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Anticoagulant Treatment in Patients with Atrial Fibrillation and Chronic Kidney Disease: Practical Issues

REVIEW

ABSTRACT

Up to 20% of patients with chronic kidney disease have atrial fibrillation, and 40%-50% of atrial fibrillation patients suffer from chronic kidney disease. The 2 diseases share several risk factors and frequently coincide with each other. Both entities are associated with a prothrombotic state, which contributes to increased thromboembolic risk. Atrial fibrillation patients with chronic kidney disease have elevated risk of stroke, major bleeding, and mortality. Clinical risk scores, including CHA_2DS_2-VASc score, HAS-BLED score, or ORBIT score have a limited value in adverse clinical outcome risk stratification in patients with severe chronic kidney disease. However, the inclusion of renal function in the $R_{(2)}$-CHA_2DS_2-VASc score does not improve significantly thromboembolic risk prediction in atrial fibrillation. There is growing evidence suggesting that biomarkers, including N-terminal pro-B-type natriuretic peptide, high-sensitivity cardiac troponin, cystatin C, or growth differentiation factor-15, might be helpful in the assessment of thromboembolic, bleeding, and/or mortality risk in atrial fibrillation patients with chronic kidney disease. The first-choice anticoagulant therapy is based on direct oral anticoagulants in this subgroup. The highest risk of adverse events is observed in end-stage renal disease, and in Europe, in contrast to the USA, solely warfarin is recommended in such atrial fibrillation patients. Treatment of atrial fibrillation patients with chronic kidney disease should be closely monitored with the selection of right anticoagulant agents at the appropriate dose. The current review paper summarizes available evidence and the challenges of the management of atrial fibrillation patients with chronic kidney disease with practical implications.

Keywords: Atrial fibrillation, chronic kidney disease, management, biomarkers, bleeding, stroke, risk stratification

EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is a common clinical entity in everyday clinical practice in the 21st century. In 2017, the number of patients affected by CKD was increased up to 843.6 million individuals worldwide. Its prevalence is likely to increase in the next decades due to population aging and diffusion of risk factors for CKD in the general population, such as diabetes, obesity, and arterial hypertension.[1] The prevalence of CKD in individuals aged ≥20 years has been reported to reach 10.4% among men and 11.8% among women.[2] The prevalence of the individual stages of CKD in general populations was 3.5% [stage 1, estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73 m^2 and albumin to creatinine ratio >30), 3.9% (stage 2, eGFR 60-89 mL/min/1.73 m^2 and albumin to creatinine ratio >30), 7.6% (stage 3, eGFR 30-59 mL/min/1.73 m^2), 0.4% (stage 4, eGFR 15-29 mL/min/1.73 m^2), and 0.1% (stage 5, eGFR < 15 mL/min/1.73 m^2).[3] In an above mentioned comprehensive systematic review of observational studies and meta-analysis, Hill et al[3] have reported a global prevalence of 13.4% for stages 1-5 CKD and 10.6% for stages 3-5 CKD. Renal function may be overestimated in underweight patients due to their reduced muscle mass (especially when calculated with the Modification of Diet in Renal Disease formula). It is well-known that CKD is associated with poor outcomes and increases the incidence of cardiovascular diseases, such as atrial fibrillation (AF) and heart failure (HF).[4] Moreover, the prevalence and incidence of AF increase with decreasing renal function due to its association

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with a proinflammatory state, hypertension, endothelial dysfunction, and left ventricular hypertrophy.[5] Furthermore, CKD is associated with high atrial pressure in the left atrium, which may lead to AF. On the other hand, the activation of the renin–angiotensin–aldosterone system (RAAS) in CKD patients is related to higher incidence of AF, in part as a result of elevated angiotensin II, which can increase atrial pressure, promote atrial fibrosis, and modulate ion channels. All these factors may lead to electrical remodeling of the atria.[6] Finally, sympathetic overactivity displays adverse impact on cardiovascular morbidity and, in the case of renal failure, on cardiovascular mortality.[7] Additionally, AF and CKD frequently coexist, at least in part due to joint risk factors; therefore, up to 20% of CKD patients present AF and 40%-50% of AF patients suffer from CKD.[8] In patients after myocardial infarction impaired renal function contributes to new-onset AF, increasing long-term all-cause mortality.[9] Nephroprotection treatment is a cornerstone in the management of CKD patients, especially in early stages of the disease, based on the use of the blockade of RAAS and new drugs such as flozins.[8] Moreover, the maintenance of renal function is important in patients with coexistent AF in terms of anticoagulant treatment.

PREDICTION OF MAJOR ADVERSE EVENTS IN CHRONIC KIDNEY DISEASE

Both AF and CKD are associated with increased risk of stroke, bleeding events, and mortality, the prevention of which is of major concern in these particularly vulnerable patients.[10-12] To stratify the risk of stroke and systemic thromboembolism in AF patients, several clinical risk scores were developed, including the most commonly used the congestive heart failure, hypertension, age (at least 75 years), diabetes, stroke / transient ischemic attack / systemic embolism, vascular disease, age (65-74 years), sex category (female) (CHA_2DS_2-VASc) score since 2010,[11,13] which has been found to be a better predictor of ischemic stroke (C-index = 0.682) than the $CHADS_2$ score (C-index = 0.608) among patients with end-stage renal disease (ESRD) ($P < .001$) undergoing renal replacement therapy, without oral anticoagulants (OACs) or antiplatelet drugs.[14] Renal function has been incorporated in a modification of the scoring systems, including the R-CHA_2DS_2-VASc and R_2-CHA_2DS_2-VASc scores, in which 1 or 2 points have been added to the original scores, respectively, in AF patients not receiving warfarin with eGFR < 60 mL/min/1.73 m^2.[15] Non-end-stage CKD in patients with CHA_2DS_2-VASc score of 0 or ≥2, after adjustment for aspirin treatment and all baseline characteristics, was associated with increased risk of stroke and thromboembolism (hazard ratio [HR] [95% CI]: 2.07 [1.13-3.79] and 1.33 [1.23-1.43], respectively). In patients without warfarin treatment, renal replacement therapy, irrespective of CHA_2DS_2-VASc score, after adjustment for aspirin treatment and all baseline characteristics, HR (95% CI): 2.01 (1.74-2.33), is related to increased risk of stroke and thromboembolism.[16] However, in anticoagulated AF patients, CKD did not improve prediction of stroke/systemic embolism, thrombotic events, and mortality regardless of the cause compared to $CHADS_2$ score and CHA_2DS_2-VASc score,[17] which reduces the interest in the modified scores, and the current European and American guidelines recommend the use of original versions of the CHA_2DS_2-VASc score.[8,18] Data from the Loire Valley Atrial Fibrillation Project did not independently add predictive value in terms of ischemic stroke-thromboembolism of renal impairment in patients with AF, beyond that of $CHADS_2$ and CHA_2DS_2-VASc scores.[19] Jong et al[20] performed a study on risk scores (AF Investigators [AFI], Anticoagulation and Risk Factors in Atrial Fibrillation [ATRIA], $CHADS_2$, Modified $CHADS_2$, CHA_2DS_2-VASc, and the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation [GARFIELD-AF] risk scores) for ischemic stroke in AF across the spectrum of kidney function. They have found that in patients without kidney function abnormalities, most scores discriminated moderately to good, while the scores were less accurate in moderate/advanced CKD.[20]

Several bleeding risk scores also include renal dysfunction as a risk factor for future bleeding events, including hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs / alcohol concomitantly (HAS-BLED) score listed in the current guidelines[8,18] and older age, reduced hemoglobin / hematocrit / history of anemia, bleeding history, insufficient kidney function, treatment with antiplatelet (ORBIT), ATRIA, and hepatic or renal disease, ethanol abuse, malignancy, older age (at least 75 years), reduced platelet count or function, rebleeding risk, hypertension (uncontrolled), anemia, genetic factors (CYP2C9 single nucleotide polymorphism), excessive fall risk, stroke ($HEMORR_2HAGES$) scores.[21-24] Definitions of renal diseases in those scores range from dialysis in the HAS-BLED score to eGFR < 60 mL/min/1.73 m^2 in the ORBIT-AF.[24]

Interestingly, the stroke risk, symptom severity, severity of AF burden, substrate severity (4S-AF) scheme was not only associated with AF management strategy but its red category predicted all-cause death and composite outcomes of ischemic stroke/transient ischemic attack/systemic embolism, major bleeding, and all-cause death.[25] In this scheme, CKD is included as one of the comorbidities in the substrate domain and thus should influence the AF patient management.[25] In patients with AF and CKD, the "Atrial fibrillation Better Care (ABC) pathway," which consists of 3 main

HIGHLIGHTS

- Chronic kidney disease (CKD) is a frequent comorbidity in patients with atrial fibrillation (AF), which increases thromboembolic and bleeding risks.
- Stroke and bleeding on anticoagulation prediction in patients with severe CKD may be improved by the use of novel biomarkers.
- Anticoagulant treatment of AF patients with CKD, with preference for direct oral anticoagulants, except for end-stage renal disease, requires regular monitoring and appropriate anticoagulant dosing.

pillars—avoid stroke (by the use of anticoagulants), better symptom management as well as cardiovascular and comorbidity optimization—was associated with lower risk of major adverse cardiovascular events and all-cause death [HR (95% CI): 0.60 (0.36-0.98)].[26]

Biomarkers have been found useful in the prediction of unfavorable events in patients with AF and are incorporated into the ABC [age, biomarkers, including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin, and clinical history of prior stroke/TIA]-stroke risk score, the ABC [age, biomarkers, including high-sensitivity cardiac troponin T (cTnT-hs), hemoglobin, and growth differentiation factor-15 (GDF-15), alternatively high-sensitivity cardiac troponin I, hematocrit, cystatin C, or creatinine clearance (CrCl), and clinical history of previous bleeding]-bleeding risk score, and the ABC (age, biomarkers, including NT-proBNP, cTnT-hs, and GDF-15, and clinical history of HF)-death risk score.[27] To our knowledge, there is increasing reliable data on the use of these scoring systems in AF patients, and further studies to evaluate their prognostic value in patients with AF and CKD are needed.

Atrial fibrillation is associated with a prothrombotic state.[11] Prothrombotic abnormalities, including platelet hyperreactivity, elevated D-dimer levels, hyperfibrinogenemia, increased levels of von Willebrand factor, and decreased activity of a disintegrin-like and metalloprotease with thrombospondin type 1 repeats 13 (ADAMTS13), have been reported also in patients with CKD.[28,29] We have shown that in anticoagulated patients with stage 4 CKD and AF, age [HR (95% CI): 1.11 (1.02-1.20)] and decreased fibrin clot permeability [HR (95% CI): 0.55 (0.34-0.90)] were independently related to thromboembolic events, while previous bleeding [HR (95% CI): 3.21 (1.22-8.45)], GDF-15 [per 100 pg/mL, HR (95% CI): 1.48 (1.29-1.69)], cystatin C [HR (95% CI): 9.24 (2.15-39.67)], and cTnT-hs [HR (95% CI): 1.30 (1.14-1.48)] independently predicted major or clinically relevant nonmajor bleedings (7.1% per year) (Figure 1), but after adjustment for age and comorbidities, only cystatin C predicted mortality.[30]

Novel biomarkers might be useful in risk assessment of thromboembolic and bleeding events in AF patients with CKD receiving OACs (Figure 1).[30] Our research demonstrated that patients with stages 3-4 CKD, compared to patients with eGFR ≥ 60 mL/min/1.73 m^2 are characterized by higher fibrinogen levels, higher endogenous thrombin potential as a measure of thrombin formation, lower fibrin clot permeability as a measure of fibrin network density, and longer clot lysis time.[15] The prothrombotic fibrin clot phenotype reported in patients with several diseases associated with prothrombotic tendency[31-33] has also been observed in those with AF and CKD in relation to elevated NT-proBNP.[34]

The prothrombotic state in CKD is enhanced in patients with more severe stages of the disease.[15,35] However, a detailed prognostic value of these prothrombotic variables across the whole spectrum of CKD remains unknown. In conclusion, in patients with CKD, the statement that "in the setting of AF, the potential value of combining several biomarkers in order to achieve an integrated assessment is still not fully established (...)" is also true.[36] It remains to be established whether any scoring system in which any biomarkers are incorporated could be effective in the prediction of both thromboembolism and safety of OAC in AF patients with impaired renal function.

ANTICOAGULATION IN CHRONIC KIDNEY DISEASE

The prevention of stroke in patients with AF based on anticoagulation is generally recommended in the vast majority of patients,[37] who have the CHA_2DS_2-VASc score of 1 in men and 2 in women (class IIa) or at least 2 in men and 3 in women (class IA).[8] The kidney function has no impact on risk assessment using this score, but its impact is reflected in the HAS-BLED score. In this score, abnormal kidney function is defined as chronic dialysis, renal transplantation, or serum creatinine ≥ 200 µmol/L.[8] Based on the results of a recent international survey, there is substantial intra- and interspecialty heterogeneity in the choice and dosing of OAC drugs depending on CKD stages.[38] The 2019 American

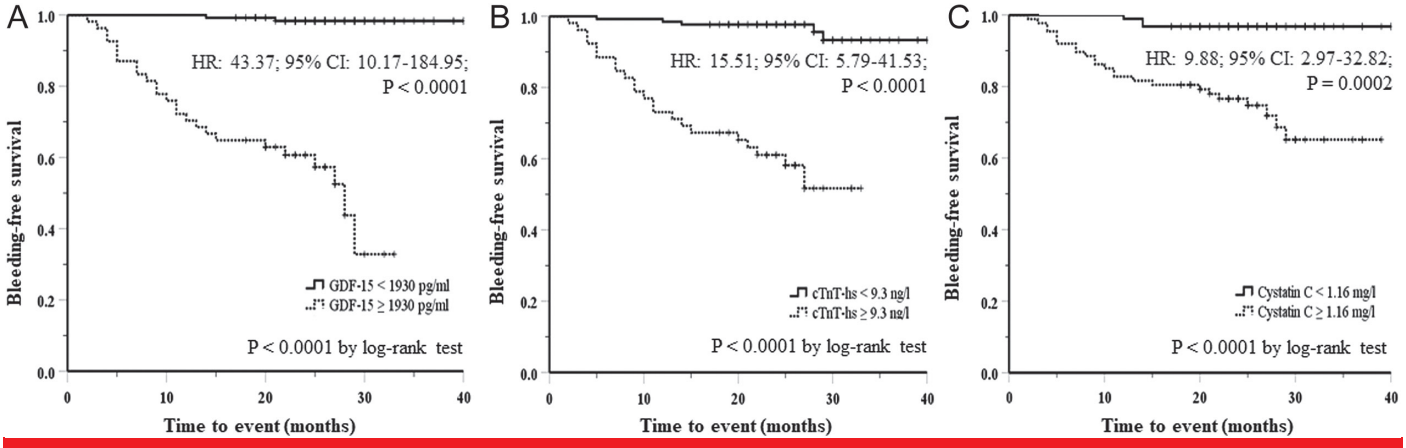

Figure 1. Relations of growth differentiation factor-15 (Panel A), high-sensitivity cardiac troponin T (Panel B), and cystatin C (Panel C) with clinically significant bleeding events in patients with stage 4 chronic kidney disease and atrial fibrillation. Reproduced with permission from (30). cTnT-hs, high-sensitivity cardiac troponin T; GDF-15, growth differentiation factor-15; HR, hazard ratio.

Table 1. The Recommended Dosing Regimens of Non-vitamin K Antagonist Oral Anticoagulants Based on Creatinine Clearance in Patients with Atrial Fibrillation [based on (41)]

Creatinine Clearance	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
50-90 mL/min	150 or 110 mg BID*	5 or 2.5 mg BID**	60 mg***	20 mg
30-50 mL/min			30 mg	15 mg
15-30 mL/min	–	2.5 mg BID		
<15 mL/min		Individualized approach		

*110 mg BID if high risk of bleeding; **2 × 2.5 mg if at least 2 criteria met out of the 3: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L); ***Dose reduction criteria: weight ≤60 kg, concomitant use of potent P-glycoprotein inhibitor.

Heart Association / American College of Cardiology / Heart Rhythm Society guidelines on the management of AF and the 2020 European Society of Cardiology guidelines on the diagnosis and management of AF generally recommend non-vitamin K antagonist oral anticoagulants (NOACs) over vitamin K antagonists (VKAs) for stroke prevention in patients with AF and also in AF patients with CKD, with the exception of advanced CKD, defined as CrCl < 15 mL/min.[8,39,40] This recommendation is also supported by a recent European Heart Rhythm Association practical guide on the use of NOACs in patients with AF.[41] The major contraindications to NOACs regardless of renal function include mechanical prosthetic valve and moderate-to-severe mitral stenosis presence.[41] NOACs (from 27% for apixaban to 80% for dabigatran), compared to warfarin (<1%), are significantly cleared by the kidneys. A dose adjustment to renal function, including based on CrCl calculated preferably using the Cockcroft–Gault equation, and potential periprocedural withdrawal of NOACs are based on renal function.[41] Importantly, reduced-dose apixaban, edoxaban, and rivaroxaban may be used in Europe in patients with CrCl of 15-29 mL/min, while dabigatran 110 mg twice daily should not be used in patients with CrCl < 30 mL/min in Europe; in the USA, this agent at a dose 75 mg twice daily is used in patients with a CrCl of 15-29 ml/min.[41] The recommended dosing regimens of NOACs are shown in Table 1. The analysis of randomized controlled NOAC trials showed slight benefits from NOACs compared with warfarin in patients with AF and decreased CrCl (Figure 2). In patients with reduced CrCl (30-49 mL/min), dabigatran 150 mg twice daily compared to warfarin has been found to be superior to warfarin in terms of stroke/systemic embolism prevention [HR (95% CI): 0.55 (0.40-0.81)], while apixaban compared to warfarin, in patients with CrCl of 25-50 ml/min, has been associated with 50% lower risk of major bleeding [HR (95% CI): 0.50 (0.38-0.66)] (Figure 2). Other NOACs have similar efficacy and safety as compared to warfarin in these subsets of AF patients, suggesting that in patients at high risk of stroke dabigatran 150 mg twice a day is the best option.

It should be highlighted that warfarin nephrotoxicity, also called "warfarin-related nephropathy," is associated with 2 main pathophysiological processes: the disruption of the glomerular filtration barrier causing bleeding into Bowman's space and the aggregation of red blood cells, forming casts in the tubules, which lead to their obstruction and ischemia.[42] Acute warfarin-related nephropathy with or without clinically overt hematuria can also occur in patients on VKAs. Moreover, the inhibition of the vitamin K-dependent matrix gamma-carboxyglutamate protein contributes to enhanced vascular calcification, leading to renal microcirculatory injuries, a decline in eGFR, and increased mortality rate.[43] NOACs are free of this adverse event and might be beneficial in AF patients with impaired renal function. The use of NOACs in AF patients is associated with a protective effect in terms of slowing the progression of kidney disease and evolution toward ESRD. Yao et al[44,45] showed that, as compared to warfarin, dabigatran, rivaroxaban, and apixaban were associated with lower rates of adverse renal outcomes, such as ≥30% reduction in eGFR compared to baseline, the incidence of acute kidney injury, or the doubling of serum creatinine levels as compared to baseline.[44,45] The other data also confirmed nephroprotective effects of rivaroxaban and dabigatran in patients with CKD.[46]

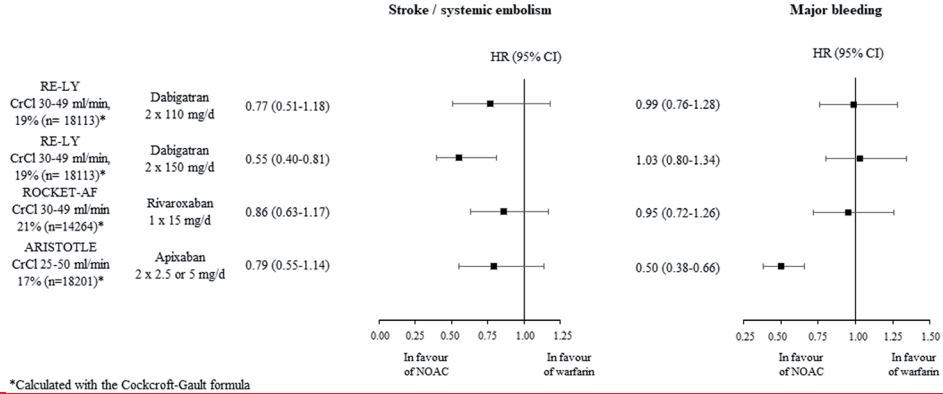

Figure 2. Efficacy and safety of non-vitamin K oral anticoagulants in seminal randomized clinical trials: atrial fibrillation patients with reduced creatinine clearance (CrCl). Based on: Hart RG, et al. Stroke prevention in atrial fibrillation patients with chronic kidney disease. Can J Cardiol. 2013; 29: S71-S78.

Evidence-based recommendations in patients with very poor renal function are limited, as such patients were often excluded from large randomized NOACs trials.[47] There are not sufficient data to recommend (it is contraindicated as per summary of product characteristics) the usage of NOACs in patients with CrCl values below 15 mL/min.[41] Apixaban is approved in the USA in ESRD, and apixaban 2.5 mg twice daily (or rivaroxaban 10 mg once daily) might be considered; nevertheless, in Europe, in contrast to the USA or Japan, real-life experience is very limited.[48] However, warfarin has limited efficacy in reducing the risk of stroke in patients on renal replacement therapy with a high risk of labile international normalized ratio; however, a nationwide Danish cohort study published in 2014 showed that in AF patients with CHA_2DS_2-VASc score ≥2, warfarin lowers the risk of overall death (HR: 0.85, 95% CI 0.72-0.99) without reduction of stroke risk and with a relative high bleeding risk.[16] Individualized approach with shared decision-making is recommended in stage 5 CKD, and most experts suggest that "anticoagulation initiation should probably be more restrictive than currently advocated by official guidelines."[48] Many experts claim that warfarin is considered harmful in advanced CKD, and the selection of right patients should be limited to very high-risk AF patients in particular following ischemic stroke or systemic embolism.[48] To increase the safety of OAC, monitoring of NOACs plasma levels might be particularly important in patients with severe renal dysfunction.[41] Moreover, systematic assessment of renal function, in terms of kidney function deterioration, is crucial in patients with CKD.

On the other hand, especially patients with increased thromboembolic risk (at least 2 additional points in the CHA_2DS_2-VASc score) with absolute contraindications for long-term OACs or patients with an elevated bleeding risk during long-term OAC may benefit from left atrial appendage occlusion.[49] Importantly, at least some of the patients after left atrial appendage occlusion may benefit from long-term half-dose direct anticoagulation compared to patients on standard antithrombotic strategy.[50] However, to our knowledge, no randomized evidence in end-stage CKD patients has been published to date.

CONCLUSIONS

The CKD and AF have joint risk factors, frequently coincide with each other and enhance prothrombotic state. Patients with AF and CKD are particularly vulnerable and have increased risk of stroke, bleeding events, and mortality. Clinical risk scores and biomarkers might be helpful in the assessment of the risk of thromboembolic and bleeding events in this group of patients. Treatment of AF in patients with CKD, especially in its severe forms, should be carefully individualized and should concern appropriate anticoagulant selection and dosing.

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