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RISK OF THROMBOEMBOLISM IN CHRONIC KIDNEY DISEASE PATIENTS WITH NON VALVULAR ATRIAL FIBRILLATION : A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Individuals with CKD are at higher risk for thromboembolic events than those without CKD whilst also at a higher bleeding risk. NVAF often coexist with CKD and heightens the risk of one another. This study aimed to investigate the risk of thromboembolism in CKD patients with NVAF.*

Methods: *This systematic review used Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 as standards. Inclusion criteria for literature eligibility are full-text literature, written in english, and published between 2014 and 2024. Exclusion criteria used for this study were editorials, review articles and identical journal that has been published, and submissions without DOI. Literatures were collected from online reference sources like Pubmed and SagePub.*

Result: *In the PubMed database, the results of our search brought up 45 articles, whereas the results of our search on SagePub brought up 382 articles. The results of the search conducted for the last year of 2014 yielded a total 10 articles for PubMed and 12 articles for SagePub. In the end, we compiled a total of 5 papers, 3 of which came from PubMed and 2 of which came from SagePub. We included five research that met the criteria.*

Conclusion: *The existence of both NVAF and CKD increase the risk of thromboembolic events. There are various modalities to analyze the risk of thromboembolism by assessing risk scores, kidney function, and utilizing transesophageal echocardiography (TEE). In order to prevent ischaemic stroke in NVAF patients, anticoagulants can be administered by in consideration to the kidney function.*

Keyword: *Thromboembolism, chronic kidney disease, non-valvular atrial fibrillation*

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, affecting 1 to 2% of the overall population. AF leads to significant cardiovascular morbidity, particularly ischemic thromboembolic stroke, as well as mortality. Among individuals with Chronic Kidney Disease (CKD), AF is even more widespread, with cardiovascular (CV) disease being the primary contributor to morbidity and mortality.[1]

AF and CKD exhibit a close association, sharing numerous risk factors such as hypertension, diabetes, obesity, and metabolic syndrome. As a result, the increasing incidence and prevalence of AF are intricately connected to a simultaneous rise in CKD, and vice versa. Moreover, the progressive deterioration of kidney function is linked to an elevated incidence of AF, reaching approximately 16% in dialysis patients. The contemporary coexistence of AF and CKD delineates a clinical scenario characterized by a markedly heightened risk of thromboembolic events, including cardioembolic stroke, systemic thromboembolism, and mortality. Additionally, an unexpectedly heightened risk of hemorrhage is observed, particularly among dialysis patients.[2]

The significant role of CKD in elevating the risk of thromboembolic events is well-established. Several factors contribute to an increased tendency for thrombus formation in CKD patients, including abnormalities in the elements of Virchow's triad (perturbations in blood flow, vessel wall, and blood constituents). Furthermore, diminished eGFR independently predicts decreased contractility and emptying velocity of the left atrial appendage. Previous studies have illustrated that compromised renal function serves as a strong predictor for cardioembolic stroke and systemic embolism. Enhancing the assessment of thromboembolic risk were proposed with R2CHADS2 score by augmenting the CHADS2 score by an additional 2 points for patients with eGFR < 60 mL/min. These factors foster the development of dense spontaneous echocardiographic contrast in the left atrium, serving as an indicator of significant blood stasis and correlating with an elevated thrombogenic risk.[3]

Non-valvular atrial fibrillation (NVAF) is an AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate-to-severe mitral stenosis.[4] NVAF and CKD are common, often co-exist, and the presence of either condition increases the risk for the other. NVAF is a known risk factor for stroke, transient ischemic attack (TIA), and/or thromboembolic events (TE). Although individuals with CKD are at higher risk for thromboembolic events than those without CKD, they are also at a higher bleeding risk. While some studies. suggest CKD is an independent risk factor for both thromboembolic and bleeding events in NVAF patients, others have reported that adding estimates of kidney function to current prediction scores does not improve prognostication. However, the studies on this topic have been limited by small or highly selected samples and/or reliance on administrative data claims codes or a single serum creatinine to identify CKD.[5]

The current guidelines for managing AF recommend oral anticoagulation (OAC) therapy to mitigate the risk of stroke or systemic thromboembolism. This recommendation is based on a comprehensive clinical evaluation that includes a thorough assessment of both thromboembolic and bleeding risks. Typically, these risks are evaluated using scores such as CHA2DS2-VASc and HASBLED. Additionally, other risk scores like CHADS2, R2CHADS2, and ATRIA, as well as bleeding risk assessment tools like ATRIA bleeding score, ORBIT, HEMORRAGES, are available for the evaluation of thromboembolism and bleeding risks, respectively. In patients with NVAF, research indicates a strong correlation between spontaneous echocardiographic contrast (SEC) and CHADS2/CHA2DS2-VASc scores, highlighting the potential utility of transesophageal echocardiography (TEE) in providing estimates to guide anticoagulant therapy.[1,6]

However, current NVAF risk scores are inadequate for use in CKD subjects, since they do not take into account the occurrence and the degree of renal function impairment. This study aims to provide a systematic review of thromboembolic risk in CKD patients wth NVAF.

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we review assessed evidence on antiplatelet medications in hemodialiysis. This is done to provide an explanation and improve the handling of patient's treatments. The main purpose of this paper is to show the relevance of the difficulties that have been identified as a whole.

The inclusion criteria for this study are: 1) The paper needs to be written in English; 2) The studied papers include several that were published between 2014, and 2024. The exclusion criteria for this study are: 1) Editorials; 2) Submissions that do not have a DOI; 3) Review articles that have already been published; and 4) Identical entries of published journal.

Search Strategy

We used “thromboembolism”, “chronic kidney disease”, ”non valvular atrial fibrillation” as keywords.The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("thromboembolic"[All Fields] OR "thromboembolism"[MeSH Terms] OR "thromboembolism"[All Fields] OR "thromboembolisms"[All Fields] OR "thromboembolization"[All Fields]) AND ("renal insufficiency, chronic"[MeSH Terms] OR ("renal"[All Fields] AND "insufficiency"[All Fields] AND "chronic"[All Fields]) OR "chronic renal insufficiency"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields]) AND ("non"[All Fields] AND "valvular"[All Fields] AND ("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields])))* AND *((y_10[Filter]) AND (fft[Filter])* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

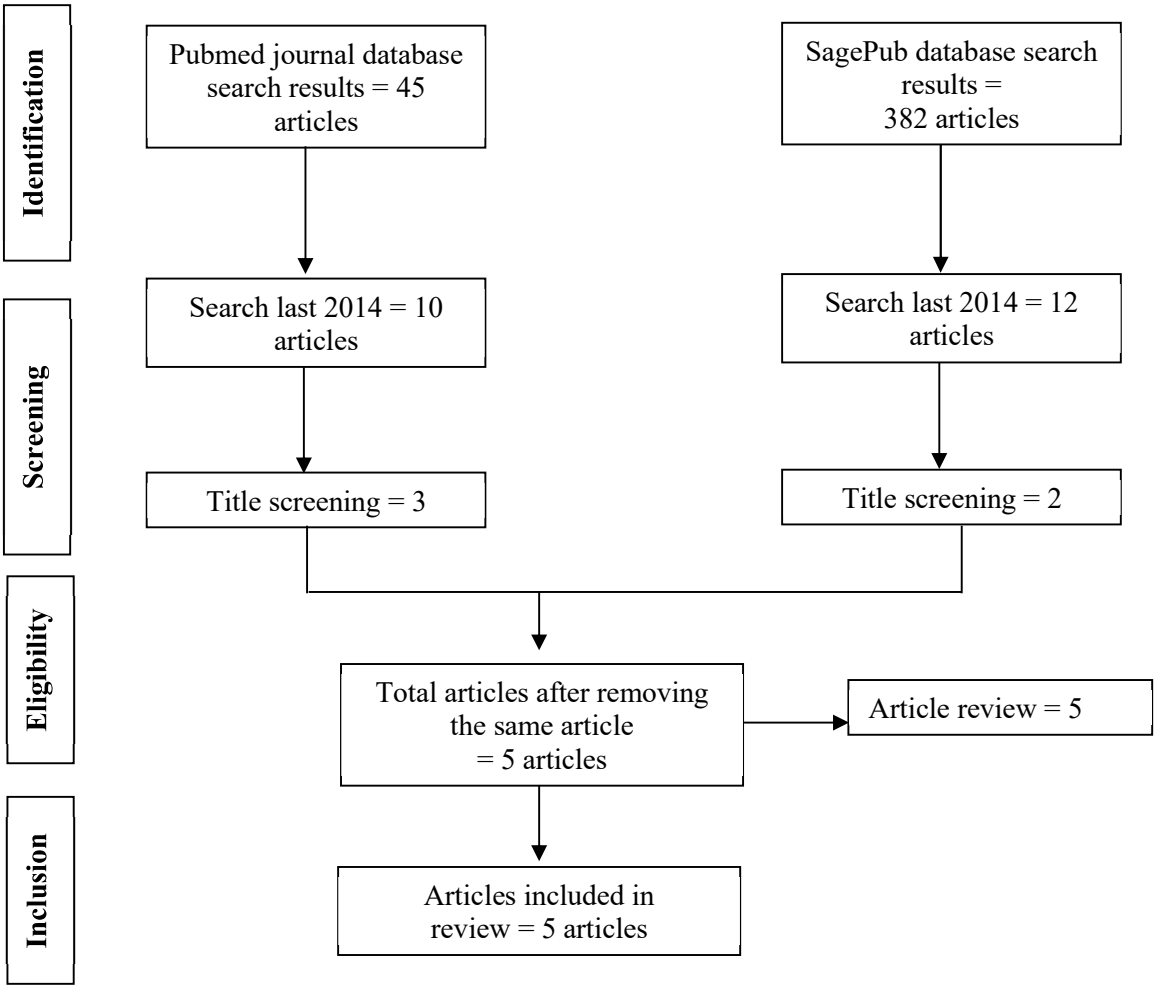

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 45 articles, whereas the results of our search on SagePub brought up 382 articles. The results of the search conducted for the last year of 2014 yielded a total 10 articles for PubMed and 12 articles for SagePub. In the end, we compiled a total of 5 papers, 3 of which came from PubMed and 2 of which came from SagePub. We included five research that met the criteria. Literatures that were included in this study are shown in Table 1.

Table 1. The litelature included in this study

Author	Origin	Method	Sample	Result
McAlister et al., 2016.[5]	Alberta, Canada	Retrospective cohort study	58,451 patients	A total of 58,451 patients (mean age 66, 31.3% with CKD) followed for median 31 months, 21.3% died, 12.6% had a thromboembolic event (4.2 per 100 patient years), and 7.8% had a major bleed (2.6 per 100 patient years). There were graded associations between kidney function and all-cause mortality (aHR 1.88 [1.79-1.98] for very high versus low risk KDIGO category), major bleeding (aHR 1.61 [1.47-1.76]), and thromboembolic events (aHR 1.13 [1.04-1.23]). All 7 prediction scores had significantly poorer c-statistics in patients with CKD: 0.50-0.59, all p
Kizawa et al, 2018.[6]	Osaka, Japan	Cohort study	581 patients	A total of 581 patients (181 women; mean age, 67 years) who underwent transesophageal echocardiography were examined. Patients were divided into 4 groups based on the estimated glomerular filtration rate (eGFR) (mL/min/1.73m2): eGFR ≥90 (n = 29), 60≤ eGFR R <90 (n = 329), 30≤ eGFR <60 (n = 209), and eGFR <30 (n = 14).

				TM was defined as the presence of LA thrombus, dense spontaneous echo contrast, or LA appendage velocity ≤25 cm/s. Out of 581 patients, 147 (25%) had TM. The prevalence of TM increased with decreasing eGFR (4%, 18%, 36%, and 86% for each group, P <0.001). Similar trends were observed for some of the clinical and echocardiographic variables including CHA2DS2-VASc score and LA size. Multivariate logistic regression analysis revealed that every 10 mL/min/1.73m2 decrement in eGFR was a significant independent correlate of TM (odds ratio 0.80, p = 0.005), along with non-paroxysmal AF (odds ratio 0.45, p = 0.004), higher CHA2DS2-VASc score (odds ratio 1.24, p = 0.012), every 5 mL/m2 increment in LA volume index (odds ratio 1.57, p <0.001), and every 10% decrement in left ventricular ejection fraction (odds ratio 0.51, p <0.001).
Loo et al., 2018.[7]	Single center	Cohort Study	6818 patients	In as-treated analyses, the rates of ischaemic stroke/SE were similar between NOACs and VKAs (HR 0.94; 95% CI 0.62 to 1.42), as were the rates of major bleeding (HR 0.86; 95%CI 0.56 to 1.33). NOACs also significantly increased the risk of GI bleeding (HR 1.78; 95%CI 1.27 to 2.48). In patients with NVAF and CKD, NOACs and VKAs remained comparable with respect to the risk of ischaemic stroke/SE (HR 0.79; 95%CI 0.40 to 1.58) and major bleeding (HR 0.88; 95%CI 0.47 to 1.62), with no difference in the risk of GI bleeding (HR 0.99; 95%CI 0.63 to 1.55). Similar results were obtained in on-treatment analyses using a time-dependent exposure.

Wang et al., 2019.[8]	Beijing, China	Retrospective study	751 patients	The risks of thromboembolic events, and all-cause and cardiovascular deaths were higher in patients with moderate CKD compared with patients with normal renal function after adjusting for other traditional risk factors (HR: 1.63, 95% confidence interval (CI): 1.03–2.58; HR: 1.55, 95% CI: 1.08–2.23; HR: 3.49, 95% CI: 1.57–7.74; respectively). Left atrial volume index >28.0 mL/m2 was an independent risk factor associated with thromboembolic events and all-cause and cardiovascular deaths (HR: 1.62, 95% CI: 1.21–2.33; HR: 1.56, 95% CI: 1.16–2.10; HR: 1.87, 95% CI: 1.07–3.28; respectively).
Cha et al., 2018.[9]	Korea	Cohort study	12,876 patients	Medical records of 12,876 consecutive patients (aged >18 years) newly diagnosed and followed up with non-valvular AF from 2000 to 2013 were reviewed. TE events, including ischemic stroke and systemic embolism, were investigated for risk factor validation. Among the total of 12,876 patients, 1,390 (10.8%) had TE events. In univariate/multivariate analysis adjusting for clinical factors and antithrombotic medications, traditional risk factors included in the CHA2DS2-VASc scheme showed statistical significance, except for female sex, which was not a predictor of events. Additionally, chronic kidney disease (CKD; hazard ratio 1.62, P<0.001) was shown to be an independent predictor of TE events. Based on the analysis, we developed a novel stratification system, CHA2DS2-VAK, omitting the female sex category and adding CKD. The new scoring system showed

				greater discrimination in event rates between score 0 and 1 patients.

Wang, et al.[10] (2019) showed that the risk of thromboembolic events and all-cause cardiovascular deaths are higher in AF patients with moderate CKD compared to patients with normal kidney function. This study demonstrates that moderate CKD and left atrial enlargement may predict thromboembolic event in AF patients.

McAlister, et al.[5] (2016) demonstrated that the presence of NVAF in CKD patients poses a risk of thromboembolic and bleeding patients due to poor kidney function. This study also highlighted that current widely used prediction scores for thromboembolic and bleeding events perform poorly in patients with any degree of CKD (KDIGO categories above low risk), highlighting the need for better risk prediction scores in NVAF patients with CKD.

Kizawa, et al.[6] (2018) showed that thrombogenic milieu (TM) as determined by the presence of left atrial (LA) thrombus or dense e spontaneous echo contrast (SEC) or poor LA appendage function had an association with CKD severity among patients with NVAF.

Loo, et al.[7] (2018) showed that patients with NVAF and CKD experience an increased risk of ischaemic stroke and adverse bleeding events the use of novel oral anticoagulants (NOAC) can be a safe alternative to vitamin K antagonists (VKA) amongst patients with NVAF and CKD.

Cha, et al.[9] (2018) showed that thromboembolic events (TE) risk stratification systems applied to AF patients such as CHA2DS2-VASc or CHADS2 have a lot to be improved by considering the presence of CKD.

DISCUSSION

NVAF and CKD are common, often co-exist, and the presence of either condition increases the risk for the other. NVAF is a known risk factor for stroke, transient ischemic attack (TIA), and/or thromboembolic events (TE). Although individuals with CKD are at higher risk for thromboembolic events than those without CKD, they are also at a higher bleeding risk. Some studies suggest CKD is an independent risk factor for both thromboembolic and bleeding events in NVAF patients.[3]

Kidney dysfunction in chronic kidney disease (CKD) heightens the likelihood of both thromboembolic and bleeding events. This is due to its association with increased arterial stiffness and the activation of various prothrombotic and inflammatory pathways. These pathways involve increased levels of C-reactive protein, interleukin-6, plasminogen activator inhibitor-1, von Willebrand factor, as well as abnormal levels of fibrinogen, fibrinopeptide A, thromboplastin, and factors VII through XII. Additionally, individuals with CKD commonly experience comorbidities like hypertension, diabetes, or heart failure, which further contribute to an elevated risk of these events.[5]

Current means to predict the risk of TE is by analyzing the risk scores of CHADS2, CHA2DS2-VASc, R2CHADS2, and ATRIA Stroke. However, Cha et al.[9] (2018) argued that these stratification system need to be refined. Improvements need to be done regarding ethnic differences, clinical factors, and biomarkers. Risk prediction can be done by analyzing genetic factors and imaging modalities.[9] Additionally, knowing that kidney dysfunction increase the likelihood of TE and NVAF patiens with CKD, the assessment of kidney function needs to be probed extensively. This assessment can be done by utilizing the KDIGO guidelines including eGFR and albuminaria levels. GFR was estimated using the mean outpatient serum creatinine measurement in each quarter and quarterly median albuminuria was measured in participants who had results of dipstick urinalys.[5]

AF often results from loss of atrial systole, dilatation of the left atrium, and increased atrial pressure load in the atrium in elderly patients. Previous research also illustrated a connection between the severity of CKD and the thrombogenic milieu (TM) in NVAF patiens. It was identified by the existence of left atrial (LA) thrombus, dense spontaneous echo contrast (SEC), or impaired LA appendage function. Transesophageal echocardiography (TEE) can be administered to provide estimates in guiding anticoagulant therapy by analyzing LA diameter, LV dimension and wall thickness, LA volume, LV ejection fraction, and LV mass. This approach is supported by Wang et al.[10], (2019) who demonstrated that left atrial volume index >28.0 mL/m2 was an independent risk factor associated with thromboembolic events and all-cause and cardiovascular deaths. Research showed strong relationship exists between SEC and CHADS2/CHA2DS2-VASc score.[6,9,10]

The current available treatment for NVAF patients to prevent ischaemic stroke is by administering oral anticoagulants (OAC) such as vitamin K antagonists (VKA). The usual VKA treatment given in NVAF patients are warfarin,

acenocoumarin and phenindione. However, VKA therapy may be challenging due to bleeding concern, especially in patients with CKD. VKA alternative such as novel oral anticoagulants (NOAC) such as dabigatran, rivaroxaban, apixaban and edoxaban can be administered to reduce ischaemic stroke in NVAF. The effectiveness and safety of NOAC remained similar to VKA in patients with CKD.[7]

CONCLUSION

The existence of both NVAF and CKD increase the risk of thromboembolic events. There are various modalities to analyze the risk of thromboembolism by assessing risk scores, kidney function, and utilizing transesophageal echocardiography (TEE). In order to prevent ischaemic stroke in NVAF patients, anticoagulants can be administered by in consideration to the kidney function.

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