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Direct oral anticoagulants versus vitamin K antagonists and no anticoagulation therapy in patients with nonvalvular atrial fibrillation and end-stage renal disease or hemodialysis: A Systematic Review and Meta-Analysis

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DIRECT ORAL ANTICOAGULANTS VERSUS VITAMIN K ANTAGONISTS AND NO ANTICOAGULATION THERAPY IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION AND END-STAGE RENAL DISEASE OR HEMODIALYSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Aims: To compare the composite outcome of stroke and major bleeding, stroke, major bleeding and all-cause mortality rates between direct oral anticoagulants (DOAC) and vitamin K antagonist (VKA) and no anticoagulation in end-stage renal disease (ESRD) and dialysis patients with nonvalvular atrial fibrillation (AF).

Methods and Results: We systematically searched MEDLINE, Embase and Cochrane Controlled Register of Trials, in November 2021, for studies comparing VKA and DOAC and no anticoagulation in patients with AF and ESRD. Twelve eligible studies were included: nine studies compared DOAC versus VKA and two studies examined DOAC versus no anticoagulation treatment. Random effects meta-analysis was performed. Compared with VKA, DOAC was associated with lower rates of the composite outcome overall (pooled OR 0.59 [0.38, 0.93], p=0.02), lower stroke rate (pooled OR 0.63 [0.44, 0.89], p= 0.009) and lower bleeding complications (OR 0.65, [0.44, 0.98], p=0.04). The DOAC use was also associated with decreased all-cause mortality compared to VKA (OR 0.54, [0.37, 0.80], p=0.002). In subgroup analysis of hemodialysis patients, no statistically significant differences were noted between DOAC and VKA for the composite outcome (OR 0.70 [0.33, 1.49], p=0.35). Compared with no anticoagulation, DOAC showed a significant lower incidence of stroke (OR 0.36, [0.19, 0.68], p=0.002) with no difference in major bleeding events. (OR 0.85, [0.48, 1.52], p=0.59)

Conclusions: In ESRD patients with nonvalvular AF, DOAC reduced stroke, major bleeding and all-cause mortality as compared to VKA. Compared with no anticoagulation, the DOAC reduced stroke rate without significantly increasing major bleeding.

Keywords: End-Stage renal disease; nonvalvular atrial fibrillation; direct oral anticoagulants; vitamin K antagonists

Abbreviations

ESRD - end-stage renal disease

AF - atrial fibrillation

VKA - vitamin K antagonists

TTR - time in therapeutic range

DOAC - direct oral anticoagulants

OAC – oral anticoagulation

RCT - randomized clinical trials

LAAO - left atrial appendage occlusion

Introduction

Patients in end-stage renal disease (ESRD), defined as having a glomerular filtration rate of <15 ml/min/1,73 m^2 or undergoing hemodialysis, present both a high bleeding and thrombotic risks[1,2] and are associated with poor outcomes. [3,4] These patients constitute a challenge for the prevention of cardioembolic stroke, namely in the case of concomitant nonvalvular atrial fibrillation (AF), where the best anticoagulation treatment is not yet defined.

The incidence of AF in patients with ESRD is higher than in the general population, particularly in those undergoing hemodialysis, [3] and increases the risk of cardioembolic stroke, independently of traditional risk factors. [4]

The prevention of thromboembolic stroke would constitute a strong indication for oral anticoagulation in these patients. However, the difficulty in balancing bleeding and thrombotic risks and the absence of prospective data makes oral anticoagulation therapy debatable in ESRD.

Traditionally, vitamin K antagonists (VKA) have been used in the ESRD population, however the data concerning its impact on reducing stroke risk and bleeding complications is conflicting.[5] The heterogeneity in the data can be partly attributed to VKA's narrow therapeutic index and highly variable time in therapeutic range (TTR) among studies and subjects. [6]

Currently, the direct oral anticoagulants (DOAC) are the preferred choice of anticoagulants in patients with nonvalvular atrial fibrillation. In four randomized controlled trials, apixaban, dabigatran, edoxaban and rivaroxaban have generally shown to be non-inferior to warfarin in stroke and systemic embolism prevention. [7–10] Since ESRD patients were excluded of the latter trials, there is no reliable data on DOAC's safety and effectiveness in this particular population.

Hence, we aim to perform a systematic review of the outcomes of existing studies and carry out a meta-analysis comparing DOAC's impact on stroke and bleeding complications to that of VKA or no anticoagulation treatment in ESRD patients with atrial fibrillation.

Methods

Protocol and Registration

This systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standard and is registered in PROSPERO database (CRD42022302042).

Database Search

We performed a systematic search on MEDLINE, Embase and Cochrane Controlled Register of Trials (CENTRAL) from inception to 16th November 2021, for selecting all eligible studies comparing VKA and DOAC in patients with AF and ERSD. The search was restricted to involve human subjects only and no date and language limits were imposed. The full search strategy is presented in **Table 1**. **Fig. 1** shows PRISMA flow diagram related to our search.

Table 1. Search Strategy.

#	**Searches using PubMed, Embase and Cochrane Controlled Register of Trials (CENTRAL) databases**
1	((''Renal insufficiency, Chronic''[MESH]) OR ((Chronic OR end-stage OR ''end stage'' OR ''endstage'' OR ''stage 5'') AND (kidney OR renal OR nephropathy) AND (insufficiency OR disease* OR failure OR disorder OR dysfunction OR impairment)) OR ESRD OR hemodialysis OR dial* OR haemodialysis))
2	"Stroke"[Mesh] OR "Stroke" OR "transient ischemic attack" OR "Cerebrovascular ischemic events" OR "cerebrovascular ischemic disease"
3	"Factor Xa Inhibitors"[Mesh] OR "Factor Xa Inhibitors" [Pharmacological Action] OR "Factor IIa Inhibitors" "Factor Xa Inhibitor" OR "Inhibitor, Factor Xa" OR "Direct Factor Xa Inhibitors" OR "Direct-Acting Oral Anticoagulants" OR "Anticoagulants, Direct-Acting Oral" OR "Direct Acting Oral Anticoagulants" OR "Oral Anticoagulants, Direct-Acting" OR "apixaban" OR "rivaroxaban" OR "edoxaban" OR "dabigatran" OR "Direct Factor Xa Inhibitor" OR "Anticoagulant, Direct-Acting Oral" OR "Oral Anticoagulant, Direct-Acting"
4	"Warfarin"[Mesh] OR "Coumadin" OR "Coumadine" OR "Acenocoumarol"[Mesh] OR "Acenocoumarol"
5	"Atrial Fibrillation"[Mesh] OR "Atrial Fibrillation" OR "Fibrillation, Atrial" OR "Fibrillations, Atrial" OR "Auricular Fibrillation" OR "Auricular Fibrillations" OR "Fibrillations, Auricular" OR "Atrial Flutter"
6	#1 AND #2 AND (#3 OR #4) AND #5

Eligibility criteria

The studies were considered eligible if the following criteria were met: (1) patients with ESRD or undergoing hemodialysis and atrial fibrillation; (2) indication and treatment with VKA or DOAC; (3) reporting of the outcomes of interest (ischemic stroke, bleeding events and all-cause mortality).

Primary and Secondary outcomes

The primary outcome was the composite of ischemic stroke and major bleeding. Secondary outcomes were ischemic stroke, major bleeding and all-cause mortality.

Data collection, extraction and management

One author (E. Andrade) systematically assessed the titles and abstracts of publications retrieved using the search strategy to identify studies who met the eligibility criteria described above. The full text of the included studies was again assessed, independently by two co-authors, to comply with the inclusion criteria. The data extracted per study includes the author and year of publication, study design and population, baseline characteristics, the exposure and the outcomes mentioned above.

Risk of bias assessment

The risk of bias assessment was performed, independently by two co-authors, using the Cochrane Collaboration's risk of bias tool for randomized clinical trials (RCT) (**Table 2**) and the Newcastle-Ottawa Scale for observational studies (**Table 3**). Only one RCT was included in the analysis, which did not have a blinding strategy for participants, due to the requirement of frequent INR measurements in patients receiving VKA. The outcome assessment, follow up and data reporting was accurate. Regarding observational studies, two studies[11,12] showed some heterogeneity in their cohorts, presenting significant age differences between treatment and control groups, reducing the comparative capacity with the other included studies. Despite this, the selection process, ascertainment of exposure, assessment of outcomes and follow up were accurate in most studies.

Table 2. Observational studies bias assessment.

Study	Selection	Comparability	Outcome
Siontis KC 2018	****	*	***
Schafer JH 2018	****	-	**
Weir Mr 2020	****	*	***
Chan KE 2015	****	-	**
Herndon K 2019	**	*	***
Lin YC 2021	****	-	***
Chang SH 2019	****	*	**
Miao B 2020	****	*	**
Jang SM 2020	****	*	**
Coleman 2019	****	*	***
Mavrakanas 2020	****	-	***

Table 3. RCT bias assessment.

Study	Random sequence generation	Allocation Concealment	Baseline Imbalances	Providers and Participants blinding	Trial context deviations	Blinding of Outcomes assessment	Incomplete outcome data	Selective Reporting
De Vriese AS 2020 - Valkyrie Study								

Statistical analysis

Statistical analysis was performed using Review manager 5.4 from the Cochrane Collaboration, computing meta-analysis of the studies for the endpoints defined (composite of ischemic stroke and major bleeding, stroke, major bleeding, and mortality). The measure of effect considered was the odds ratio favoring DOACs versus VKA or "no anticoagulation", and its 95% confidence interval was estimated by the Mantel-Haenszel method using a random effects model. The statistical significance of the overall effect was assessed by the Z-statistic approximation and its p-value, interpreted at a 5% significance level. Heterogeneity between studies was evaluated by the Higgins and Higgins statistics. Publication bias was evaluated by Egger's Test, funnel and Galbraith plots analysis.

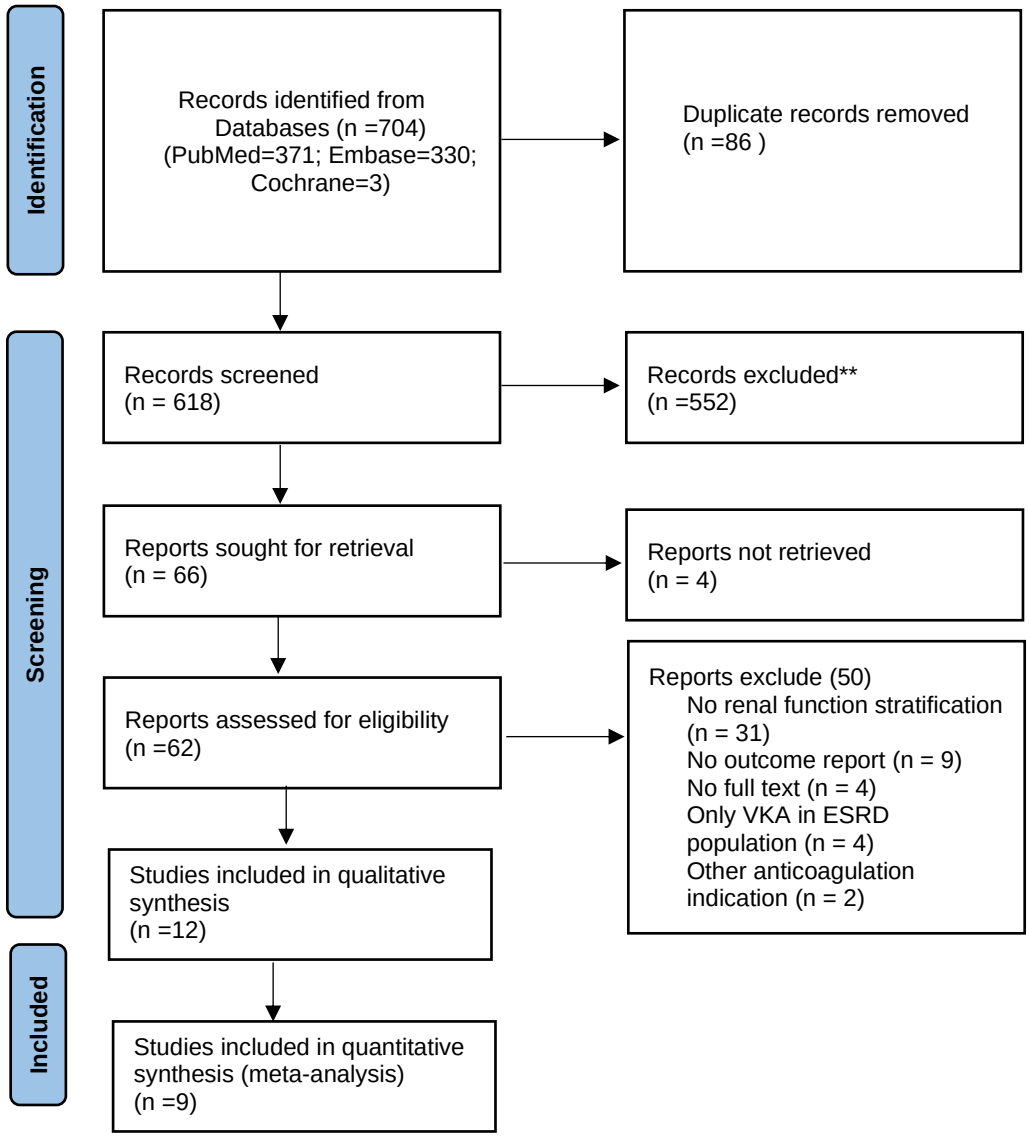

Figure 1. PRISMA flowchart to the included studies.

Results

Search Results

The literature search yielded 704 articles, of which 644 were excluded either due to duplicates removal or after abstract and title analysis, study type (RCT or observational studies reporting the use of DOAC or VKA or no anticoagulation treatment) and study population (patients with nonvalvular AF and ESRD). The remaining 62 articles were assessed for full-text review, leading to exclusion of 50 publications: 31 studies did not report the outcome of interest, nine studies did not report ESRD patients outcomes, four studies did not have DOAC exposure in ESRD patients and two studies reported other oral anticoagulation indication than nonvalvular AF. Lastly, 12 eligible studies were included for qualitative and quantitative analysis. Nine studies compared DOAC versus VKA and two studies compared DOAC versus no anticoagulation treatment. Baseline characteristics of the studies are shown in **Table 4.**

Table 4. Characteristics of included studies.

				Sample size		CHA2DS2-VASc, mean (SD)		Renal Function	
Author Publication	**Design**	**Duration of follow-up (months)**	**Control**	**DOAC**	**Control**	**DOAC**	**Control**	**Stage 5 (S5) (GFR< 15ml/min/1.73m2) Dialysis (D)**	**Outcomes**
Siontis KC [24] **2018**	Observational study – Retrospective (OS-R)	63	Warfarin	Apixaban - 2351	Warfarin-23172	5.27 (1.77)	5.24 (1.79)	S5 - 25 523 D - 25523	Apixaban associated with lower risk of bleeding, stroke and mortality.
Schafer JH [11] **2018**	OS-R	DOAC – 8.8 VKA – 9.7	Warfarin	Apixaban - 105	Warfarin - 120	4.8(1,6)	4,8(1,6)	S5 – 225 D - 194	Apixaban associated with lower risk of bleeding after 6 months. No differences in stroke rates.
Mavrakanas T [25] **2020**	OS-R	48	No anticoagulation	Apixaban - 521	No anticoagulation - 1561	NA	NA	S5 – 2082 D - 2082	No differences in ischemic stroke and clinically important bleeding rates. Apixaban associated with lower rates of all-cause mortality.
Chan KE [12] **2015**	OS-R	48	Warfarin	Dabigatran – 281 Rivaroxaban - 244	Warfarin - 8064	Dabigatran – 2.3 (1,0) Rivaroxaban – 2.2 (1.0)	2,4 (1,0)	S5 – 8590 D - 8590	Dabigatran and rivaroxaban associated with higher risk of major bleeding.
Herndon K [26] **2019**	OS-R	72	Warfarin	Apixaban - 23	Warfarin - 31	NA	NA	S5 – 54 D - 46	No differences in major bleeding and stroke rates.
Lin YC [27] **2021**	OS-R	55	Warfarin	Rivaroxaban - 173	Warfarin - 3185	3.8 (1.5)	3.7 (1.6)	S5 – 3358 D – N/A	Rivaroxaban associated with fewer thrombotic events but similar bleeding rates.
Chang SH [28] **2019**	OS-R	192	Warfarin No anticoagulation	(Apixaban, Rivaroxaban and Dabigatran) – 280	Warfarin – 520 No anticoagulation- 2971	4.7 (1.5)	4.6 (1.7)	S5 – 1523 D – 940	DOAC associated with lower risk of stroke and major bleeding than warfarin, but similar rates when compared to no anticoagulation
Coleman [29]**2019**	OS-R	72	Warfarin	Rivaroxaban - 1896	Warfarin - 4848	4.(2,5)	4.(2,5)	NA	No difference in stroke risk reduction but significantly reduction in major bleeding with rivaroxaban.
De Vriese AS [19] **2020**	Randomized Controlled Trial (RCT)	18	Warfarin	Rivaroxaban - 46	Warfarin - 44	4.8 (1.5)	4.7 (1.4)	S5 – 90 D - 90	No significant differences in stroke rates. Lower rates of fatal bleeding with rivaroxaban.
Weir MR [30] **2020**	OS-R	80	Warfarin	Rivaroxaban - 142	Warfarin - 293	4.5 (1.5)	4.5 (1.5)	S5 – 435 D - 347	No differences in stroke and major bleeding rates.
Miao B [21] **2020**	OS-R	48	Apixaban	Rivaroxaban - 787	Apixaban - 1836	NA	NA	NA	No differences in the risks of stroke or systemic embolism, ischemic stroke or major bleeding between rivaroxaban and apixaban.
Jang SM [31] **2020**	OS-R	83	Rivaroxaban	Apixaban – 4	Rivaroxaban - 2	5.3 (2.5)	5.3 (2.5)	NA	No differences in major bleeding and stroke rates.

Direct Oral Anticoagulation versus Vitamin K antagonists

Of the nine studies included, comparing DOAC and VKA, only six reported data on stroke incidence in the follow-up. For the primary endpoint, DOAC was associated with lower rates of the composite outcome of stroke and major bleeding, compared to VKA (pooled OR 0.59 [0.38, 0.93], p=0.02, I^2 =94%) **(Fig. 2).**

Regarding secondary outcomes, there was a significantly lower stroke rate with DOAC compared to VKA (pooled OR 0.63 [0.44, 0.89], p= 0.009) (**Fig. 3**). For this outcome, a moderate amount of heterogeneity was present (I^2=64%). Furthermore, the Egger's regression test showed that the effect's size was independent from the precision (p=0.792). Additionally, the Begg and Mazumdar test proved that the effects were not related to the study's variance (Kendall's tau= -0.333; p=0.381).

In terms of major bleeding events, DOAC showed lower bleeding complications than VKA (OR 0.65, [0.44, 0.98], p=0.04) (**Fig. 3**). The significant heterogeneity reported for this outcome is probably due to different impact of individual DOAC on major bleeding events (I^2=88%). The Egger test showed no dependence between the effect's size and precision (p=0.408). The Begg and Mazumdar test confirmed that the effects were not related to their variance (Kendall's tau= - 0.2; p=0.484).

The funnel plots analysis showed no evidence of publication bias, which was subsequently confirmed by Galbraith plots (**Supplementary Material**).

There were three studies reporting all-cause mortality. The DOAC use was associated with decreased mortality compared to VKA (OR 0.54, [0.37, 0.80], p=0.002, I^2=31%) (**Fig. 2**).

Regarding only patients undergoing hemodialysis, the composite outcome of stroke and major bleeding showed no statistically significant differences between DOAC and VKA (OR 0.70 [0.33, 1.49], p=0.35, I^2 =95%).

Four studies reported stroke incidence in patients undergoing dialysis, and no statistically significant difference in stroke event rate was identified between DOAC and VKA groups (OR 0.80, [0.44, 1.43], p=0.45, I^2=66%) (**Fig. 3**).

Six studies reported major bleeding events in patients undergoing dialysis, and there was no statistically significant difference in bleeding complications between DOAC and VKA treatments (OR 0.66, [0.34, 1.26], p=0.20, I^2=90%) (**Fig. 3**).

There was insufficient data to perform an all-cause mortality analysis in this subgroup of patients.

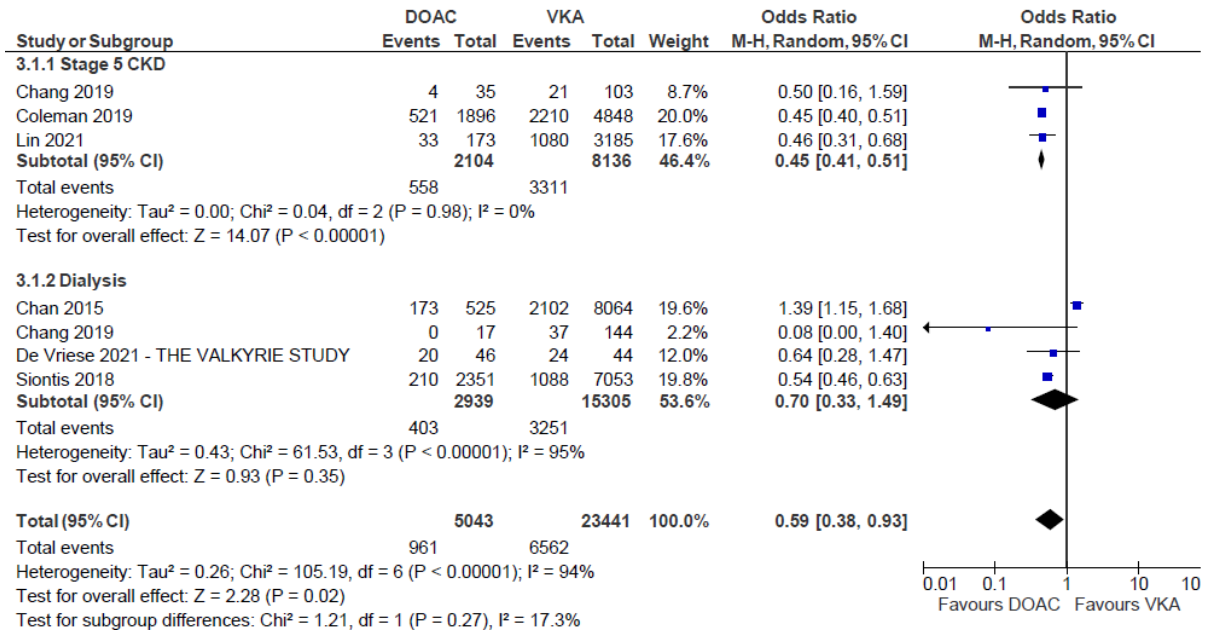

Figure 2. Direct oral anticoagulation versus Vitamin K antagonists – Composite outcome.

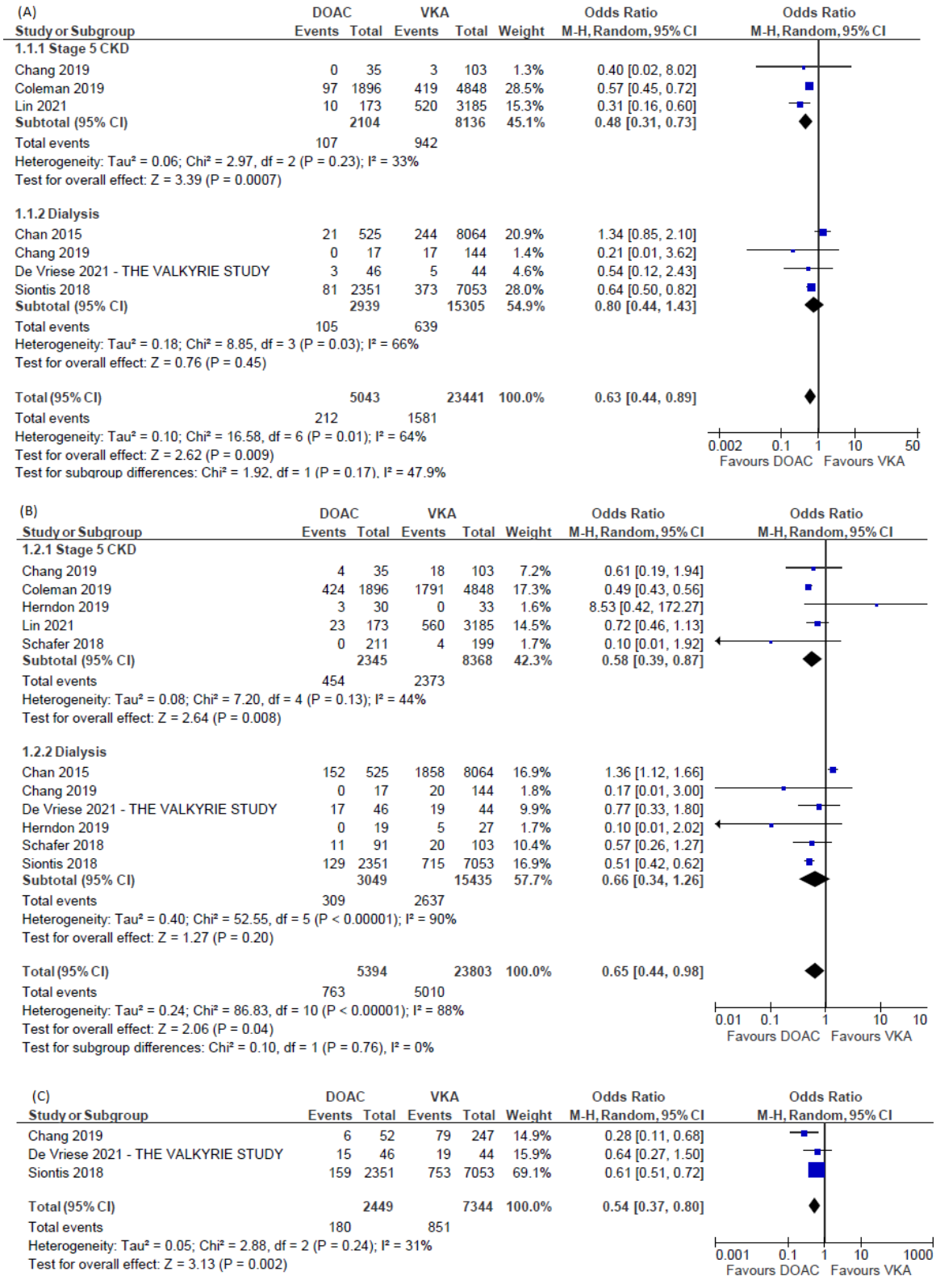

Figure 3. Direct Oral Anticoagulation versus Vitamin K antagonists

(A) stroke, (B) major bleeding, (C) all-cause mortality

Direct Oral Anticoagulation versus no anticoagulation treatment

There were two studies comparing DOAC with no anticoagulation treatment. No difference in the composite outcome rates was identified (OR 0.66, [0.26, 1.67], p=0.38, I^2=64%) **(Fig. 4)**. Data showed a significant lower incidence of stroke with DOAC compared with no anticoagulation (OR 0.36, [0.19, 0.68], p=0.002, I^2=0%) (**Fig. 4**). For this outcome, no heterogeneity was detected. No difference in major bleeding events was identified (OR 0.85, [0.48, 1.52], p=0.59, I^2=67%) (**Fig. 4**). There was moderate heterogeneity for this outcome.

There was insufficient data to perform an all-cause mortality analysis regarding DOAC versus no anticoagulation.

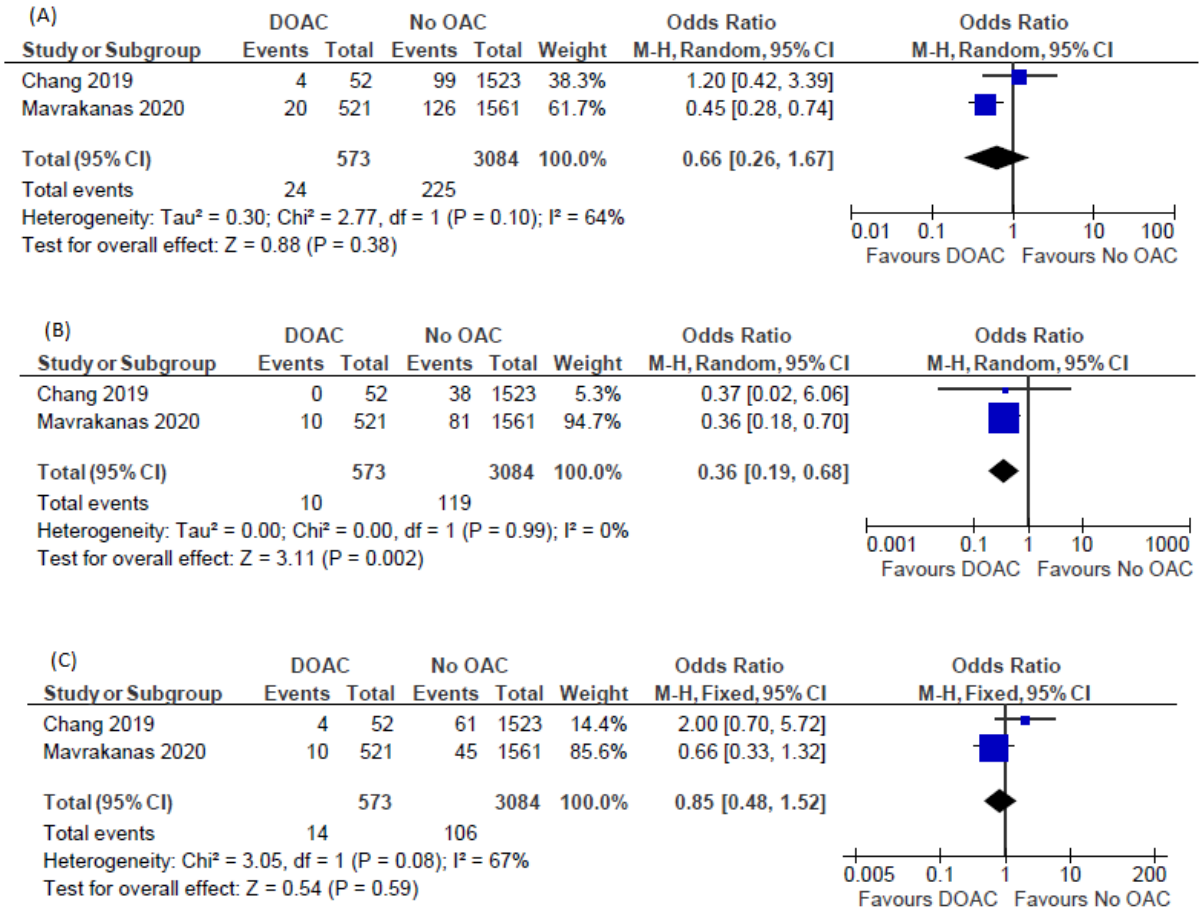

Figure 4. DOAC versus No Anticoagulation. (A) Composite outcome, (B) Stroke, (C) Major bleeding.

Discussion

In this systematic review and meta-analysis, which included nonvalvular AF patients with ESRD, DOAC significantly reduced the composite endpoint (stroke and major bleeding) and all-cause mortality as compared to VKA. However, regarding only those undergoing hemodialysis, no significant differences were found in stroke or bleeding events. To the best of our knowledge, this is the first meta-analysis to include a comparison between DOAC and no anticoagulation treatment. We found that oral anticoagulation when compared to placebo reduced stroke rate without significantly increasing major bleeding in ESRD patients. Additionally, our analysis contains the most recently published data, including the results from the only published RCT comparing DOAC and VKA in the high-risk renal disease setting.

Traditionally, VKA has been the most used anticoagulation strategy in the ESRD population with nonvalvular AF, despite the paucity in clinical data and the uncertainty of its role in the prevention of cardioembolic stroke in this particular population. The largest meta-analysis to date, evaluating the safety and efficacy of warfarin in patients with ESRD and AF showed no reduction in stroke risk with an augmented risk of bleeding, [13] which is one of the most important causes of mortality in patients undergoing hemodialysis.[14] Moreover, warfarin use is linked to vascular calcification, which is an independent predictor of mortality in renal disease patients. [15] Furthermore, our results showed that VKA increase all-cause mortality as compared to DOAC in the ESRD setting.

A previous meta-analysis of the major trials comparing DOAC and VKA demonstrated a favorable efficacy and safety of DOAC in patients with a renal function up to a clearance of 25 mL/min. [16] Moreover, there is no robust clinical data supporting DOAC or VKA use in ESRD/hemodialysis patients for stroke prevention. Nonetheless, the American Heart Association/ Heart Rhythm Society guidelines give a class IIb recommendation for oral anticoagulation with apixaban in ESRD and dialysis patients, [17] which is mainly based on pharmacokinetic data.

The DOAC have different pharmacokinetic profiles and different interactions with dialysis. Dabigatran, edoxaban, rivaroxaban and apixaban have a renal clearance of 80%, 50%, 33% and 27%, respectively. [18] Regarding dabigatran, its interaction with hemodialysis is significant, mainly for being a dialyzable drug, and therefore the balance between dose and effect is unpredictable. Results from a large retrospective study comparing a low dose rivaroxaban (15 mg) and VKA in hemodialysis patients showed a higher bleeding rate associated with rivaroxaban as compared to warfarin. [12] More recently, the only published RCT comparing DOAC and VKA in hemodialysis showed a reduction in bleeding complications with rivaroxaban 10 mg as compared to warfarin, with no differences in the stroke rate. [19] The

RENAL-AF (*Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation*) randomized patients to apixaban 5 mg BID versus warfarin for stroke prevention in nonvalvular AF. This trial, stopped early due to loss of funding (originally powered to enroll 760 patients), reported similar rates of bleeding and stroke between DOAC and VKA. [20] Of note, TTR with warfarin was only 44%, with a large proportion of patients in the subtherapeutic range, and cardiovascular death was higher with DOAC (11% vs 6%).

Our study, which mostly included studies on apixaban and rivaroxaban, suggests that DOAC are superior to VKA in stroke reduction in ESRD patients with AF, however, no significant benefit was shown in patients undergoing hemodialysis. Miao et al. compared apixaban and rivaroxaban in patients with ESRD and AF, and reported no differences in safety and efficacy outcomes. [21] A comparative meta-analysis between rivaroxaban and apixaban in this setting would shed light on which DOAC would benefit ESRD patients the most.

Our work also focused on understanding whether oral anticoagulation is of benefit in this high-risk renal disease population, owing to the evidence of recurrent and severe bleeding events in ESRD patients taking oral anticoagulation. [22] A large retrospective study with 8410 patients, compared cardiovascular outcomes between oral anticoagulation and no anticoagulation in patients with ESRD and AF. [23] The authors reported no reduction in stroke rate with oral anticoagulation and higher rates of intracranial bleeding and hospitalization for bleeding compared with no anticoagulation therapy. These results should be cautiously interpreted, as the majority of patients in the anticoagulation group were taking warfarin (<1% on DOAC). Our study, comparing DOAC with no anticoagulation treatment, demonstrated a significant reduction in stroke rate with DOAC and no significant differences in bleeding events between groups, supporting the use of DOAC in the ESRD population. There is a clear need for randomized control trials to support these findings and the currently ongoing AXADIA (NCT02933697) and SAFE-D (NCT03987711) might help fill the data gaps.

Limitations

Our meta-analysis has several limitations: i) the majority of the studies included were observational, thus increasing the risk of bias and limiting the power of our results; ii) most studies did not report the dose of the DOAC used, limiting the homogeneity of our pooled analysis, and preventing a more precise correlation with renal function, iii) the high heterogeneity that we found between the studies, which might be explained by the different study designs and sample sizes, iv) most of the included studies were studies on apixaban or rivaroxaban, thus underpowering our analysis of the DOAC as a class; v) different studies reported different methods to assess creatinine clearance and thus renal function, with some

using Cockcroft-Gault equation and others using CKD-EPI equation, what could lead to a heterogeneous renal disease stage classification; vi) we used a random model effect to perform meta-analysis and a limitation associated with this model is a likely disproportional weight given to small sample studies.

Conclusion

In ESRD patients with nonvalvular AF, DOAC reduced stroke, major bleeding and all-cause mortality as compared to VKA. Compared with no anticoagulation, the DOAC reduced stroke rate without significantly increasing major bleeding.

Funding

None.

Conflicts of Interest

None of the authors declare any conflicts of interest that could influence the work presented in this paper.

Supplementary Material

Supplementary material to this paper is available at: https://drive.google.com/drive/folders/1Wxomi8fmBQ3wLtlmyOm9u1Yc4zZr2Xra?usp=sharing

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