Understanding and Managing Atrial Fibrillation in Patients with Kidney Disease

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Abstract

Chronic kidney disease (CKD) is on the rise due to the increased rate of related comorbidities such as diabetes and hypertension. Patients with CKD are at higher risk of cardiovascular events and atrial fibrillation is more common in this patient population. It is estimated that the prevalence of chronic atrial fibrillation in patients with CKD is two to three times higher than general population. Furthermore, patients with CKD are less likely to stay in sinus rhythm. Atrial fibrillation presents a major burden in this population due to difficult treatment decisions in the setting of a lack of evidence from randomized clinical trials. Patients with CKD have higher risk of stroke with more than half having a CHADS2 score ≥ 2. Anticoagulation have been shown to significantly decrease embolic stroke risk, however bleeding complications such as hemorrhagic stroke is twofold higher with warfarin. Although newer novel anticoagulation drugs have shown promise with lower intracranial hemorrhage risk in comparison to warfarin, lack clinical trial data in CKD and the unavailability of an antidote remains an issue. In this review, we discuss the treatment options available including anticoagulation and the evidence behind them in patients with chronic kidney disease suffering from atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the general population and represents a major burden to health systems due to its taxing management and challenging treatment decisions. Its prevalence varies with age; about 1% in patients younger than 60 years of age and approximately 8 % in patients older than 80 years of age.[1]

Atrial fibrillation is associated with significant mortality and morbidity due to the increase in risk of stroke and impairment of cardiac function. This becomes increasingly significant in those patients with underlying structural heart problems and chronic diseases such as heart failure, diabetes, chronic hypertension and chronic kidney disease. It is estimated that caring for patients with atrial fibrillation costs five times more than a patient without AF.[2]

Chronic kidney disease (CKD) has been on the rise in US population. Its prevalence is estimated to be around 13% with nearly

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3% increase in the last 20 years.[3] CKD is associated with increase morbidity and mortality, with cardiac disease representing the major cause of death in patients with end stage renal disease (ESRD).[4]

The prevalence of AF in CKD patients is two to three times that in the general population. Soliman et al. examined 3,267 patients from the Chronic Renal Insufficiency Cohort, a prospective cohort of patients with CKD, and found AF to be present in 18% of patients.[5] This increases significantly to 25% in patients above 70 years of age. Using a multivariable adjusted model, AF was found to be significantly associated with age, female sex, smoking, history of heart failure and history of cardiovascular diseases. In ESRD, the rates of AF have been reported to be between 7% and 27%.[6] This wide range has been attributed to differences in age of populations examined, length of hemodialysis, and clinical tools used in the documentation of AF between different studies. In Abe et al. holter monitoring was used in detecting ECG abnormalities in 221 outpatients receiving dialysis, 7% of those patients have either persistent 3% or paroxysmal 4% atrial fibrillation.[7] The use of Holter monitoring in only symptomatic patients may explain the low rate in this study. In contrast, a study by Genovesi et al. atrial fibrillation rates in patients on long term hemodialysis was 27%, paroxysmal in 3.5%, persistent in 9.6%, and permanent in 13.9%.[8] Differences in age and length of dialysis may explain the high rate in this study.

CHADS2 score has been used to risk stratify those patients with higher risk of stroke. Patients with CKD have higher risk of stroke

with more than half having a CHADS2 score ≥ 2 (Graph1). In a study by Nakagawa et al. decreased estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m² combined with CHADS2 score ≥ 2 was associated with higher all-cause (12.9% vs 1.4% per year, hazard ratio [HR] 6.9, p <0.001) and cardiovascular (6.5% vs 0.2% per year, HR 29.7, p <0.001) mortalities compared to preserved eGFR (≥60 ml/min/1.73 m²) combined with CHADS2 score < 2.[9] Since CKD is more prevalent in older population, this represent a major burden due to increase prevalence of preexisting conditions in this population such as diabetes, congestive heart failure and hypertension, so the majority of patients will require anticoagulation.[10] Although the management of atrial fibrillation has been clearly established in patients with normal renal function, the weight of evidence in patient with CKD and ESRD remains scarce.

Renal Disease and Atrial Fibrillation - Cardiovascular Risks

Patients with renal disease and AF have combined increase in morbidity and mortality rates. The United States Renal Data System (USRDS) estimates an annual mortality rate of 5% in patients with ESRD and AF compared to 3 % in those patients without AF.[11,12] In a study by Abbott et al. 3,374 patients were examined from the USRDS and Dialysis Morbidity and Mortality Study Wave II cohort study of hospitalized atrial fibrillation.[13] The 3 year mortality rate of patients with ESRD and AF who had been hospitalized was 53 %, significantly higher than controls at 45%. Moreover in a single center study by Vázquez et al. the 4 year mortality rate in patients with ESRD and AF have been considerably higher than patients without AF alone, 80% vs 29% respectively.[14]

A bidirectional association has been described between CKD and cardiovascular disease. In a study Elsayed et al. data pooled from longitudinal community based studies revealed that cardiovascular disease is not only independently associated with kidney function decline but also a factor in the development of kidney disease itself.[15] Adding to this complexity, a bidirectional relationship has been described between chronic AF and CKD. In a prospective observational cohort study, which included 235,818 patients from a voluntary health check up program in Japan, kidney dysfunction increased the risk of new onset AF while the presence of AF resulted in an increase in the rate of kidney function decline and the development of proteinuria.[16]

Difficulties in the management of patients with cardiac disease can be due to multiple factors. For example, patients with CKD are less likely to undergo angioplasties even in the setting of acute myocardial infarction.[17,18] Moreover, the lack of evidence based decisions in CKD population, due to the routine exclusion of these patients from clinical trials, interferes with the ability to make therapeutic decisions. Concerns regarding Drug elimination and pharmacokinetics in patients with CKD may result in the need of dosage modification or influence drug choice.[17] Anticoagulation by itself can be extremely challenging given that the CKD population is at an increased risk of thrombosis and bleeding. Adding to all this complexity is the prevalence of comorbid conditions and the age variability in this patient population.

Pathophysiology

Two main components play a major role in the development of AF. Ectopic electrical activity, mainly from pulmonary veins, provides the trigger for initiating reentry involving aberrant circuits. This however cannot be maintained without an appropriate substrate. Atrial remodeling has been implicated in the development of AF and persistence.[19,20] Atrial stretch provoked by hemodynamic overload, such in patients with ESRD, can promote structural and electrical alterations seen in tachyarrhythmia triggered mechanisms.[20,21] Furthermore, AF by itself can cause atrial remodeling through fibrosis, collagen deposition, fatty infiltration, molecular changes in ion channels and apoptosis.[22,23] Thus, chronic remodeling plays an important role in patients with AF; the longer the heart remains in AF the harder to maintain sinus rhythm.[24]

Electrolytes disturbances, such as hypokalemia, during dialysis sessions have been implicated in brief paroxysmal AF episodes most noted during the last two hours of dialysis.[25,26] Inflammation and oxidative stress play a major role in the pathophysiology of AF. Elevated inflammatory markers have been associated with new onset and persistent AF.[27] CKD is also associated with inflammation starting at early stages. Elevated inflammatory markers including C-reactive protein (CRP) have been reported in CKD. In addition, CRP has been suggested as an outcome predictor for patients on hemodialysis.[28]

Table 1:	Antiarrhythmic Drugs		
Antiarrhythmic Drug	**Standard Dose**	**Renal Dose**	**Special Considerations**
Flecainide	50-150 mg Q12	CrCl < 35: 50 mg Q12 with frequent plasma level monitoring	
Propafenone	IR 150-300 mg Q8 ER 225-425 mg Q12	No data available, cautious administration	
Amiodarone	600-1200 mg/day for total of 10 grams then 100-200 mg/day	No dose adjustment	
Dronedarone	400 mg Q12	No dose adjustment	Serum creatinine levels increase by about 0.1mg/dL
Dofetilide	500 mcg Q12	CrCl 40-60: 250mcg Q12 CrCl 20-40: 125mcg Q12 CrCl < 20: contraindicated	Continuous ECG monitoring for 3 days
Ibutilide	1 mg IV over 10 minutes, may repeat after 10 minutes if needed	No dose adjustment	Continuous ECG monitoring for 4 hours
Sotalol	80-120 mg Q12	CrCl 40-60: 80mg/day CrCl < 40: contraindicated.	Continuous ECG monitoring for 3 days
Disopyramide	400-800 mg/day in divided doses CrCl 30-40: 100mg Q8 CrCl 15-30: 100mg Q12 CrCl < 15: 100mg Q24	CrCl 30-40: 100mg Q8 CrCl 15-30: 100mg Q12 CrCl < 15: 100mg Q24	CrCl <40: Avoid ER
Quinidine	Gluconate ER: 324-648 mg Q8-12 Sulfate IR: 200-400 mg Q6-8 Sulfate ER: 300-600 mg Q8-12	Reduce dose and monitor serum levels	Continuous ECG monitoring for 3 days

ER- extended release; IR- immediate release

Furthermore, the renin-angiotensin system may provide another link. Renin angiotensin gene expression and increase activation of angiotensin converting enzyme have been noted in atrial fibrillation.[29] CKD as well has been closely related to rennin angiotensin system. The use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) have been shown to be beneficial in decreasing the incidence of AF after MI and maintaining sinus rhythm in patients with long lasting persistent atrial fibrillation.[30-33] Furthermore, treatment with ACEI and ARBs has been shown to slow the progression of CKD.[34]

Management of Arrhythmia

Management of arrhythmia in CKD is complicated due multiple factors. Lack of evidence due to the common exclusion of CKD patients from most trials have left clinicians with very difficult treatment decisions. Though rate-control vs rhythm-control in patients with AF has been studied in general population, no clear evidence exist regarding best approach in patients with CKD. Furthermore pharmacokinetic consideration, concurrent comorbidities, and variability of CKD patients make the task even more cumbersome.

Rhythm control in AF can be achieved through pharmacological or electrical cardio version. Although evidence in patients with CKD is lacking, evidence from AFFIRM (The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation),[35] STAF (Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study)[36] and RACE II (The effect of rate control on quality of life in patients with permanent atrial fibrillation: data from the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II)[37] trials suggest rate-control as preferable approach over rhythm-control. In the AFFIRM trial, 4,060 patients with history of paroxysmal or chronic AF were assigned either to rate-control or an effort to maintain sinus rhythm. Both groups received warfarin. Patients in the sinus rhythm group could stop warfarin therapy after 4 weeks if they maintained sinus rhythm while receiving an antiarrhythmic drug. No significant increase in mortality was noted after 5 year follow-up. Similar stroke rates were noted in both groups; nevertheless all-cause hospitalization was significantly lower in rate-control group.[35] In the STAF trial, 200 patients were randomized either to rhythm-control or rate-control and followed for a mean of 19.6 ± 8.9 months. There was no difference in the primary end point between rhythm-control (5.54%/year) and rate-control (6.09%/year). Primary end point was a combination of death, cardiopulmonary resuscitation, cerebrovascular event, and systemic embolism.[36] Hospitalizations were noted to be higher in the rhythm-control group. Furthermore, in RACE II trial, no difference was noted in quality of life between rhythm-control and rate-control groups.[37]

Few studies have addressed cardioversion outcomes in patients with renal disease. Williams et al. examined patients with CKD and post myocardial AF, and found that patients with CKD were less likely to be discharged in sinus rhythm post cardioversion 70% compared to patients with normal renal function 84%.[38] In a small prospective study that followed patients after electrical cardioversion, Schmidt et al. concluded that impaired renal function was associated with an increased risk of atrial fibrillation recurrence.[39] Furthermore, maintenance of sinus rhythm was associated with improvement in eGFR in patients with mild or moderate renal insufficiency.

Multiple antiarrhythmic drugs can be used in patients with CKD, nevertheless each comes with its cautionary tale (Table 1). Propafenone is a good choice with low proarrhythmic potential in patients with CKD since it is metabolized by the liver. Nevertheless it should be avoided in patients with structural heart disease such as heart failure and significant left ventricular hypertrophy.[40] Sotalol is water soluble thus renally excreted, caution should be advised in patients with CKD, hypokalemia and hypomagnesemia due to its proarrhythmic effects. Increase risk of torsades des points with sotalol has been observed in patients on dialysis.[41] Amiodarone is a reasonable choice but its long term effect limits its use. The CASCADE (The Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation) study evaluated antiarrhythmic drug therapy in 228 patients who had survived an episode of out-of-hospital ventricular fibrillation and who were thought to be at high risk for recurrence.[42] Patients treated with amiodarone, even at the low doses were at higher risk for thyroid dysfunction and pulmonary toxicity. Dronedarone is mostly excreted in feces, so no initial adjustment of dose necessary. It is less effective than amiodarone and contraindicated in type III/IV NYHA heart failure.[43] Ibutilide is intravenous agent, it's a good agent for cardioversion of AF or A-flutter in CKD but caution should be taken in hypokalemia and hypomagnesemia status due to its proarrhythmic potential.[44] Dofetilide is mostly renally excreted; need dosage adjustment in patients with CKD due to increase risk of ventricular arrhythmias.[45] Flecainide is mainly renally excreted, its toxicity have been reported with severe CKD.[46] Not recommended in CKD patients.

Rate control in patients with CKD can be achieved by multiple agents such as lipophilic β-blockade (commonly metoprolol and carvedilol), non-dihydropyridine calcium channel blockers such as diltiazem and antiarrhythmic drugs such as amiodarone. Digoxin can be used but caution should be taken due to increase risk of digitalis toxicity secondary to its narrow therapeutic window especially in dialysis patients.[47] Water soluble β- Blockers such as atenolol, sotalol and nadolol should be avoided. Slow release formulation of verapamil

Table 2:	Bleeding risk in patients with CKD	
Study Name	**Agent**	**Bleeding risk**
Friberg et al.[63]	No Anticoagulation	Multivariate analysis showing 1.05 hazard ratio for intracranial bleeding and 1.59 hazard ratio for major bleeding in patients with renal disease.
Hart et al.[65]	Adjusted-dose warfarin Fixed-dose warfarin + aspirin	Adjusted-dose warfarin: eGFR ≥ 60 ml/min per 1.73 m2, 2 year rate(%) of all major bleed is 2.5 Stage 3 CKD, , 2 year rate(%) of all major bleed is 6.3 Fixed-dose warfarin + aspirin: eGFR ≥ 60 ml/min per 1.73 m2, 2 year rate(%) of all major bleed is 3.6 Stage 3 CKD, , 2 year rate(%) of all major bleed is 6.3
Wieloch et al.[66]	Warfarin	eGFR ≥ 60 ml/min per 1.73 m2 risk/patient year (%) was 1.7 eGFR < 30 ml/min per 1.73 m2 risk/patient year (%) was 7.7
Olesen et al.[54]	Warfarin/Aspirin	Patients with no renal disease had a 3.54 Event Rate per 100 Person-yr Patients with non end-stage CKD had a 8.77 Event Rate per 100 Person-yr Patients with ESRD had a 8.89 Event Rate per 100 Person-yr
Chan et al.[67]	Warfarin	Patients on hemodialysis had increase risk of hemorrhagic stroke (Hazard ratio of 2.22)
Winkelmayer et al.[68]	Warfarin	Patients on hemodialysis had increase risk of hemorrhagic stroke (Hazard ratio of 2.38)

CKD: Chronic Kidney Disease, eGFR: estimated glomerular filtration rate

may increase the risk of bradycardia secondary to third-degree AV block and hypotension especially in ESRD patients.[48] Further more verapamil and diltiazem should not be used in patients with left ventricular function of less than 40% due to their negative inotropic effect.[49]

Catheter ablation is established effective technique in treating AF. Few studies have examined catheter ablation in patients with kidney disease. Naruse et al. examined 221 patients with CKD (defined as an eGFR <60 mL/min/1.73 m2) with AF who underwent successful catheter ablation.[50] After a mean follow-up of 32 months, the study concluded that patients with CKD have a higher recurrence rate 57% compared to patients with normal kidney function 33%. However, patients with CKD in the study were noted to be older with higher rates of hypertension and larger left atrial volumes which make it harder to conclude that renal function was purely responsible for higher recurrence rates. In another small study patients on hemodialysis with AF who underwent successful catheter ablation had a higher recurrence rate compared with age and sex matched patients not on dialysis.[51]

Anticoagulation in CKD

Patients with CKD and AF are at increased risk of thromboembolism due to disorganized atrial contraction.[17] Multiple studies have addressed the higher risk of stroke in patients with kidney disease. Genovesi et al. performed a prospective study examining the risk of stroke in 476 patients on hemodialysis, 15.4% of patients with AF had stroke compared to only 12.4 % of patients with sinus rhythm.[52] Go et al. examined 10,908 patients with AF and CKD and found that compared with patients with eGFR ≥ 60 mL/min, patients with eGFR 45 – 59 mL/min had a relative risk of 1.16 for stroke and patients with eGFR < 45 mL /min had a relative risk of 1.39.[53] Olesen et al. using danish registries have examined 132,372 patients with non-end stage chronic kidney disease and reported an increase risk of stroke and thromboembolism among patients with CKD.[54]

It's clear that patients with CKD have an added risk of thromboemolism with AF. Paradoxically, the risk of bleeding in this population is higher than general population. Vázquez et al. examined the hemorrhagic complications of ESRD patients on anticoagulation with a mean follow-up of 20 months. It was demonstrated that patients on anticoagulation had a 2.36 fold increase of hemorrhage risk compared to patients not on anticoagulation.[55] In prospective study by Shimizu et al., hemorrhagic stroke was significantly increased in patients with eGFR < 60 mL/min/1.73 m2.[56] Furthermore, in a subgroup analysis of the more recent AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and 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) bleeding risk was higher in patients with CKD.[57-59]

CHADS2 scheme is the most widely used scoring systems to identify patients at higher risk of stroke and in need of anticoagulation (1 point is given for congestive heart failure, 1 point for hypertension, 1 point for age>75, 1 point for diabetes mellitus, and 2 points for transient ischemic attack or previous stroke). Each 1 point on CHADS2 scoring system correlates to a factor of 1.5 increase in stroke rate per 100 patient-years without antithrombotic therapy.[60] In patients

with CHADS2 score of ≥ 2, anticoagulation is recommended. In patients with low CHADS2 score < 2 further stratification is needed using CHA2DS2-VASc, which include additional risk factors such as female gender, Age > 65, and vascular disease. It's proposed that CHA2DS2-VASc is a better tool in predicting low risk patients who are less likely to benefit from anticoagulation. Wizemann et al., have demonstrated increase risk of stroke in patients with elevated CHADS2 on hemodialysis.[61] Nevertheless, no studies have been done to assess the value of CHADS2 and CHA2DS2-VASc in patients with CKD.

HAS-BLED scoring system has been used to identify those patients on anticoagulation who are at higher risk of bleeding.[62] It assigns 1 point for each bleeding risks which includes hypertension, abnormal liver or renal function, stroke, history of bleeding, labile INR, and drugs). Patients with HAS-BLED score ≥ 3 are considered high risk. This scoring system defines renal dysfunction as the presence of ESRD with long term hemodialysis therapy, history of renal transplantation or serum creatinine ≥ 2.26 mg/dL. It ignores mild to moderate renal dysfunction which could have a significant impact on bleeding risks. Friberg et al., have shown that renal function is a significant predictor of major bleeding.[63] But again, no specific studies have addressed the risk of bleed in correlation to multiple stages of CKD.

Few studies have assessed the use of anticoagulation with warfarin in patients with CKD (Table 2). Lai et al. demonstrated beneficial use of anticoagulation in patients with AF and CKD with decrease in the incidence of thromboembolic events without increase in the risk of bleeding.[64] Hart et al. examined AF patients participating in the SPAF (Stroke Prevention in Atrial Fibrillation III) trial and found that among the 516 participants with stage 3 CKD, ischemic stroke/systemic embolism was reduced 76% in the adjusted-dose warfarin group compared to the aspirin/low-dose warfarin group.[65] A very recent swedish study examined 3,536 patients on warfarin and found no correlation between glomerular filtration rate and thromboembolic events but glomerular filtration rate levels < 30 ml/min/1.73 m2 were particularly associated with high risk of bleeding.[66]

Table 3:	New novel anticoagulation dose adjustment		
Drug Name	**Study**	**Excretion**	**Dosages and renal adjustment (manufacturer's recommendations)**
Dabigatran	RE-LY[75]	Mostly renal	CrCl > 30 ml/min : 150 mg orally twice daily CrCl 15- 30 ml/min : 75 mg orally twice daily CrCl < 15 ml/min : Avoid
Rivaroxaban	ROCKET AF[57]	Partially renal	CrCl > 50 ml/min : 20 mg orally once daily CrCl 15 - 50 ml/min : 15 mg orally once daily CrCl < 15 ml/min : Avoid
Apixaban	ARISTOTLE[59] AVERROES[58]	Partially renal	Recommended dose: 5 mg orally twice daily No dose adjustment required in patients with mild, moderate, or severe renal impairment alone In patients with at least 2 of the following: - age ≥80 years - body weight ≤60 kg - serum creatinine ≥1.5 mg/dL The recommended dose is 2.5 mg orally twice daily CrCl < 15 ml/min : Avoid

CKD: Chronic Kidney Disease, CrCl: creatinine clearance, AVERROES : Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment, ARISTOTLE : Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, RE-LY (Randomized Evaluation of Long-term anticoagulation therapy), and 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

Furthermore, observational studies in hemodialysis patients resulted in conflicting data. Chan et al. examined a large database of US dialysis provider and identified 1,671 patients on hemodialysis with preexisting AF.[67] The study revealed an increase risk of hemorrhagic stroke (HR 2.22) and ischemic stroke (HR 1.81) in patients on warfarin with double the risk of any type of stroke in patients with warfarin use compared to patients without warfarin use. It's important to note that some of weaknesses in the study include the lack of information regarding the indication and the length of warfarin use. Winkelmayer et al. in large retrospective observational study found increase hemorrhagic stroke risk (HR 2.38) with no difference in ischemic stroke, gastrointestinal bleed, or overall mortality in dialysis patients with newly diagnosed AF being treated with warfarin.[68] Moreover, in a much larger study by Olesen et al., a significant decrease in the risk of ischemic stroke and systemic embolization in ESRD patients with AF on warfarin was observed.[54]

The lack of controlled randomized studies, of different stages of CKD, makes it difficult to draw conclusions regarding warfarin use in this population and the validity of currently use risk stratification systems for stroke prevention and bleeding assessment is unclear given that these mechanisms differ in CKD patients compared to the general population.

Warfarin use can be further prohibited in patients with CKD due to its side effects. Vascular calcification is a known side effect to warfarin.[69] Warfarin inhibit vitamin K- dependent proteins including G1a protein which play a major rule in bone mineralization and preventing vascular calcifications.[70] This becomes especially important in patients with CKD and dialysis where patients already suffer from vasculopathy with high mortality rates.[71] Hemodialysis patients who received long term warfarin have been found to have increase risk of vertebral fracture, aortic calcifications and mortality. Also long term warfarin use has been associated with lower bone density.[72] The degree of actual burden in patients with CKD is yet to be examined.

Warfarin related nephropathy have been also described in literature. Faster progression of CKD has been reported in patients with overanticoagulation (INR>3). Although the exact mechanism is unknown, it is proposed to be caused by glomerular hemorrhage and renal tubular obstruction.[73] Patients with CKD have been shown to have a high risk of developing warfarin related nephropathy. Brodsky et al. demonstrated that in those patients on long term warfarin therapy, 33 % of CKD patients developed warfarin related nephropathy compared to16% in patients without CKD. Warfarin induced nephropathy was associated with increased mortality as well.[74]

In the last few years multiple new oral anticoagulation drugs have been introduced (Table 3). Three of these drugs, dabigatran (a direct thrombin inhibitor), apixaban and rivaroxaban (Factor Xa inhibitors) have been studied in a large phase III randomized trials and shown promising results. These agents are becoming more popular due to the lack of frequent dose adjustment, few food and drug interactions and faster onset of action. Moreover, these agents have been shown to have less intracranial hemorrhage risk when compared to warfarin, an increasingly feared complication of warfarin due to its difficult management and possible deadly outcome.[17] Nevertheless, fatal bleeding worldwide has been reported secondary to their use and the lack of an antidote remains an issue. Furthermore, these drugs may interact with common cardiac medications such as amiodarone,

verapamil, and dronedarone which may increase the risk of bleeding.

In the RE-LY (Randomized Evaluation of Long-term anticoagulation therapy) study, dabigatran was shown to be superior to warfarin in stroke and systemic embolization prevention, however higher gastrointestinal bleed rates were reported.[75] Although patients with severe renal dysfunction have been excluded from the study, the Food and Drug Administration (FDA) approved the use of dabigatran 75 mg twice daily in patients with eGFR 15-30 mL/min. On the other hand and due to the lack of evidence the European Medicine Agency does not recommend its use in patients with eGFR < 30mL/min.[76]

Rivaroxaban has been compared to warfarin in the ROCKET AF study. It was shown to be non inferior to warfarin for stroke and systemic embolization reduction with lower rates of major bleeding.[77] In ARISTOTLE, apixaban was found to be superior to warfarin in stroke and systemic embolization reduction with lower rates of bleeding.[78,79] Both Rivaroxaban and apixaban demonstrated no difference in heterogeneity in the treatment effect in multiple stages of CKD. Furthermore a subanalysis of ARISTOTLE showed bleeding to be less common in patients with moderate to severe CKD in patients using apixaban compared to patients on warfarin.[79]

Aspirin and Clopidogrel

It is well established that aspirin is inferior to warfarin in stroke prevention. In a sub group analysis of AVERROES study, apixaban have been shown to reduce the stroke and systemic embolization by 68% in patients with eGFR 30-60 mL/min who are unsuitable for warfarin compared to aspirin.[80, 81]

Clopidogrel have been shown to inhibit platelets less effectively in patients with renal impairment. Proposed mechanisms include the lack of gpIIb/IIIa receptor due to pre-occupation with uremic toxins and activation of inhibitory mechanisms of nitric oxide.[17]

Conclusion

Patients with CKD are more likely to have AF than the general population. Evidence suggests that kidney dysfunction increases the risk of new onset AF while the presence of AF results in an increase in the rate of kidney function decline and the development of proteinuria.[16]

Patients with CKD and AF are difficult to manage due to lack of evidence based treatment in this patient population. Furthermore, risk stratification modules commonly used to assess stroke and bleeding risks such as CHADS2 and HAS-BLED have not been fully validated in CKD patients of different stages of the disease.

Best treatment approach of rate-control vs rhythm-control remains controversial in patients with CKD due to lack of evidence and pharmacokinetic consideration remains a major hassle.

Anticoagulation as well, in CKD population, is challenging. Warfarin has been associated with more bleeding in CKD patients. Although newer agents have shown promise with decrease risk of intracranial hemorrhage, fatal bleeding has been reported and the lack of antidote remains a challenge.[17]

It is clear that the burden of providing care to patients with CKD is complicated. Individualization of treatment and sound clinical judgment may be the only safeguard until further evidence regarding treatment options is available.

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