REVIEW ARTICLE

Management of patients with atrial fibrillation and chronic kidney disease in light of the latest guidelines

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KEY WORDS

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ABSTRACT

Atrial fibrillation (AF) frequently occurs in patients with chronic kidney disease (CKD), and the rate reaches even 30% in patients with end-stage renal disease (ESRD). Patients with AF and CKD have a significantly higher risk of thrombotic complications, particularly ischemic stroke, and at the same time, a higher bleeding risk (proportionally to the grade of renal failure). In addition, AF and CKD share a number of comorbidities and risk factors, which results in increased mortality rates. Moreover, disturbances in hemostasis are common complications of kidney disease. Their occurrence and severity correlate with worsening renal function, including ESRD. At present, the incidence of bleeding is declining, while thrombotic complications have become the predominant cause of mortality. Prophylactic antithrombotic treatment reduces the rate of stroke and other thrombotic complications. Vitamin K antagonists (VKAs) have long been used in anticoagulant therapy, and more recently, non-vitamin K oral anticoagulants (NOACs) have been introduced, which are direct thrombin inhibitors. NOACs are a valuable anticoagulant option in this group of patients as long as a summary of product characteristics is followed. They are at least as effective as warfarin, while being safer, especially when it comes to intracranial hemorrhage. Renal function should be evaluated before initiation of NOACs and reevaluated when clinically indicated. Importantly, disturbances in hemostasis in patients with CKD and ESRD may lead to unexpected complications, such as extensive bleeding. If anticoagulation is administered to patients on dialysis, effects of an individual dialysis modality as well as interactions with other drugs given (eg, heparin) should be considered.

Introduction   Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring in 1% to 2% of the general population.[1,2] The percentage of patients with AF increases with age from 0.14% in those younger than 50 years old, 4% in those between 60 and 70 years old, to 14% in those over 80 years old.[3] AF is a well-known risk factor for cardiovascular morbidity, especially thromboembolic complications (including ischemic stroke), and mortality that resulted in 112 000 deaths in 2013, compared with 29 000 deaths in 1990.[1,2,4]

During the past 10 years, chronic kidney disease (CKD) has been also identified as a major risk factor for cardiovascular morbidity and mortality, with rapidly increasing prevalence.[5] Impairment of kidney function has a well-established link with AF because it leads not only to anatomic and metabolic changes in the cardiovascular system but also to alterations in the endocrine and nervous systems, hematopoiesis, and inflammatory response, which increases the risk of AF.[2] The overload of the extracellular fluid might lead to left ventricular hypertrophy and ventricular diastolic dysfunction, which causes atrial remodeling, a well-known pathogenesis of AF.[6]

AF frequently occurs in renal failure population and ranges from 19% to 24%, rising to 27% in patients with end-stage renal disease (ESRD).[5,7] In the Framingham Heart Study,[8] the prevalence of AF in patients with CKD was 15-fold higher than that in the general population, while in the Chronic Renal Insufficiency Cohort study,[9] AF was

present in 18% of 3267 patients with CKD and was associated with older age, female sex, smoking, and history of heart failure. Moreover, the increased risk of AF was observed even in patients with a relatively preserved renal function (estimated glomerular filtration rate [eGFR], 60–90 ml/min/1.73 m^2).[10] In a population-based study of almost 27 000 American adults, REGARDS,[11] CKD was associated with an increased prevalence of AF regardless of severity, but recent population-based studies have demonstrated a relationship between the prevalence of AF and the stage of CKD.[9,10,12] According to the Atherosclerosis Risk in Communities (ARIC) study,[10] the hazard ratio of developing new-onset AF was 3.2-fold higher in patients with severely impaired renal function.[10] The prevalence of AF was the highest among those with stage 4 or 5 CKD, even after multivariable adjustment.[11]

In addition, albuminuria was strongly associated with AF among participants with stages 3–5 CKD.[11] The ARIC study[10] also reported a 2-fold increase in the risk of AF in patients with microalbuminuria. The percentage of patients with persistent AF increases in accordance with both the decline in eGFR and the presence of proteinuria. These associations remain independent even when adjusted for the various patients' characteristics.[13]

End-stage renal disease In ESRD patients, the prevalence of AF varies between 7% and 27%.[8,14,15] The incidence of AF has been estimated to be between 3.1 and 5.9 per 100 patient-years.[16-18] A large cohort study of over 258 000 older dialysis patients (≥65 years) showed crude AF incidence rate of 148/1000 person-years.[19] In addition, the authors reported an increase in the incidence of AF by 11% over 12 years.[19]

It is well established that ESRD is associated with several cardiovascular comorbidities and risk factors that may induce the development of AF, such as aging, hypertension, diabetes mellitus, coronary artery disease, left ventricular hypertrophy, and congestive heart failure.[20,21] Moreover, severe renal failure and dialysis lead to hemodynamic and metabolic changes that can contribute to the increased risk of AF.[22] During dialysis, short self-terminated episodes of AF often occur. In most studies reporting specific data on AF subtypes, the prevalence of paroxysmal AF in patients with ESRD exceeded the rates for persistent and permanent AF, ranging between 3.5% and 12.7%.[23] In about 40.6% of patients, paroxysmal AF gradually transformed to the permanent type after a mean follow-up of 36.9 months.[24]

Anemia As one of the major complications of CKD is anemia, its link with AF has been investigated. In the Ibaraki prefectural health study of 132 000 Japanese patients,[25] the rate of AF was significantly higher in the group with anemia. Moreover, participants with both anemia and CKD were at a particularly high risk for new-onset AF.[25] Correction of hemoglobin concentrations by erythropoiesis-stimulating agents was shown to reduce left ventricular hypertrophy and cardiovascular events, as well as inhibit episodes of AF in predialysis patients with CKD.[26]

Stroke AF is associated with a 5-fold increase in the risk of stroke.[1] Patients with AF and renal failure have a higher risk of ischemic stroke than patients without renal failure.[27,28] Nakagawa et al[29] showed that patients with an eGFR of less than 60 ml/min/1.73 m^2 and a CHADS$_2$ score of 2 or higher had almost an 11-fold higher risk of ischemic stroke.

Lower eGFR is associated with increased risk of ischemic stroke and other systemic embolism, independently of known risk factors in AF patients.[30] The adjusted hazard ratio for thromboembolism is 1.39 for an eGFR of less than 45 ml/min/1.73 m^2 and 1.16 for an eGFR of 45 to 60 ml/min/1.73 m^2, compared with an eGFR exceeding 60 ml/min/1.73 m^2.[30] Furthermore, stroke is significantly higher in patients with CKD regardless of the baseline CHA$_2$DS$_2$-VASc score routinely used in thromboembolic risk assessment. In the Danish National Registry[31] of over 132 000 patients with CKD and AF, the risk of stroke was nearly 2-fold higher in patients receiving dialysis or kidney transplant. Vazquez et al[18] showed that AF was associated with a 9.8-fold increased risk of stroke among dialysis patients compared with those with sinus rhythm. On the other hand, in the US Renal Data System study of patients with ESRD, there was only a 1.8-fold higher rate of ischemic stroke in AF patients.[32] Although some studies[18,32,33] have demonstrated that the presence of AF increases the risk of stroke in ESRD patients, other studies have not reported this association.[34,35] Genovesi et al[17] showed that AF is associated with greater total and cardiovascular mortality but the rate of stroke did not significantly differ between patients with AF and sinus rhythm. Similarly, in the RAKUEN study[36] of 423 patients on maintenance hemodialysis, AF was independently associated with all-cause mortality and major bleeding, but not with increased risk of ischemic stroke. Thromboembolism rates according to eGFR are shown in FIGURE 1.

Mortality Both CKD and AF share a number of risk factors and are associated with increased mortality. In the study of 1050 elderly Chinese patients with coronary artery disease, mortality was significantly higher in AF patients with CKD than in non-AF patients.[37] The paroxysmal type of AF was strongly associated with a higher risk of death, while persistent and permanent AF did not influence the mortality.[37] Bansal et al[38] reported that incidents of AF were associated with a 66% increase in the relative rate of death in adults with CKD. Similarly, Genovesi et al[17] showed that in patients on dialysis, AF is independently associated with higher rates of death. Within the nationally comprehensive US Renal Data System,

FIGURE 1 Rate of arterial thromboembolism according to estimated glomerular filtration rate (eGFR)
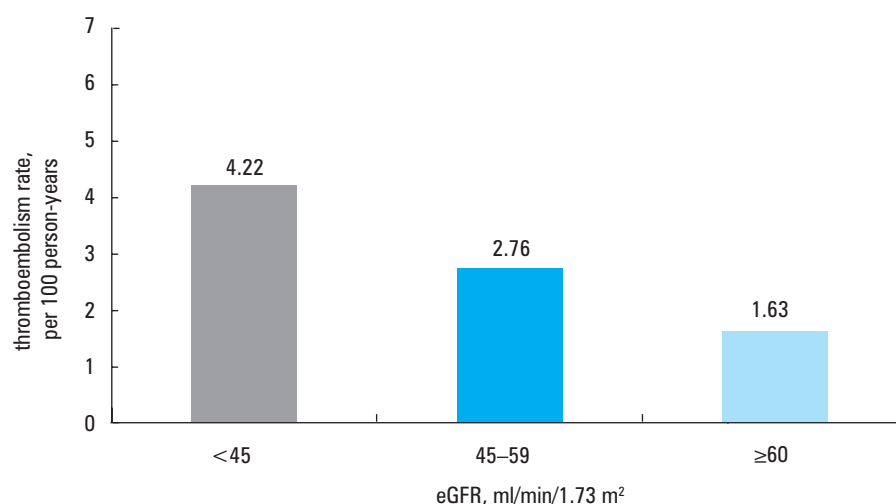
the adjusted 1-year risk of death was 45% higher for dialysis patients with AF.[39]

Chronic kidney disease in patients with atrial fibrillation CKD is present in 10% to 15% of AF patients and may increase the risk of AF-related cardiovascular complications.[40] Whether renal impairment influences the development of different types of AF is unclear. The observations from a study of over 1500 patients showed that impaired renal function is associated with permanent type of AF.[41] The odds of permanent AF in patients with CKD were increased 1.82 times as compared with patients with preserved renal function.[41] Anavekar et al[42] reported that each 10-unit reduction of eGFR was associated with a 10% increase in the relative risk of death or nonfatal cardiovascular complications in patients with AF.

R_2CHADS_2 score Although CKD is a well-established predictor for stroke, it is not a component of the CHA_2DS_2VASc score. The main reason for this is that patients with decreased eGFR were excluded from the randomized clinical studies that evaluated this score.[43] However, there are studies that included renal dysfunction in stroke risk stratification. There is a prediction rule, R_2CHADS_2, where R stands for renal risk. The eGFR of less than 60 ml/min/1.73 m[2] confers a score of 2.[43] Piccini et al[44] validated the R_2CHADS_2 score for the population with an eGFR of 30 to 60 ml/min/1.73 m[2] from the ROCKET-AF and ATRIA studies. The authors concluded that the R_2CHADS_2 score improved the net reclassification index only by 6.2% compared with CHA_2DS_2VASc and 8.2% compared with $CHADS_2$, which is not surprising since CKD is associated with the factors of the CHA_2DS_2VASc score.[44] In a study of 524 patients with AF, including those with advanced CKD and on hemodialysis, this new clinical prediction rule had a better discriminatory power than the $CHADS_2$ and CHA_2DS_2VASc scores.[43] As the majority of the studies did not prove that CKD added to stroke prediction, the score did not become popular.

Management of atrial fibrillation in patients with chronic kidney disease **Disturbances in hemostasis in chronic kidney disease** The endothelial cell layer is the "guardian" of the molecular traffic between the blood and surrounding tissue, and endothelial integrity plays a pivotal role in many aspects of vascular function, such as control of vasomotor tone and permeability. In patients with CKD, ongoing endothelial damage in the capillary system of the renal medulla and accompanying vascular rarefaction are thought to be central processes favoring progressive kidney damage.[45] Both proinflammatory and biochemical markers of endothelial dysfunction are increased in CKD. Moreover, disturbances in hemostasis are common complications of kidney diseases. Their occurrence and severity correlate quite well with the progressive loss of renal function to ESRD. Both bleeding diathesis and thromboembolism have been identified.[46-51] At present, the incidence of bleeding is apparently declining, whereas thrombotic complications have become the predominant causes of mortality. The intensity of hypercoagulability is thought to be related to the degree of hypoalbuminemia, being more evident at serum albumin levels of less than 2 g/dl, with an implicated participatory role of the associated hypertriglyceridemia and changes in arachidonic acid metabolism that accompany the metabolic response to hypoalbuminemia. Both bleeding and prothrombotic tendencies may have profound implications in patients with CKD and AF requiring anticoagulant therapy.[52,53] Therefore, the use of anticoagulants is a dilemma in this patient group.

Anticoagulant therapy Oral anticoagulation is an effective therapy to reduce the risk of stroke related to AF. It is well known that higher efficacy in stroke prevention is accompanied by higher risk of major bleeding.[54] According to the European Society of Cardiology (ESC) guidelines, cardiologists, specialists in internal medicine, and general practitioners are obliged to use the CHA_2DS_2-VASc and HAS-BLED scores to assess stroke risk and bleeding risk, respectively.[1] Anticoagulation is recommended in AF patients at

high risk of stroke (CHA$_2$DS$_2$-VASc score ≥2) and should be considered if there is a score of 1. In such therapy, a number of medications can be used, including warfarin, a vitamin K antagonist (VKA) that blocks the formation of multiple active vitamin K-dependent coagulation factors or non–vitamin K oral anticoagulants (NOACs): the direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Among NOACs, only dabigatran at a dose of 150 mg twice daily was proved to be superior to warfarin in preventing ischemic stroke.[55] The benefit of dabigatran versus warfarin for stroke prevention was independent of age and renal function.[56] The benefit of dabigatran versus warfarin in reducing extracranial bleeding was significantly attenuated with increasing age, but the reduction in hemorrhagic stroke was not.[56] The NOACs such as rivaroxaban, apixaban, and edoxaban are neither superior nor worse than warfarin in preventing ischemic stroke and systemic embolic events.[57,58] The most important advantage of new drugs is that they have a significantly lower risk of intracranial bleeding compared with warfarin.[55,59] Dabigatran, edoxaban, and rivaroxaban are associated with a higher risk of gastrointestinal bleeding compared with warfarin.[55,59] Only apixaban is superior to warfarin in the rate of gastrointestinal bleedings.[58]

All NOACs are partially eliminated via the kidneys. Renal function should be assessed by calculating the eGFR with the Cockcroft–Gault formula. Treatment with NOACs, except for dabigatran, in patients with severe renal impairment (eGFR <30 ml/min/1.73 m²) is approved in Europe but it is not recommended according to the European guidelines because there are no effectiveness and safety data in this population.[1] Renal function should be assessed during treatment with NOACs at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline.[1] Such situation is most frequently observed in old, compromised patients with many comorbidities prone to hypovolemia or dehydration, and in case of concomitant use of certain medicinal products. No dose adjustment is necessary in patients with mild renal impairment. For patients with moderate renal impairment (eGFR, 30–50 ml/min/1.73 m²), the recommended dose of dabigatran is 220 mg taken as a single 110-mg capsule twice daily, and rivaroxaban, 15 mg, taken once daily.[1] Based on pharmacokinetic measurements, the Food and Drug Administration (FDA) has approved in the United States a low dose of dabigatran (75 mg twice daily) for patients with severe renal insufficiency.[60] The dose should be also reduced in patients with high risk of bleeding (HAS-BLED score >3). No dose adjustment of apixaban is necessary in patients with mild or moderate renal impairment. Patients with severe renal impairment (creatinine clearance, 15–29 ml/min/1.73 m²) should receive a lower dose of apixaban, 2.5 mg twice daily. Patients with serum creatinine

of 1.5 mg/dl or higher associated with an age of 80 years or older or body weight of 60 kg or less should also receive the lower dose of apixaban. There is no clinical evidence for patients with an eGFR of less than 15 ml/min/1.73 m² or for patients undergoing dialysis; therefore, apixaban is not recommended in these patients.

Although NOACs are getting popular nowadays, VKAs are still widely used. However, NOACs are used sparingly in CKD population (FIGURE 2). According to the paper published in 2012, VKAs are involved in physiological regulations beyond coagulation, including soft tissue calcification, cell growth, and apoptosis resulting in structural damage to the kidney vasculature.[61] Interestingly, warfarin has been associated with biopsy-proven nephropathy in patients with and without renal impairment, which is related to increased mortality.[62] Patients with AF receiving oral anticoagulation showed a decline in renal function that was greater in those taking warfarin than in those receiving dabigatran, and it was amplified by diabetes and previous VKA use.[63] This is one of the reasons for recommending NOACs over warfarin in patients with mild and moderate CKD.

Dabigatran   Phase I studies on dabigatran showed an approximately 2.7-fold higher exposure to dabigatran in volunteers with moderate renal insufficiency (eGFR, 30–50 ml/min/1.73 m²) than in those without renal impairment (eGFR ≥80 ml/min/1.73 m²).[46] In a small number of volunteers with severe renal insufficiency (eGFR, 10–30 ml/min/1.73 m²), the exposure to dabigatran was approximately 6-fold higher and the half-life was approximately 2-fold longer than those observed in a population without renal insufficiency.[64] Clearance of dabigatran by hemodialysis was investigated in 7 patients with ESRD without AF. Dialysis resulted in a decrease in dabigatran concentrations by 50% to 60%, depending on blood flow rate. The anticoagulant activity of dabigatran decreased with decreasing plasma concentrations due to the procedure.[64] That is why dialysis is considered to be one of the methods to abolish anticoagulant effect of dabigatran in patients with severe bleedings or patients in need of major invasive procedures.[60] Almost half of the RE-LY patients (45.8%) had an eGFR of 50–80 ml/min/1.73 m². The median eGFR was 68.4 ml/min/1.73 m².[55]

Fortunately, idarucizumab, a humanized antibody to rapidly and specifically reverse the anticoagulant effects of dabigatran in cases of emergency surgery or urgent procedures or in situations of life-threatening or uncontrolled bleeding, was approved by the European Commission and FDA late in 2015.[65] Before that, renal replacement therapy (RRT) appeared to be effective in reducing dabigatran concentrations, and in case reports, this has been associated with a reduction in the duration and/or severity of bleeding. However, a rebound in concentrations may be seen following withdrawal of RRT, suggesting that a prolonged
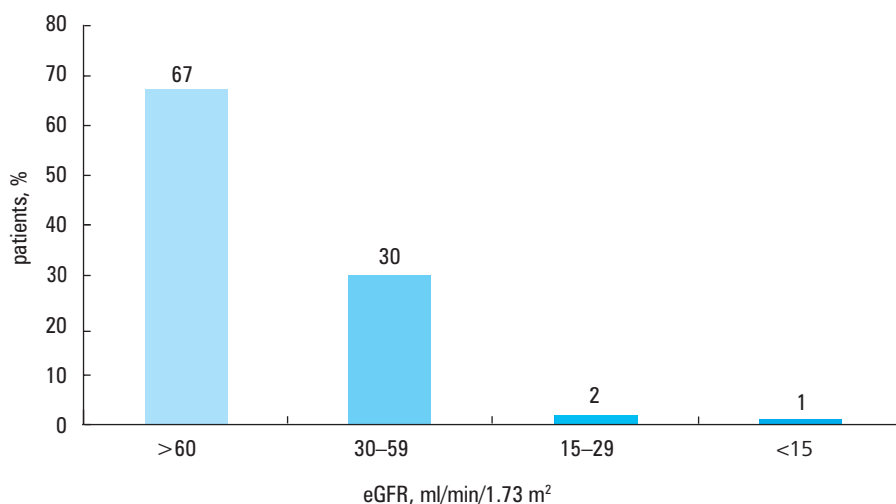
course of RRT may be more effective.[66] Andexanet alfa, a recombinant factor Xa variant that binds factor Xa inhibitors but lacks coagulant activity and ciraparantag (PER977, a universal antidote targeted at reversing factor Xa inhibitors), may provide the most effective and safe way of reversal. These agents are under clinical development.[67]

The main advantage of NOACs over warfarin is that they do not antagonize vitamin K and a patient no longer has to avoid foods containing this nutrient. Disadvantages include a higher cost to consumers and lack of long-term data supporting their use. As the use of NOACs in patients with CKD increases, it will be important to monitor their safety, and clinicians who prescribe them should carefully monitor kidney function and recognize the possibility of adverse effects.

Rivaroxaban Rivaroxaban is eliminated by the kidneys in about 35%. In the ROCKET-AF study, 21% of the patients had moderate renal impairment (eGFR, 30–50 ml/min/1.73 m^2).[57] An increase in rivaroxaban exposure correlated with a decrease in renal function. In individuals with mild (eGFR, 50–80 ml/min/1.73 m^2), moderate (eGFR, 30–49 ml/min/1.73 m^2), and severe (eGFR, 15–29 ml/min/1.73 m^2) renal impairment, plasma rivaroxaban concentrations were increased 1.4-, 1.5-, and 1.6-fold, respectively. There are no data in patients with creatinine clearance of less than 15 ml/min. Due to the high plasma protein binding, rivaroxaban is not dialyzable. According to the ESC guidelines, rivaroxaban is not recommended in patients with an eGFR of less than 30 ml/min/1.73 m^2.[1]

Apixaban Apixaban is eliminated by the kidneys in about 27%. In a randomized, double-blind trial, ARISTOTLE, which compared apixaban with warfarin, there were 16.5% of patients with an eGFR of less than 50 ml/min/1.73 m^2.[58] In a subgroup analysis of the ARISTOTLE trial for patients with impaired renal function, Hohnloser et al[54] showed that apixaban was superior to warfarin in reducing stroke or systemic embolism, major bleeding, and mortality, irrespective of kidney function. In addition, apixaban was associated with less

major bleeding compared with warfarin, regardless of renal function. Patients with impaired renal function (eGFR ≤50 ml/min/1.73 m^2) seemed to have the greatest reduction in major bleeding with apixaban.[68]

In a meta-analysis involving 40 145 patients from 6 trials and evaluating the risk of bleeding of apixaban compared with conventional agents (VKA and/or warfarin, low-molecular-weight heparin, aspirin, and placebo), the risk of bleeding with apixaban in patients with mild renal impairment was significantly lower compared with conventional anticoagulants. However, in patients with moderate to severe renal impairment, the risk of bleeding was found to be similar.[69]

Edoxaban Edoxaban is eliminated by the kidneys in about 50%. The analyses of the ENGAGE-AF TIMI 48 trial[59] also indicated a preserved bleeding benefit for edoxaban compared with VKAs in patients with an eGFR of 30 to 50 ml/min/1.73 m^2.

Anticoagulant treatment in patients with end-stage renal disease In ESRD, endothelial dysfunction, atherosclerosis, and cardiovascular complications are almost universal. So far, a handful of reports have dealt with disturbances in hemostasis and endothelium in hemodialyzed patients.[46-51,70] The principal cause of these abnormalities is the uremic state, and as a rule, it is at least partially reversible with the institution of adequate RRT. The pathogenesis of uremic bleeding is multifactorial. It has been attributed to platelet dysfunction, abnormal platelet-vessel wall interactions, and altered rheological properties of the blood flow.[49,50] The most important determinants of the pathogenesis of the prothrombotic state in uremia are increased levels of clotting factors and decreased levels of clotting inhibitors, hyperfibrinogenemia, diminished fibrinolytic activity, and platelet hyperaggregability.[48-50]

It is likely that multiple factors are responsible for platelet dysfunction in uremia. Three of the factors that may contribute are the retention of uremic toxins, anemia, and nitric oxide.[70] Both impaired platelet aggregation induced by different

stimuli as well as hyperaggregability were reported in uremia.[50] Indirect evidence suggests that hypercoagulability in hemodialysis is associated with the following laboratory alterations: hyperfibrinogenemia, enhanced activity of factor VII, factor VIII, von Willebrand factor, tissue factor, and tissue factor pathway inhibitor, and low activity of antithrombin III, protein C and S, and factors II, IX, X, and XII, despite their normal or elevated plasma concentrations.[49,50,71] In continuous ambulatory peritoneal dialysis, a peculiar coagulation profile is observed, namely, hyperfibrinogenemia, elevated activity of factors II, VII, VIII, IX, X, and XII, high concentrations of protein S, and normal concentrations of antithrombin III and protein C.[72-74] In dialyzed patients, both impaired overall fibrinolytic activity and hyperfibrinolysis have been reported, probably secondary to activation of the coagulation cascade.[48,75]

The risk profile and benefit of anticoagulation in patients with ESRD and AF remain unclear. The clinical guidelines from the Kidney Disease: Improving Global Outcomes do not recommend warfarin therapy for stroke prevention in AF among dialysis patients.[5] Chen et al,[76] in the nationwide cohort analyses of over 134 000 patients with ESRD, found that antiplatelet or warfarin treatment could not lower the risk of ischemic stroke in patients with ESRD. Similarly, in the study of 1626 patients on dialysis (both hemodialysis and peritoneal dialysis), warfarin did not reduce ischemic stroke but increased the risk of bleeding.[77]

On the other hand, in a single-center observational study of Chinese patients with nonvalvular AF, in CKD patients on peritoneal dialysis, who had similar ischemic stroke risk as their non-CKD counterparts, warfarin therapy was associated with a reduction in the risk of ischemic stroke without a higher risk of intracranial hemorrhage.[78] In the Swedish Atrial Fibrillation Cohort study of 307 000 patients with AF, of whom over 13 000 had a previous diagnosis of renal failure, most patients with renal failure benefited from warfarin treatment, despite their high bleeding risk.[79] The incidence of the combined endpoint ischemic or hemorrhagic stroke or death was lower among those who used warfarin.[79]

Although the FDA did not formally approve the use of apixaban in patients with an eGFR of less than 15 ml/min/1.73 m², it recommends the standard dose regimen if apixaban is used in hemodialyzed patients. These assertions were not tested in randomized trials and are done based on pharmacokinetic measurements.[60] In the most recent study on 1516 incident hemodialysis patients in Japan, the rates of mortality and cardiovascular events were compared between patients with and without AF, and between AF patients receiving and not receiving warfarin treatment.[80] Even after adjustments for various factors, AF remained an independent risk factor for mortality and cardiovascular events. Interestingly, no difference in any parameter was noted between the groups that did and did not receive warfarin treatment.

According to the 2014 American Heart Asssociation/American College of Cardiology/Heart Rhythm Society) guidelines, it is reasonable to prescribe warfarin for oral anticoagulation for patients with a CHA₂DS₂-VASc score of 2 or higher and end-stage CKD (eGFR <15 ml/min/1.73 m²).[81] However, the management of AF in ESRD is still a major issue. The dilemma surrounding AF in ESRD will not be resolved until a suitable randomized controlled trial is conducted.[82] Such a trial comparing therapy of AF with warfarin and aspirin is apparently in progress in Korea (NCT #01668901). NOACs are not recommended in patients with end-stage CKD or receiving dialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits.[81] Therefore, the utility of NOACs in patients with AF and ESRD is unknown. Primary prevention of AF with β-blockers in patients with ESRD may be a better answer.[83]

As all of the NOACs are, at least in part, eliminated by the kidneys, the assessment of kidney function before considering this type of therapy is a prerequisite. The most common methods used to estimate the GFR are the measurement of creatinine clearance, and the estimation formulas based on serum creatinine levels include the Cockcroft–Gault, Modification of Diet in Renal Disease (MDRD), and the Chronic Kidney Disease Epidemiology Collaboration formulas. However, serum creatinine levels can only be used to estimate GFR in individuals with stable kidney function. Drug dosing guidelines have historically been developed using the Cockcroft–Gault formula to estimate kidney function. Most pharmacokinetic studies for drug dosing in renal disease were performed using the Cockcroft–Gault formula because it was recommended by the FDA prior to publication of the MDRD study equation.[84] Thus, kidney function is estimated using the Cockcroft–Gault formula to provide drug dose adjustment or contraindication to therapy when kidney function is significantly impaired. However, in a large simulation study, there was a high concordance rate (89%) for kidney function estimates obtained by the Cockcroft–Gault and by the recalibrated MDRD study formulas for the assignment of kidney function categories used for drug dosing adjustment.[85] Thus, for most patients, both the MDRD and Cockcroft–Gault formulas can be used to estimate kidney function for drug dosing,[86] bearing in mind that in the case of a significant difference in eGFR by both formulas, yielding different dosage or withdrawal, the Cockcroft–Gault formula should be used.

Non-vitamin K oral anticoagulants and laboratory monitoring   NOACs do not require routine monitoring of coagulation. Neither the dose nor the dosing intervals should be altered in response to changes in laboratory coagulation parameters for the current registered indications. The international

FIGURE 3 Risk of stroke and systemic emboli or major bleeding according to kidney function in patients treated with non-vitamin K oral anticoagulants or warfarin
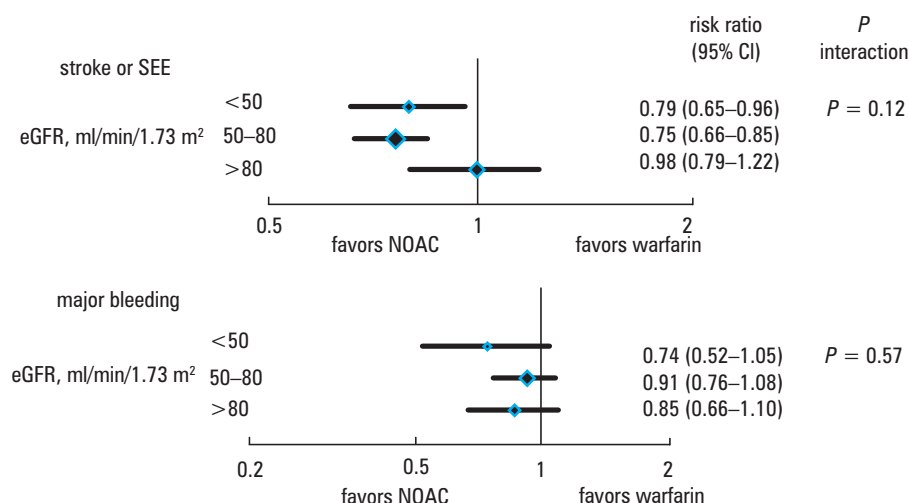
normalized ratio in patients on NOACs should not be used to assess the anticoagulation effect. The activated partial thromboplastin time may provide a qualitative assessment of the presence of dabigatran. Also the thrombin time (TT) is very sensitive to the presence of dabigatran and a normal TT excludes even low levels of dabigatran.[60] Diluted TT (dTT) tests are available that can more accurately predict dabigatran anticoagulation. A dTT test shows a direct linear relationship with dabigtran concentrations and is suitable for the quantitative assessment of dabigatran concentrations. The ecarin clotting time assay provides a direct measure of dabigatran activity, but it is not readily available.[60]

Factor Xa inhibitors demonstrate a concentration-dependent prolongation of the prothrombin time (PT). The PT may provide a qualitative assessment of the presence of rivaroxaban. For edoxaban and apixaban, the PT cannot be used for assessing their anticoagulant effects. However, the PT is not specific and can be influenced by numerous other factors (eg, hepatic impairment, cancer, vitamin K deficiency).[60,87]

Patients requiring an urgent surgical intervention If an urgent surgery is required, NOACs should be discontinued and the intervention should be delayed, if possible, until at least 12 hours, and ideally 24 hours, after the last dose. There are currently no data on cut-off values of any coagulation test below which elective or urgent surgery is possible without excess bleeding risk.[60]

If surgery cannot be delayed, reversal of the anticoagulant may be considered. Idarucizumab is a monoclonal antibody designed for the reversal of anticoagulant effects of dabigatran. Andexanet alfa is designed to reverse the anticoagulant effects of factor Xa inhibitors (rivaroxaban, apixaban; Clinicaltrials.gov NCT02329327), but is still in phase III of a clinical trial.[60]

Summary AF frequently occurs in the renal failure population, reaching almost 30% in patients with ESRD. AF patients with renal failure have a significantly higher risk of thrombotic complications including ischemic stroke and also bleeding risk proportionally to the grade of renal failure. Moreover, both CKD and AF share a number of risk factors and are associated with increased mortality. NOACs including apixaban, dabigatran, and rivaroxaban have been approved by international regulatory agencies to prevent venous thromboembolism as well as treat AF and venous thromboembolism in individuals with CKD. However, alterations in their metabolism in the setting of CKD may impact their efficacy and lead to an increased risk of bleeding. CKD is more prevalent than we thought and affects over 4 million people in Poland. However, data on AF, CKD, and the use of NOACs are rather limited. It is also important for internists and primary care physicians to consider the use of NOACs in patients with CKD, when kidney function permits. They also should carefully monitor kidney function and recognize the potential for adverse effects. Thus, we will gain new knowledge and may choose and wisely use NOACs with the highest possible benefit for our patients, even those vulnerable ones with advanced CKD or on RRT.

Renal function should be evaluated before initiation of direct thrombin or factor Xa inhibitors and reevaluated when clinically indicated. We also should bear in mind that disturbances in hemostasis in CKD and ESRD may produce unexpected complications, such as extensive bleeding. However, the most recent National Institute for Clinical Excellence guidelines on CKD consider treatment with apixaban in preference to warfarin in people with a confirmed eGFR of 30 to 50 ml/min/1.73 m[2] and nonvalvular AF who have 1 or more of the following risk factors: prior stroke or transient ischemic attack, age of 75 years or older, hypertension, diabetes mellitus, or symptomatic heart failure.[88] If anticoagulation is administered to patients on RRT, effects of each dialysis modality as well as interactions with other administered drugs (eg, heparins) should be considered. This issue is pending in other available nephrology guidelines.

Prophylactic antithrombotic treatment reduces mortality and the rates of stroke and systemic emboli. NOACs constitute a valuable anticoagulant therapy in this group of patients as long as the summary of product characteristics is followed.[89] They are at least as effective as warfarin, while being safer, especially when it comes to intracranial hemorrhage (FIGURE 3).

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Postępowanie u pacjentów z migotaniem przedsionków i przewlekłą chorobą nerek w świetle najnowszych wytycznych

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STRESZCZENIE

Migotanie przedsionków (*atrial fibrillation* – AF) często występuje u pacjentów z przewlekłą chorobą nerek (*chronic kidney disease* – CKD), a odsetek wzrasta nawet do 30% u pacjentów ze schyłkową niewydolnością nerek (*end-stage renal disease* – ESRD). Chorzy z AF i CKD mają znacznie większe ryzyko powikłań zakrzepowych, szczególnie udaru niedokrwiennego mózgu, a jednocześnie większe zagrożenie krwawieniami (proporcjonalne do stopnia niewydolności nerek). Ponadto łącznemu występowaniu AF i CKD towarzyszą liczne schorzenia i czynniki ryzyka, co prowadzi do zwiększonej śmiertelności. Co więcej, chorobie nerek często towarzyszą zaburzenia krzepnięcia. Ich obecność oraz stopień ściśle koreluje z pogarszającą się funkcją nerek włączywszy ESRD. Obecnie ryzyko krwawień zmniejsza się, podczas gdy powikłania zatorowe są jedną z najważniejszych przyczyn zgonu. Profilaktyczne leczenie przeciwzakrzepowe obniża ryzyko udaru mózgu i innych powikłań zatorowych. W terapii przeciwkrzepliwej od wielu lat stosowane są leki z grupy antagonistów witaminy K (*vitamin K antagonist* – VKA), a w ostatnich latach wprowadzono nowe doustne antykoagulanty (*novel oral anticoagulants* – NOAC), będące bezpośrednimi inhibitorami czynników krzepnięcia. NOAC stanowią wartościową terapię przeciwkrzepliwą w tej grupie pacjentów pod warunkiem, że postępujemy zgodnie z zaleceniami z charakterystyki produktu leczniczego. Są one co najmniej tak skuteczne jak warfaryna, a przy tym bezpieczniejsze, szczególnie w odniesieniu do krwotoków wewnątrzczaszkowych. Przed leczeniem z zastosowaniem NOAC zaleca się zbadanie czynności nerek oraz powtórzenie badania w przypadku wskazań klinicznych. Należy pamiętać, że zaburzenia krzepnięcia u chorych z AF i ESRD mogą prowadzić do nagłych powikłań, takich jak rozległe krwawienie. Jeżeli terapia przeciwkrzepliwa jest stosowana u chorych dializowanych, muszą być wzięte pod uwagę zarówno rodzaj dializy jak i wpływ interakcji z innymi lekami przeciwkrzepliwymi (np. heparyną).