the Boolean operator "and." The electronic search strategy is provided in Supplementary Table 1, http://links.lww.com/MD/D293. In addition, we screened the reference lists of the review articles to identify the additional reports.

2.2. Inclusion and exclusion criteria

Studies satisfying the following criteria were included: study type, observational studies (prospective or retrospective); study subjects, older patients (≥65 years) with concomitant AF and CKD; comparsions, anticoagulation therapy (nonvitamin K antagonist oral anticoagulants [NOACs], vitamin K antagonists [VKAs], and unfractionated or low molecular weight heparin) versus nonanticoagulation therapy; and the efficacy outcomes included all-cause death and ischemic stroke/transient ischemic attack (TIA), and the safety outcome was total bleeding. Studies that enrolled patients with renal transplant or certain publications (eg, reviews, editorials, letters, and animal studies) were excluded in this meta-analysis.

2.3. Quality assessment

The quality of the included studies was appraised using the Newcastle–Ottawa Scale (NOS) by 3 reviewers (H-WF, ZB-X, and H-Z) independently.[27] Three reviewers (H-WF, ZB-X, and H-Z) scored the bias risk of the cohort studies in 3 domains including selection of cohorts, comparability of cohorts, and assessments of outcome. We defined studies with an NOS score ≥6 stars as moderate-to-high quality and studies with an NOS score <6 stars as low-quality.[28]

2.4. Data extraction

The retrieved studies were screened by 2 reviewers (ZB-X and H-Z) independently. The first phase of screening was performed by reading titles and/or abstracts. The second phase of screening was to review the full text. ZB-X and H-Z reviewed the eligibility of the retrieved articles. Disagreements were settled by discussion with a third author (H-WF). Ultimately, articles meeting the eligibility criteria were included.

For each study, the extracted information included the following characteristics: name of the first author, year of publication, study design, inclusion criteria, age, proportion of male patients, total number of patients, duration of follow-up, and endpoints

2.5. Statistical analysis

For each study, the effect measurements estimate chosen were the risk ratios (RRs) and the corresponding 95% confidence intervals (CIs). We selected a random-effects model to evaluate the treatment outcomes, which accounts for variability both within studies and between studies. The heterogeneity across the included studies was measured with an I^2 statistical test, where values of 25%, 50%, and 75% represent low, intermediate, and high inconsistency, respectively. In the sensitivity analysis, we excluded the included studies one by one. We performed the subgroup analysis based on dialysis versus nondialysis.

All the statistical analyses were performed using the Review Manager Version 5.3 software (Cochrane Collaboration, Copenhagen, Denmark).

3. Results

The search steps are illustrated in Figure 1. A total of 1187 potential articles (935 through PubMed, 221 through Embase, and 31 through the Cochrane Library) were identified. After duplicates were removed, 1142 records remained. Based on the screenings of the titles and/or abstracts, 1114 records were excluded, and 28 articles remained for the full-text review. Twenty-one articles were subsequently excluded because 4 studies compared the outcomes of NOACs with VKAs, 1 study did not report the outcomes of interest, and 16 studies did not report the outcomes in older AF patients with CKD. Finally, a total of 7 retrospective studies[19–25] involving 24,794 participants were included in this meta-analysis.

3.1. Characteristics of included studies

The baseline characteristics of the 7 included studies are shown in Table 1. Three studies[22,23,25] enrolled AF patients with nondialysis CKD, while 4 studies[19–21,24] included AF patients with dialysis. Among AF patients with CKD, 9994 (40.3%) patients used anticoagulants, and 14,800 (59.7%) patients were the nonusers. The anticoagulants used were VKAs (9184, 91.9%), NOACs (726, 7.3%), and unfractionated or low molecular weight heparin (84, 0.8%). The follow-up time of the included studies ranged from 0.9 to 9.0 years. Most of the included studies were conducted in the Europe and North

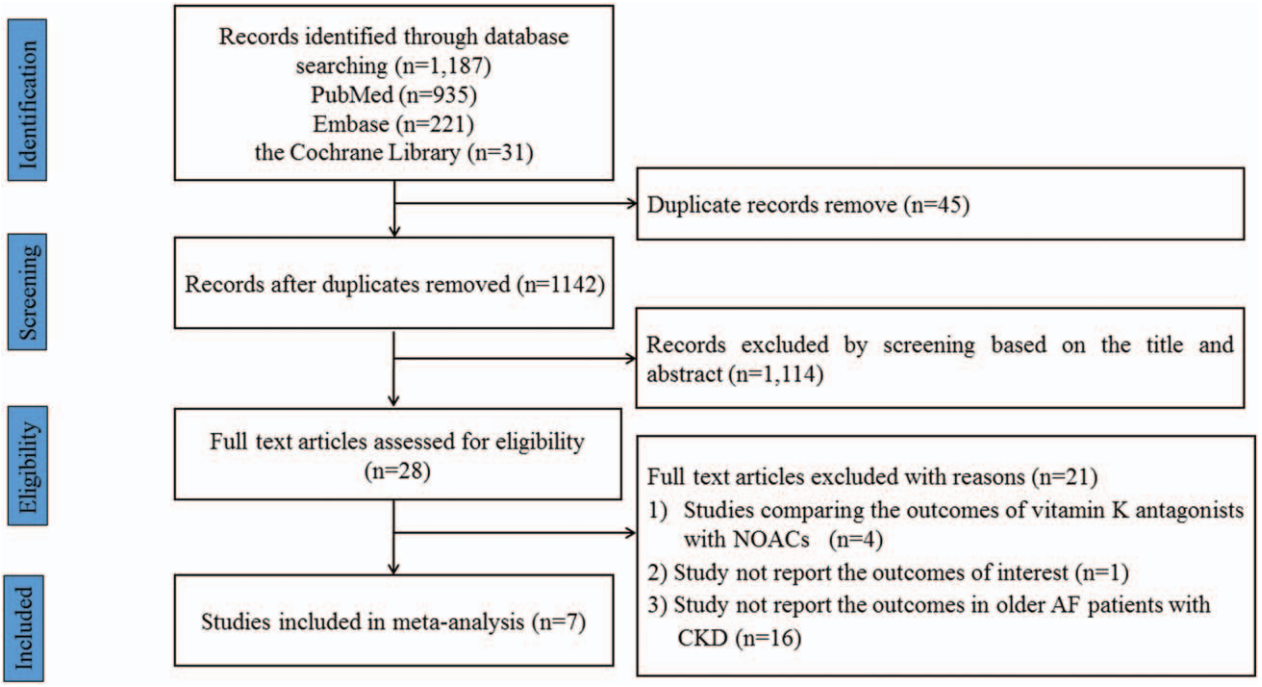

Figure 1. Diagram of the study selection process for the meta-analysis.

America. In addition, the quality of the included studies was generally good, with an NOS score of 7 to 9 (Table 2).

3.2. Efficacy and safety of anticoagulants versus nonanticoagulants

3.2.1. Ischemic stroke/TIA. Data for ischemic stroke/TIA were available in 7 studies. As shown in Figure 2, compared with nonanticoagulation, anticoagulation therapy had a comparable risk of ischemic stroke/TIA (RR 1.06, 95% CI 0.76–1.50) in older patients with AF and CKD (Fig. 2). In view of a significant heterogeneity across the included studies ($I^2 = 88\%$), we performed the subgroup analysis based on dialysis versus nondialysis. The pooled results still showed a similar risk of ischemic stroke/TIA between anticoagulation and nonanticoagulation in patients with dialysis (RR 1.18, 95% CI 0.88–1.58) or without dialysis (RR 0.91, 95% CI 0.46–1.79).

3.2.2. All-cause death. Five studies reported the all-cause death in AF patients with CKD. As presented in Figure 3, compared with nonanticoagulation, anticoagulation therapy significantly reduced the risk of all-cause death by 38% (RR 0.72, 95% CI 0.61–0.84). In the subgroup analysis, compared with nonanticoagulation, the use of anticoagulation therapy was associated with a decreased risk of all-cause death in patients with nondialysis (RR 0.66, 95% CI 0.54–0.79), but did not reduce the risk of all-cause death in patients with dialysis (RR 0.87, 95% CI 0.60–1.27).

3.2.3. Bleeding. Compared with nonanticoagulation, anticoagulation significantly increased the risk of bleeding by 26% (RR 0.72, 95% CI 1.03–1.54; Fig. 4). In the subgroup analysis, anticoagulants increased the risk of bleeding in patients with dialysis (RR 1.37, 95% CI 1.09–1.74), but did not increase the risk of bleeding in patients with nondialysis (RR 1.17, 95% CI 0.86–1.60).

3.3. Sensitivity analysis

The aforementioned results were stable in the sensitivity analysis by excluding the included studies one by one.

4. Discussion

Anticoagulation therapy is recommended for AF patients with CKD and patients on dialysis by guidelines.[29,30] However, the role of anticoagulation therapy in older patients with AF and CKD is still ill-defined. In the current meta-analysis, we first evaluated the efficacy and safety of anticoagulation therapy in the older patients with AF and CKD. On the basis of the predefined inclusion criteria, a total of 7 studies with 24,794 participants were selected and assessed in the final analysis. Our results suggested that anticoagulation therapy reduced the risk of all-cause death in older patients with CKD and AF, but increased the bleeding risk in older AF patients with dialysis.

AF is the most common arrhythmia in CKD patients. AF and CKD coincide in many patients, as these conditions have a common pathophysiology and a number of similar risk factors. Elderly is associated with the increased risks of thromboembolism and bleeding; and therefore, elderly is included in the $CHA2DS_2$-VASc score[31] and HAS-BLED score.[32] Moreover, older patients with CKD are easy to discontinue the use of anticoagulants because of safety concerns.[18] The benefit-risk profiles of anticoagulation therapy remain unclear in the older patients with AF and CKD.

Our results showed that compared with nonanticoagulation therapy, anticoagulation therapy had a comparable risk of ischemic stroke/TIA in older patients with AF and CKD regardless of dialysis. Among older patients with AF and CKD, the risks of thromboembolic events would increase. Furthermore, the risk of thromboembolism increases with the progression of renal function deterioration. The anticoagulant

Table 1

Clinical characteristics of the 7 included studies.

Study design	Wizemann, 2010		Winkelmayer, 2011		Shah, 2014		Jun, 2017		Keskar, 2017		Tan, 2019		Kumar, 2018	
Renal function	Retrospective		Retrospective		Retrospective		Retrospective		Retrospective		Retrospective		Retrospective	
	Dialysis		Dialysis		Dialysis		eGFR <60 mL/min/1.73 m^2		eGFR <45 mL/min/1.73 m^2		Dialysis		eGFR <50 mL/min/1.73 m^2	
Country	International*		US		Canada		Canada		Canada		US		UK	
	User (n = 363)	Nonuser (n = 1881)	User (n = 237)	Nonuser (n = 948)	User (n = 756)	Nonuser (n = 870)	User (n = 3146)	Nonuser (n = 3146)	User (n = 1417)	Nonuser (n = 1417)	User (n = 1651)	Nonuser (n = 4114)	User (n = 2424)	Nonuser (n = 2424)
Age, y	NA	NA	68.9	68.9	75.3	75.1	NA	NA	81.7	82.0	73.9	75.1	81.7	81.9
Male	NA	NA	41.3%	43.2%	60.7%	61.3%	NA	NA	41.4%	40.9%	43.6%	43.0%	45.3%	44.2%
Hypertension	NA	NA	82.7%	82.1%	77.0%	75.3%	NA	NA	90.3%	90.8%	98.1%	98.8%	80.4%	80.0%
Diabetes	NA	NA	60.3%	59.7%	43.7%	39.1%	NA	NA	45.9%	45.3%	68.2%	73.0%	25.9%	24.7%
CHF	NA	NA	77.6%	76.2%	41.3%	34.4%	NA	NA	52.0%	52.2%	64.9%	70.6%	22.0%	22.8%
CAD	NA	NA	46.8%	47.2%	62.2%	59.4%	NA	NA	54.3%	53.4%%	63.5%	67.5%	14.0%	13.4%
Prior stroke/TIA	NA	NA	NA	NA	5.6%	5.1%	NA	NA	9.2%	9.1%	11.0%	14.1%	21.7%	21.9%
Cancer	NA	NA	5.5%	5.1%	NA	NA	NA	NA	17.1%	18.1%	14.5%	16.1%	NA	NA
CHADS2	NA	NA	≥2	≥2	23.3%	31.5%	NA	NA	NA	NA	NA	NA	NA	NA
					$CHADS_2$ 0-1	$CHADS_2$ 0-1								
CHADS2VaSc	NA	NA	NA	NA	NA	NA	NA	NA	4.3	4.3	18.9%	14.5%	4.2	4.2
											CHADS2VaSc 0-1	CHADS2VaSc 0-1		
Follow-up, y	8.0	8.0	1.9	1.9	9.0	9.0	1.0	1.0	0.7	0.7	0.7	0.7	1.4	1.4

* included Belgium, France, Germany, Italy, Spain, Sweden, United Kingdom, Australia, New Zealand, Canada, Japan, United States.

AF = atrial fibrillation, CAD = coronary artery disease, CHF = congestive heart failure, eGFR = estimated glomerular filtration rate, N = number, NA = not available, TIA = transient ischemic attack, UK = United Kingdom, US = United States, y = year.

used in the majority of patients was warfarin in the present meta-analysis. As an important endogenous calcification inhibitor, synthesis of matrix Gla protein is vitamin K dependent; and thus, warfarin may promote vascular calcification by the carboxylation of the matrix GLA protein.[33,34] Moreover, older patients with CKD usually have the highest burden of vascular calcification, which may lead to higher rates of ischemic stroke or lacunar infarcts. The effect of warfarin on atherosclerosis may offset the benefits of anticoagulation in older patients with AF and CKD. Lacunar infarcts have better clinical prognosis and may explain the observed lower rate of all-cause death in patients prescribed anticoagulants.[35] Anticoagulation therapy may improve the severity of stroke but not stroke risk itself, thereby leading to the reduced risk of all-cause death.

Our results showed that anticoagulation therapy increased the risk of bleeding in AF patients with dialysis, but not in patients with nondialysis. Among patients with CKD, the risk of bleeding increases with the progression of renal function deterioration.[13,36]

Both renal dysfunction and elderly are the risk factors of bleeding.[32] Older patients with CKD are vulnerable to bleeding, especially for those patients on dialysis. A series of factors could increase the risk of bleeding in patients with CKD, including increased vascular prostaglandin I_2, chronic inflammation, abnormal platelet adhesion, and aggregation.[37,38] Moreover, the presence of uremic toxins is thought to increase the bleeding risks in dialysis patients.[39] In addition, older patients on dialysis need routine heparin anticoagulant therapy during dialysis, which may increase the risk of bleeding. These factors might explain that the use of anticoagulants was not associated with a lower risk of ischemic stroke/TIA in dialysis patients, but rather an increased risk of bleeding.

5. Limitations

Several limitations might affect the validity of this meta-analysis. First, although most of the included studies adjusted for a series of confounding variables, we still could not exclude the effects of residual confounding due to the nature of observational studies. Second, the majority of patients received warfarin in our included analysis. There were no studies reporting the bleeding rates of NOAC users. Therefore, we could not compare the effects of NOACs with warfarin in older patients with AF and CKD. Third, our current analyses were limited to some outcomes including ischemic stroke/TIA, all-cause death, and bleeding. We did not assessed other outcomes such as osteoporosis (VKAs could increase the risk of osteoporotic fracture[40]). Fourth, the significant heterogeneity existed across the included studies in some comparisons. As such, we should draw a relatively conservative conclusion based on the results of the random-effects model. Further studies are still needed to confirm our results. Fifth, the protocol of this meta-analysis was not registered in PROSPERO. Nevertheless, we found no relevant protocol of this topic in PROSPERO. Finally, the time within therapeutic range of warfarin users was not considered due to the limiting data.

6. Conclusions

Based on current published studies, compared with nonanticoagulation, anticoagulation therapy is associated with a reduced risk of death in older AF patients with nondialysis, but an

Table 2

Quality assessment of the included studies.

	Selection					Outcome			
Study	Exposed Cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest	Comparability	Assessment of Outcome	Length of Follow-up	Adequacy of Follow-up	Total
Wizemann, 2010	*	*	*	*	*	*	*	*	8
Winkelmayer,2011	*	*	*	*	*	*	*	*	8
Shah,2014	*	*	*	*	*	*	*	*	8
Jun,2017	*	*	*	*		*	*	*	7
Keskar,2017	*	*	*	*	*	*	*	*	8
Tan, 2019	*	*	*	*	*	*	*	*	8
Kumar,2018	*	*	*	*	*	*	*	*	8

Asterisks represent stars used in the Newcastle–Ottawa Scale.

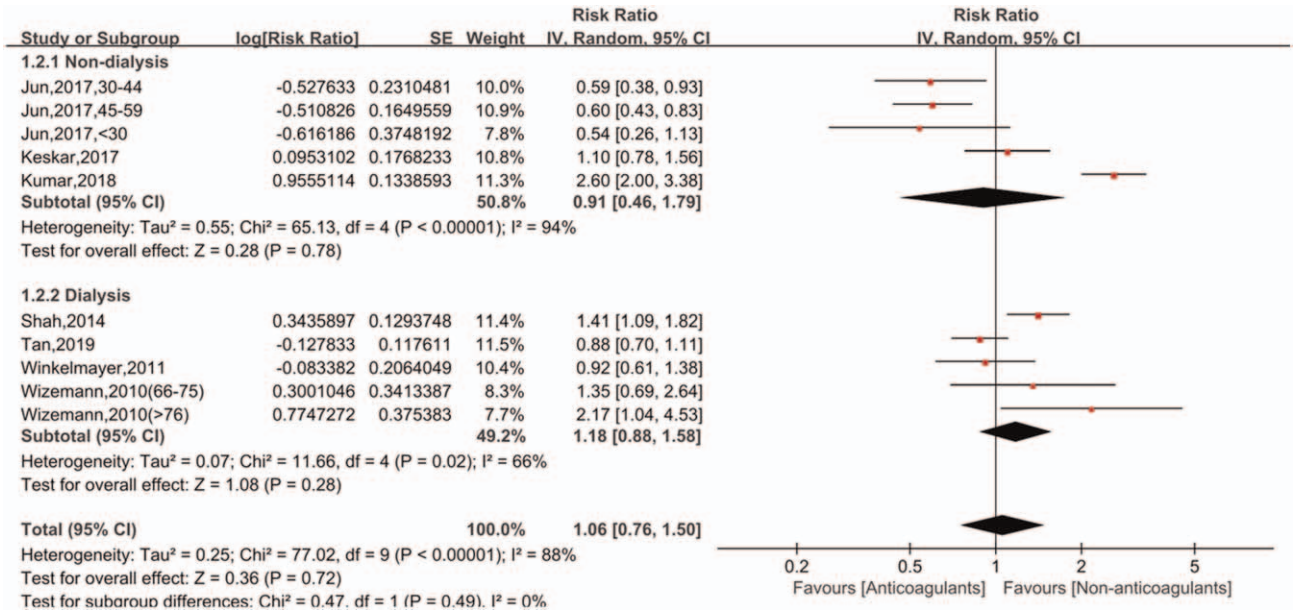

Figure 2. Forest plot for the outcome of ischemic stroke/TIA between anticoagulants and nonanticoagulants in older AF patients with CKD. AF = atrial fibrillation, CI = confidence interval, CKD = chronic kidney disease, IV = inverse of the variance SE = standard error, TIA = transient ischemic attack.

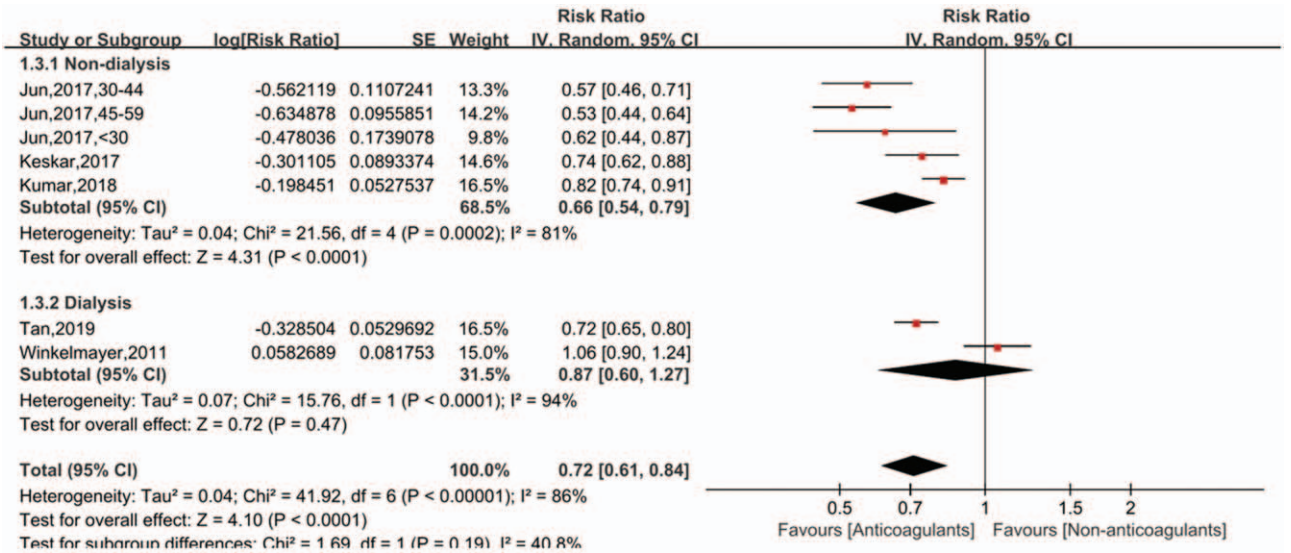

Figure 3. Forest plot for the outcome of all-cause death between anticoagulants and nonanticoagulants in older AF patients with CKD. AF = atrial fibrillation, CI = confidence interval, CKD = chronic kidney disease, IV = inverse of the variance, SE = standard error.

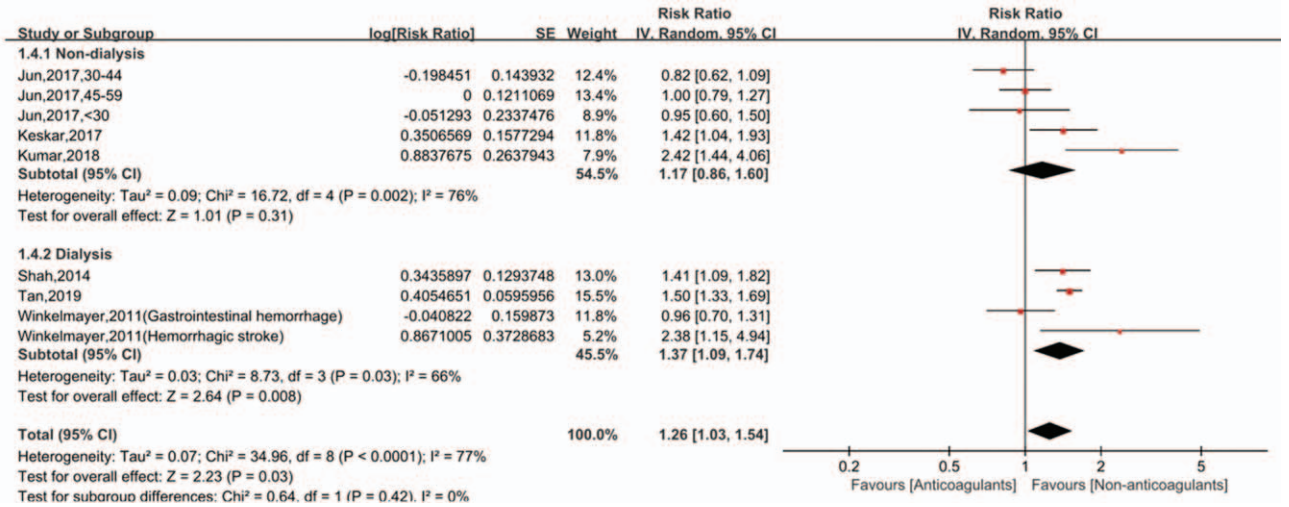

Figure 4. Forest plot for the outcome of bleeding between anticoagulants and nonanticoagulants in older AF patients with CKD. AF = atrial fibrillation, CI = confidence interval, CKD = chronic kidney disease, IV = inverse of the variance, SE = standard error.

increased risk of bleeding in older patients with dialysis. Further high-quality prospective studies are needed to confirm our findings.

Author contributions

Data curation: Wenfeng He, Hao Zhang, Zhengbiao Xue.
Formal analysis: Hao Zhang, Zhengbiao xue.
Investigation: Zhengbiao Xue.
Methodology: Wenfeng He, Wengen Zhu, Zhengbiao Xue.
Software: Wenfeng He, Hao Zhang, Zhengbiao Xue.
Supervision: Zhengbiao Xue.
Validation: Wenfeng He, Wengen Zhu.
Writing – original draft: Hao Zhang, Zhengbiao Xue.
Writing – review & editing: Wenfeng He, Zhengbiao Xue.

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