

Risk of Ischemic Stroke and Stroke Prevention in Patients with Atrial Fibrillation and Renal Dysfunction

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Abstract

Chronic kidney disease (CKD) has been identified as an important risk factor for new-onset atrial fibrillation (AF) and would significantly increase the risk of AF-related strokes. Stroke prevention in AF patients with CKD is a big challenge, especially for patients with end-stage renal disease (ESRD) undergoing long-term dialysis. In addition to an increase risk of stroke, renal dysfunction was also associated with a higher risk of hemorrhage due to dysregulation of coagulation and uremia-mediated platelet dysfunction. Therefore, the net clinical benefit balancing stroke risk reduction and increased risk of bleeding should be weighed carefully before initiating oral anti-coagulants for ESRD patients. Several studies investigating whether warfarin should be used for stroke prevention in AF patients with ESRD have been published and showed inconsistent results. Since none of these studies was a prospective and randomized trial, the best strategy for stroke prevention in AF patients with ESRD undergoing dialysis remained unknown and more data are necessary to answer this issue.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and its prevalence is projected to continuously increase over the next few decades.¹ Asymptomatic AF was common (39.7%) in daily cardiology practice, being associated with elderly age and more comorbidities.² AF patients usually have several important comorbidities, such as hypertension, diabetes and heart failure, and “lone AF” is becoming uncommon.³ The incidence of AF significantly increased when patients have more systemic diseases. In the previous study from Taiwan, the risk of new-onset AF increased from 0.77 per 1000 person-years for patients with a CHADS₂ (congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, and prior stroke or transient ischemic attack) score of 0 to 34.6 per 1000 person-years for those with a score of 6.⁴ AF is an important risk factor of ischemic stroke with a worse prognosis and higher recurrence rate compared to that of non-AF related stroke.⁵ The risk of AF-related stroke is not homogenous and mainly depends on the presence or absence of clinical risk factors. Several scoring systems, including CHADS₂ and CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female) schemes,^{6,7} which incorporated clinical

important factors have been developed to estimate the risk of stroke and guide anti-thrombotic therapies for AF patients.

Although renal dysfunction is not included in the CHADS₂ or CHA₂DS₂-VASc schemes, it has been identified as an important risk factor for new-onset AF and would significantly increase the risk of AF-related strokes.⁸⁻¹⁰ Moreover, renal dysfunction has been reported to be a significant predictor of in-hospital mortality in patients suffering a stroke.¹¹ The strategy about stroke prevention in AF patients with renal dysfunction, especially for those with end-stage renal disease (ESRD) undergoing dialysis, is complex. A substantially increased risk of bleeding with or without oral anticoagulants (OACs) is an important concern when treating these patients. In this review, we will focus on discussing the risk of AF, AF-related stroke and strategy for stroke prevention for patients with renal dysfunction and ESRD.

Risk of New-Onset AF in Patients with Renal Dysfunction

AF and renal dysfunction are frequently coexistent in the clinical practice. One-third of AF patients had stage III to V chronic kidney disease (CKD) with a glomerular filtration rate (GFR) lower than 60 mL/min/1.73m² (Figure 1).¹²⁻¹⁵ The prevalence of AF for subjects without CKD, and with stage 1 to 2, stage 3, and stage 4 to 5 CKD was 1.0%, 2.8%, 2.7% and 4.2%, respectively.¹⁴ The prevalence of AF is much higher in ESRD patients undergoing maintenance hemodialysis which was reported to be 13-27%.¹⁶⁻¹⁸ The risk of new-onset AF was also higher in patients with renal insufficiency compared to those without renal dysfunction. In a recent nationwide study from Taiwan which enrolled 404,703 patients without past

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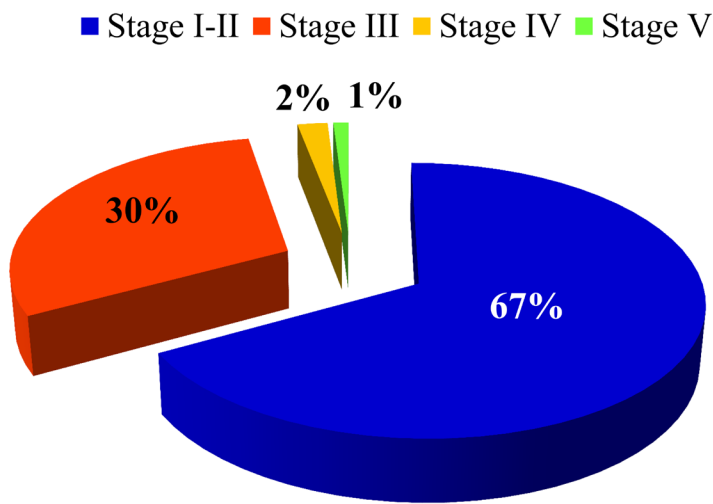


Figure 1: Distributions of renal function in AF patients. One-third of AF patients had stage III to V chronic kidney disease with a glomerular filtration rate smaller than 60 mL/min/1.73m². AF = atrial fibrillation. *The figure was modified from the figure by Hart et al. published in *Can J Cardiol* 2013.¹⁵

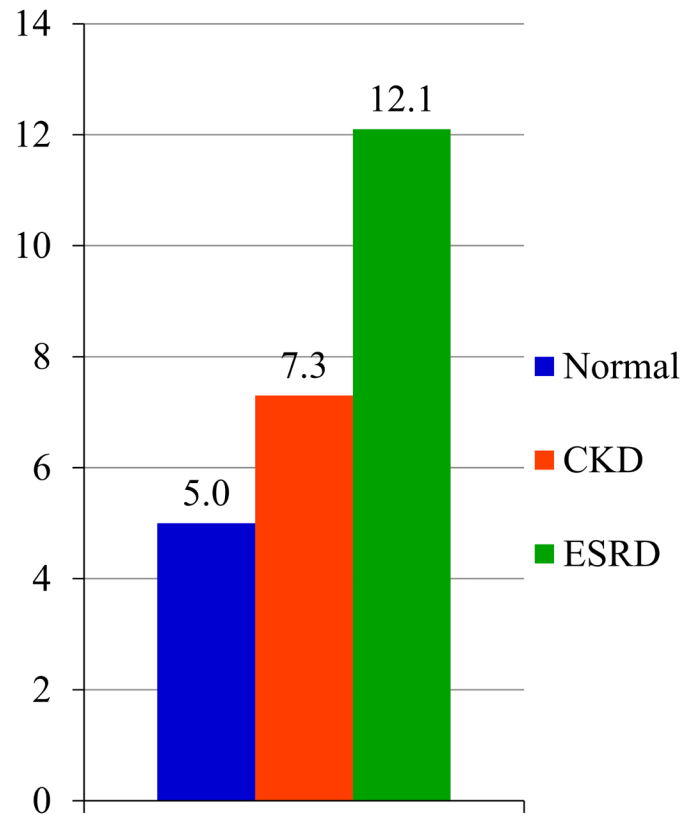
history of AF (134,901 subjects each in control, CKD and ESRD groups), the incidence of AF increased from 5.0 per 1000 person-years for control subjects to 12.1 per 1000 person-years for ESRD patients (Figure 2).¹⁹ Interestingly, the occurrence of AF was reported to be associated with increased risk of developing ESRD in adults with CKD with a hazard ratio (HR) of 1.67.²⁰ The mechanism behind the close relationship between CKD and AF may be multifactorial, including systemic inflammation, similar clinical risk factors for both conditions and modulation of the renin-angiotensin systems.^{21,22} In a recent study which enrolled 40 ESRD patients who have received implantations of implantable cardioverter defibrillators and undergone dialysis, device-detected AF occurred significantly more often on a dialysis day and especially during hemodialysis.²³ The finding suggested that the fluctuation of intra-vascular volume and electrolytes and activation of sympathetic nervous system may contribute the pathogenesis of AF development for ESRD patients.

Renal Dysfunction and Risk of Ischemic Stroke in AF

Several studies have demonstrated that renal dysfunction was an important risk factor of ischemic stroke in AF patients. In the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, 676 thromboembolic events occurred during the follow up of 33,165 person-years among 10,980 AF patients without use of OACs. The risk of thromboembolic events was 39% greater if estimated GFR (eGFR) fell below 45 mL/min/1.73m² compared to an eGFR > 60 mL/min/1.73m².¹² A recent meta-analysis performed by Zeng et al. which analyzed 18 studies involving 538,479 patients has demonstrated that AF patients with eGFR <60 mL/min/1.73m² compared with those with eGFR ≥60 mL/min/1.73m² experienced a significantly increased risk for developing thromboembolic events (relative risk, 1.62 [95% confidence interval = 1.40-1.87; P<0.001]). The annual rate of thromboembolic events increased by 0.41% (95% confidence interval = 0.17%-0.65%) for a 10 mL/min/1.73m² decrease in renal function.²⁴ In a recent Danish registry study of 132,372 individuals with AF, 3,587 individuals had CKD, which was associated with increased risk of both ischemic stroke and bleeding.⁸ In ROCKET-AF (Rivaroxaban Once-daily, oral, direct factor Xa

inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation), 14,264 patients with nonvalvular AF and estimated GFR ≥ 30 mL/min were randomized to rivaroxaban or dose-adjusted warfarin, reduced creatinine clearance was a strong, independent predictor of stroke and systemic embolism, second only to prior stroke or transient ischemic attack.²⁵ In our previous study which enrolled 547 AF patients after catheter ablation, renal dysfunction, defined as an eGFR < 60 mL/min/1.73 m² was an important risk factor of ischemic stroke even among patients with a CHA2DS2-VASc score of 0-1.²⁶

Although renal dysfunction has been demonstrated to be a significant risk factor of ischemic stroke in AF patients, the question to be answered is whether adding renal dysfunction into the scoring systems, such as CHADS2 and CHA2DS2-VASc scores, could improve the accuracy of stroke prediction. A scoring system, named R2CHADS2, which incorporates the components of the CHADS2 score and awards 2 points for renal dysfunction, was derived from the subjects enrolled in ROCKET AF trial and validated among participants in ATRIA study.²⁵ The authors demonstrated that R2CHADS2 scheme could improve net reclassification index by



Incidence of AF per 1000 person-years in Taiwan

Figure 2: Incidence of new-onset AF among control subjects and patients with CKD and ESRD undergoing dialysis. The incidence of AF increased from 5.0 per 1000 person-years for control subjects to 12.1 per 1000 person-years for ESRD patients. AF = atrial fibrillation; CKD = chronic kidney disease; ESRD = end-stage renal disease. *The data used in the figure were from the paper by Liao et al. published in *Kidney Int.* 2014.¹⁹

Table 1: Summary of the studies investigating the treatments for stroke prevention in AF patients with ESRD

Author (year)	Study design	Patient number	Main findings
Wizemann et al. ⁴¹ (2010)	Longitudinal cohort	ESRD patients undergoing hemodialysis – Age < 65 years: 1,001 Age 66-75 years: 1,137 Age >75 years: 1,107	Warfarin use could not prevent stroke in patients younger than 75 years. Warfarin use was associated with a higher risk of stroke for patients older than 75 years (HR = 2.17; 95% CI = 1.04-4.53).
Winkelmayer et al. ⁴⁶ (2011)	Longitudinal cohort	ESRD patients undergoing hemodialysis - 237 warfarin users and 948 propensity-matched nonusers over 2287 person-years of follow-up	The occurrence of ischemic stroke was similar (HR = 0.92; 95% CI = 0.61-1.37), whereas warfarin users experienced twice the risk of hemorrhagic stroke (HR = 2.38; 95% CI = 1.15-4.96).
Shah et al. (2014) ⁴⁷	Population-based retrospective cohort ICD codes-based study	1,626 dialysis patients (46% under warfarin use)	Warfarin use, in comparison with no-warfarin use, was not associated with a lower risk for stroke (HR = 1.14; 95% CI = 0.78-1.67) but was associated with a 44% higher risk for bleeding (HR = 1.44; 95% CI = 1.13-1.85). Propensity score-adjusted analyses yielded similar results.
Friberg et al. (2014) ³⁴	Population-based retrospective cohort ICD codes-based study	13,435 AF patients with renal failure with or without long-term dialysis (3,766 with warfarin use)	Most patients with renal failure benefited from warfarin treatment, despite their high bleeding risk. The incidence of the combined endpoint ischemic or hemorrhagic stroke or death was lower among those who used warfarin than among those who did not use warfarin (HR = 0.76, 95% CI = 0.72-0.80).
Chen et al. (2014) ⁴⁸	Population-based retrospective cohort ICD codes-based study	Propensity-matched analysis for ESRD patients undergoing dialysis – Control (n = 840) versus warfarin (n = 250) versus anti-platelet drugs (n = 840)	Anti-platelet or warfarin treatment could not lower the risk of ischemic stroke in patients with ESRD
Bonde et al. (2014) ⁴⁹	Population-based retrospective cohort ICD codes-based study	1,728 ESRD patients undergoing renal replacement therapy	In patients receiving renal replacement therapy with a CHA2DS2-VASc score > 2, warfarin was associated with lower risk of all-cause death (HR = 0.85, 95% CI = 0.72 to 0.99). However, the use of warfarin was not associated with a lower risk of fatal stroke or fatal bleeding (HR = 1.30, 95% CI = 0.77-2.20).

6.2% compared with CHA2DS2-VASc and by 8.2% compared with CHADS2.²⁵ However, in another study performed by Roldán et al. which enrolled 978 AF patients under warfarin treatment in Spain, adding renal dysfunction (1 point if eGFR was 30-60 ml/min, and 2 points if eGFR was < 30 ml/min) to the CHADS2 and CHA2DS2-VASc stroke risk scores did not independently add predictive information.²⁷ Banerjee et al. investigated this issue among participants in the Loire Valley Atrial Fibrillation Project and found that renal impairment was not an independent predictor of ischemic stroke in patients with AF and did not significantly improve the predictive ability of the CHADS2 or CHA2DS2-VASc scores.²⁸ In 2 studies which compared R2CHADS2 and CHA2DS2-VASc scores among AF patients post catheter ablation, R2CHADS2 was not superior to CHA2DS2-VASc in predicting thromboembolism.^{29,30} Besides, the CHA2DS2-VASc score could further differentiate thromboembolic risk in the low-risk strata based on R2CHADS2 score and may be superior in the subgroup with AF recurrences.²⁹

Another new scoring system, named ATRIA score, which included renal dysfunction (eGFR < 45 ml/min or end-stage renal disease) and proteinuria in the model was derived from the ATRIA cohort.³¹ The ATRIA score ranged from 0 to 15, and it was stratified into low (0 to 5 points), moderate (6 points), and high (7 to 15 points) risk categories to fit annualized event rates of <1%, 1% to <2%, and ≥2% per year, respectively.³¹ In the ATRIA cohort, the C-index was greater and net reclassification improvement was positive comparing the ATRIA score with the CHADS2 or CHA2DS2-VASc scores. However, in a recent study from Taiwan which analyzed 186,570 AF patients without antithrombotic therapies, the CHA2DS2-VASc score performed better than ATRIA score in predicting ischemic stroke as assessed by c-indexes (0.698 vs. 0.627, respectively; $p < 0.0001$). The CHA2DS2-VASc score also improved the net reclassification index by 11.7% compared with ATRIA score ($p < 0.0001$).³² Importantly, the study demonstrated that the patients categorized as low-risk by use of the ATRIA score (score 0-5) were not necessarily low-risk, and the annual stroke rates can be as high as 2.95% at 1-year

follow-up and 2.84% at 15-year follow-up. In contrast, patients with a CHA2DS2-VASc score of 0 had a truly low risk of ischemic stroke, with an annual stroke rate of approximately 1%.³² Another study using the Danish registry database showed similar findings as that observed in Taiwan AF cohort.³³ Based on these findings of studies mentioned above, adding renal dysfunction into the CHA2DS2-VASc score may not be able to improve the accuracy for predicting ischemic stroke.

Stroke Prevention in AF Patients with Non-Dialysis Dependent CKD

Stroke prevention in AF patients with CKD is a big challenge, especially for ESRD patients undergoing long-term dialysis. Renal dysfunction is associated with both increased risk of stroke and hemorrhage (HR = 1.27) due to dysregulation of coagulation and uremia-mediated platelet dysfunction.³⁴ The registry study from Denmark showed the benefit of vitamin K antagonist (VKA) therapy on ischemic stroke/systemic thromboembolism outcomes in the setting of CKD, although both VKA and aspirin were associated with an increased risk of bleeding.⁸ A recent study demonstrated that VKAs have poor efficacy and safety profiles in patients with non-dialysis dependent severe CKD (eGFR < 30ml/min) compared to patient with moderate renal impairment (eGFR 30-60ml/min) or normal renal function.³⁵ Patients with severe CKD were at high risk of stroke and major bleeding during VKA treatment compared with those without renal impairment, HR = 2.75 and 1.66, or with moderate CKD, HR = 3.93 and 1.86, respectively.³⁵ Importantly, variability of International Normalized Ratios during the entire treatment period significantly increased with each stage of CKD compared to control, suggesting that patients with CKD tended to have unstable anticoagulant control with VKAs.³⁵ Recently, Jun et al. further demonstrated that reduced kidney function was associated with an increased risk of major bleeding among older adults with AF starting warfarin; excess risks from reduced eGFR were most pronounced during the first 30 days of treatment.³⁶

The non-VKA oral anticoagulants (NOACs) have changed the

landscape of stroke prevention in AF by offering physicians and patients a safer and more convenient choice compared to warfarin. However, patients with an eGFR < 30 mL/min were excluded from the trials of dabigatran (The Randomized Evaluation of Long-Term Anti-coagulation Therapy <RE-LY>) and rivaroxaban (ROCKET-AF).^{37,38} In the trial of apixaban (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation < ARISTOTLE>), a small percentage of patients (1.5%) with an eGFR < 30 mL/min have been enrolled.³⁹ Therefore, apixaban is the only NOACs which could be used for patients with stage IV CKD. Unlike dabigatran whose excretion largely depends on renal route (~80%), the majority of apixaban was excreted by liver (~73%), and therefore the accumulation of apixaban in CKD patients may not be a serious concern. In the subgroup analysis of ARISTOTLE trial, apixaban treatment reduced the rate of stroke, death, and major bleeding, regardless of renal function.⁴⁰ Besides, patients with an eGFR < 50 mL/min seemed to have the greatest reduction in major bleeding with apixaban compared to warfarin.⁴⁰ However, there is no head-to-head study comparing the efficacy and safety of different NOACs, whether apixaban is a favorable choice of NOACs in patients with renal impairment remains uncertain.

Stroke Prevention in AF Patients with ESRD Undergoing Dialysis

The optimal strategy for stroke prevention in AF patients with ESRD undergoing dialysis is unclear. Internationally, warfarin prescribing patterns for hemodialysis patients with AF vary widely in the world, from 2% in Germany to as high as 37% in Canada.⁴¹ Even in Canada, a national survey of nephrologists showed that most respondents were consistently uncertain about warfarin use for AF in ESRD patients, particularly because of uncertainty on how best to balance the prevention of ischemic stroke against bleeding risk.⁴² Patients with ESRD undergoing dialysis were excluded in the generation and validation of stroke risk calculator scores, such as CHADS₂ and CHA₂DS₂-VASc scores. The uncertainty about how to predict stroke risk among ESRD patients makes it even more difficult for clinical physicians to make decisions about stroke prevention. Until recently, the usefulness of CHADS₂ and CHA₂DS₂-VASc scores in predicting ischemic stroke was validated in a nationwide study from Taiwan which analyzed more than 10,000 AF patients with ESRD undergoing dialysis.⁴³ Similar to general AF population without ESRD, the CHA₂DS₂-VASc score performed better than CHADS₂ and was also able to further refine risk stratification among patients with a CHADS₂ score of 0 or 1.^{44,45}

The next question is how to treat these patients regarding stroke prevention. During hemodialysis sessions, patients would receive heparin for anticoagulation and its effect can be prolonged a few hours after the procedure which could increase the risk of bleeding. Table 1 summarized 6 published studies investigating whether warfarin or aspirin should be used for stroke prevention in AF patients with ESRD.^{34,41,46-49} These studies showed inconsistent results with 4 of them did not demonstrate benefits of warfarin use for stroke prevention in ESRD patients undergoing dialysis. One study performed by Bonde et al. using Danish registry database showed that warfarin use was associated with a reduced risk of mortality among ESRD patients, but the risk of combined endpoint with fatal stroke or fatal bleeding was similar between users and non-users.⁴⁹ The only one study which demonstrated that warfarin use can provide net

clinical benefits balancing ischemic stroke, hemorrhagic stroke and death was performed by Friberg et al.³⁴ In this study, 13,435 patients with renal failure (3,766 under warfarin use) were identified from Swedish Patient registry based on the disease or procedure codes. The authors demonstrated that patients with both AF and renal failure will probably benefit most from having the same treatment as is recommended for other patients with AF, without setting a higher or lower threshold for treatment.³⁴ Since these studies showed different results and none of them was a prospective and randomized trial, the best strategy for stroke prevention in AF patients with ESRD undergoing dialysis remained unknown and more data are necessary to answer this issue.

Conclusion

In summary, renal dysfunction was a risk factor of new-onset AF and was associated with an increased risk of ischemic stroke in AF patients. Although several studies were published regarding the use of warfarin in AF patients with ESRD undergoing dialysis, more data are necessary to understand whether warfarin use has net clinical benefits considering stroke risk reduction and major bleeding in this special population..

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