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REVIEW

Kidney Function and the Use of Vitamin K Antagonists or Direct Oral Anticoagulants in Atrial Fibrillation

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ABSTRACT

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with a five-fold increase in the risk for ischemic stroke. Therefore, lifelong use of anticoagulants is crucial to reduce the morbidity and mortality burden of AF. The incidence of AF in chronic kidney disease (CKD) is two to three times greater than in the general population, and there is a mutual aggravation of the two conditions as well as the presence of both an increased thromboembolic risk in CKD and an increased bleeding risk in severe CKD. The preservation of kidney function in patients with cardiovascular diseases is important, as the latter is the leading cause of death in patients with eGFR <60 mL/min/1.73 m^2. Similarly, kidney dysfunction is a serious limitation to the use of many cardiovascular drugs, including anticoagulants. Evidence is present for the faster progression of kidney disease with vitamin K antagonists, likely due to the vitamin K-related process of vascular calcification. Conversely, direct oral anticoagulants (DOACs) have been shown to reduce the progression of CKD and have a beneficial effect as far as the modulation of inflammation and oxidative stress are concerned in experimental models. Another less-discussed problem is the use of DOACs in advanced CKD.

Keywords: arrhythmia, anticoagulants, bleeding, renal failure, systemic thromboembolism

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INTRODUCTION

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia, with about 2–4% of adults being affected. Its prevalence has both increased by more than 30% during the past 20 years[1,2] and is expected to further increase in the future with the aging of the population. Around 37 million people are estimated to be affected by AF as of 2017.[2] AF is associated with a significant decrease in the quality of life in more than 60% of the patients and has a possible causal relationship with the development of left ventricular dysfunction and heart failure, as well as an increased risk of hospitalizations and all-cause mortality.[2] One of the most debilitating complications of AF is ischemic stroke, the risk being about five times higher in the presence of AF.[2] Cardioembolism is accountable for up to 30% of all ischemic strokes, with AF being the main underlying etiology.[3]

Chronic kidney disease (CKD) is a common disorder associated with a progressive loss of kidney function, affecting more than 10% of the world's population, with an increase of nearly 37% between 1990 and 2013, and is a leading contributor to all-cause mortality.[4] AF is more common in patients with CKD compared to the general population, and it is now known that the two diseases aggravate each other.[5] Anticoagulants are the cornerstone

of systemic thromboembolism reduction in patients with AF, and their use has the highest class of recommendation and level of evidence (class I, level A according to the European Society of Cardiology) in patients with registered AF and an estimated high risk of thrombosis. Recently, data has emerged that the use of anticoagulants itself can influence kidney function in various ways.[2]

ATRIAL FIBRILLATION AND ANTICOAGULATION

AF is a supraventricular form of arrhythmia sustained by the presence of multiple micro reentry circuits in the atria causing a rapid and disorganized atrial activity, resulting in irregular conduction through the AV node and irregular ventricular contractions. AF is a thrombogenic arrhythmia, predisposing to the formation of a thrombus, localized typically in the left atrial appendage.[2] The lack of efficient atrial contraction due to the arrhythmia leads to blood stasis, and there is also proof of the other two elements of Wirchow's triad being present in AF — endothelial dysfunction and hypercoagulability.[6] The risk factors for the appearance and progression of AF are multiple, including age, hypertension, diabetes mellitus, renal dysfunction, obesity, chronic obstructive pulmonary disease, alcohol use, as well as the presence of coronary artery disease, heart failure, valvular heart disease, and congenital heart malformations, which makes the management of such patients a multi-faceted task. A great number of the aforementioned risk factors can be modified, emphasizing the importance of a multidisciplinary approach in clinical practice.[2]

THROMBOSIS RISK AND ANTICOAGULANTS

The CHA_2DS_2-VASc Score is currently recommended for the risk assessment of thromboembolic stroke in non-valvular atrial fibrillation, alongside the estimation of the bleeding risk using the HAS-BLED score. The risk for thromboembolic stroke in the general population is determined by the presence of specific risk factors (congestive heart failure or left ventricular dysfunction, arterial hypertension, age ≥65 or >75, diabetes mellitus, previous stroke, transitory ischemic attack or thromboembolism, vascular diseases such as prior myocardial infarction, peripheral artery disease, or aortic plaque and female sex) and not the form of atrial fibrillation — paroxysmal, persistent, long-standing, or permanent, or the number of episodes. Anticoagulation is recommended in all patients with a calculated CHA_2DS_2-VASc score ≥2 in men or ≥3 in women, and its duration should be lifelong.[2]

Vitamin K antagonists are a group of anticoagulants that inhibit the enzyme responsible for the recycling of the inactive form of vitamin K to its active form — the vitamin K epoxide reductase. Vitamin K is necessary for the normal activity of coagulation factors II, VII, IX, and X, as well as protein C and protein S from the fibrinolytic system.[7] Historically, vitamin K antagonists were discovered in the 1940s and have been used ever since for the prevention of systemic thromboembolism and in the prevention and treatment of venous thromboembolism.[8] The reduction of thromboembolic stroke is known to be about 60%.[9] There are some inconveniences with the use of vitamin K antagonists, namely the many interactions with drugs, supplements, and food, as well as changes in effectiveness due to liver and thyroid function.[10] It is therefore required to monitor the prothrombin time and adjust the dose (most accurately expressed as the INR [international normalized ratio]) usually monthly with the use of vitamin K antagonists due to the risk of the treatment being either ineffective or increasing the bleeding risk. The time in the therapeutic range (in the case of AF being INR between 2 and 3) has to be more than 70% in order for the treatment with vitamin K antagonists to be considered effective.[2]

The novel or direct anticoagulants (NOACs or DOACs) selectively inhibit a factor from the coagulation cascade — dabigatran inhibits factor II (thrombin), while rivaroxaban, apixaban, and edoxaban inhibit factor Xa. They emerged in the 2010s and demonstrated a non-inferior effectiveness[11–14] to a well-controlled treatment with vitamin K antagonists for systemic thromboembolism in non-valvular AF (referring to patients without a mechanical valvular prosthesis, or moderate or severe mitral stenosis), while for the most part providing a better safety profile, especially with intracranial hemorrhage, and also a reduction in all-cause mortality. Additionally, DOACs have fewer interactions with drugs or food and a predictable pharmacokinetic and pharmacodynamic profile, making monitoring of specific coagulation markers unnecessary in the clinical practice and allowing for a fixed dose regime. Due to the aforementioned considerations, the current European Society of Cardiology guidelines recommend the use of DOACs for the prevention of systemic thromboembolism in non-valvular AF in preference to vitamin K antagonists – class I, level of recommendation A.[2]

Patients with severe and end-stage renal failure, however, were not included in the major randomized NOAC clinical trials, and those drugs are currently contraindicated in patients on hemodialysis in Europe.[2] Nevertheless, it is possible to use the low-dose regime of rivar-

oxaban, edoxaban, and apixaban in creatinine clearance as low as 15 mL/min with the possible benefit of bleeding risk reduction compared to vitamin K antagonists based on observational data.[2]

ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE: A VICIOUS CIRCLE

AF and CKD share common risk factors, such as age, heart failure, obesity, arterial hypertension, and diabetes mellitus, to the point where about two-thirds of the cases of CKD are caused by the latter two diseases.[15] It is known that AF and CKD increase the prevalence and progression of each other, and the combination of the two is not at all uncommon in the general population. In CKD stages 1 and 2, the incidence of AF over a period of 2 years is 12.2%; in stages 3 to 5 it is 14.4%, while in patients without CKD, it is 7.5%.[16] The risk for AF increases with the decline in renal function, being 1.3 times higher in stage 2 of CKD, 1.6 times higher in stage 3, and 3.2 times higher in stage 4 of CKD according to a study by Alonso et al.[17] The presence of macroalbuminuria and microalbuminuria further increase the risk of AF — it is up to 13.1 times higher in individuals with urinary albumin-creatinine ratio (ACR) ≥300 mg/g and estimated glomerular filtration rate (eGFR) between 15–29 mL/min/1.73 m^2 compared to normal kidney function.[17]

There are many pathways in which CKD can lead to the appearance of AF. CKD is a state of chronic inflammation, uremic toxicity, and oxidative stress, which causes apoptosis and fibrosis in the atria and promotes remodeling associated with AF. Additionally, it also promotes the appearance of classic risk factors for AF such as congestive heart failure and arterial hypertension.[18] CKD is known to cause changes in normal myocardial electric activity as well as electrolyte disturbances. The increased renin and aldosterone levels in CKD result in fluid retention and an increase in preload, which contributes to the appearance of AF. There is evidence of calcium overload in the pulmonary veins and increased sympathetic activity, both of which are pro-arrhythmogenic.[19]

On the other hand, AF promotes the decline in renal function due to its prothrombotic qualities and the likely occurrence of silent thromboembolic kidney infarctions.[20] Renal failure increases the risk of stroke by up to 30 times in advanced stages by the acceleration of vascular calcification and endothelial dysfunction, as well as the accumulation of other risk factors for atherosclerosis in those patients.[21] Paradoxically, CKD elevates both the risk of systemic thromboembolism by about 50% and that of significant bleeding as well as the risk of all-cause death in patients with nonvalvular AF. There is a proportional increase in the incidence of intracranial and major gastrointestinal bleeding with the severity of CKD — stages 4 and 5 were associated with a 2.65-fold increase for gastrointestinal bleeding and 1.59-fold increase for intracranial bleeding compared to normal renal function based on a retrospective electronic record database cohort study, encompassing 85,116 people in Israel over a period of 11 years.[22] The risk is independently elevated for both cardioembolic and hemorrhagic stroke and also for cerebral microbleeds, and large- and small-vessel disease with proof of worse functional outcome and mortality, especially in patients on dialysis, likely due to uremic thrombocyte dysfunction and the use of periprocedural anticoagulants.[23]

KIDNEY FUNCTION AND ANTICOAGULANTS

Kidney function is also associated with cardiovascular morbidity and mortality and alters the pharmacokinetics of different drugs, limiting the use of many cardiovascular drugs, including the majority of the prognosis-changing drugs in the treatment of heart failure and ischemic heart disease. End-stage kidney failure (eGFR <15 mL/min/1.73 m^2) and the need for hemodialysis are also contraindications to the use of all NOACs in European countries,[2] making vitamin K antagonists the only available option for a great number of patients.[24] The preservation of kidney function is therefore pivotal in improving the prognosis of patients with AF. Cardiovascular drugs known to improve kidney outcomes are angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) as well as sodium–glucose co-transporter-2 (SGLT2) inhibitors, while the avoidance of nonsteroidal anti-inflammatory drugs and other nephrotoxic agents is generally advised.

One less discussed topic is the effect that anticoagulants themselves have on kidney function. In addition to the production of hepatic coagulation factors, vitamin K is also necessary for the synthesis of extrahepatic vitamin K-dependent proteins (VKDPs), which are not related to hemostasis but to the process of arterial calcification. Vitamin K is involved in the carboxylation of the matrix G protein (MGP), a VKDP that plays a key role in the inhibition of soft-tissue calcification.[25] Accelerated calcification of the arteries with vitamin K antagonists has been proven both in animal experimental models and in human studies. In 2004, a small study[26] showed that the 25-month use of the vitamin K antagonist marcoumar was associ-

ated with a higher degree of calcification of aortic valve specimens acquired after aortic valve replacement surgery for aortic stenosis or insufficiency compared to the lack of such use, and that result drew interest to the topic of vitamin K antagonists and their role in calcification. A recent meta-analysis[27] on the effect of vitamin K antagonists and cardiovascular calcification, encompassing 35 studies, confirmed that they were associated with a significantly increased risk of coronary calcification (OR 1.21; 95% CI 1.08–1.36), dependent also on the duration of treatment. The calcification was even more pronounced (OR 1.81; 95% CI 1.43–2.42) in the extra-coronary vessels — the aorta, the carotid arteries, the breast arteries, and the arteries of the lower extremities.

Another group of authors reported significant medial arterial calcification of the breast arteries with warfarin use.[28] This specific type of arterial calcification (of the media) is similar to the calcification described in CKD.[29] Vascular calcification is pronounced in advanced kidney failure due to changes in mineral and bone metabolism and is aggravated by the occurrence of vitamin K deficiency.[30]

Brodsky et al.[31] reported that the use of vitamin K antagonists with an INR >3 is known to cause acute kidney injury and coined the term warfarin-related nephropathy (WRN), due to glomerular hemorrhages and tubular obstruction by red blood cell casts in patients with and without previously known CKD. This phenomenon is also likely responsible for the progression of kidney function decline, alongside the vitamin K metabolism disturbance. The incidence of presumptive WRN is reported to be 33% among patients with a previous CKD and 16.5% among no-CKD patients and is related to an increased mortality.

COMPARISON OF SAFETY AND EFFICIENCY OF ANTICOAGULANTS IN RENAL FAILURE

Comparisons between the effects of DOACs and of vitamin K antagonists in different stages of kidney failure have been done. In a recent meta-analysis by Gui,[32] encompassing the five randomized phase III clinical trials of the four currently available NOACs versus warfarin trials[11–14,33] with pooled data of close to 73,000 participants with non-valvular AF, the efficacy (defined as stroke or systemic embolism) and safety (major bleeding) of the aforementioned drugs in patients with renal failure were investigated. Due to the exclusion of patients with severe renal dysfunction (eGFR 15–29 mL/min/1.73 m^2) and patients on kidney replacement therapy from those trials, the analyzed population consisted of patients with mild renal failure (eGFR 50–79 mL/min/1.73 m^2) and moderate renal failure (eGFR 30–49 mL/min/1.73 m^2). In the mild renal dysfunction group (53,028 patients), NOACs significantly reduced the appearance of stroke or systemic embolism by 22% compared to warfarin, while in moderate renal dysfunction (12,532 patients) the reduction was again similar and significant, of 20%. Bleeding reduction with NOACs was significant in mild renal dysfunction (OR 0.85; 95% CI 0.75–0.97), but not in moderate renal dysfunction despite the presence of a beneficial trend (OR 0.78; 95% CI 0.59–1.03). Additionally, the authors analyzed the renal function change from the dabigatran, rivaroxaban, and apixaban trials (RE-LY, ROCKET-AF, and ARISTOTLE; no data was available for edoxaban), which showed a trend for renal function decline over the period of 1 year for the three NOACs as well as for warfarin with no statistical difference, despite the presence of a non-significant benefit for the NOACs. When analyzing efficacy and safety in patients that had worsening renal function (defined as a decline of creatinine clearance at the 12-month follow-up of more than 20% compared to the baseline) and in those with a stable renal function, NOACs had significantly lower rates of both stroke and systemic embolism (a mean reduction of 28%) and bleeding (20%) in stable renal function compared to warfarin. In worsening renal function, the reduction was again significant and even greater for the efficacy endpoint (HR 0.66; 95% CI 0.42–0.89), but non-significant for bleeding (HR 0.93; 95% CI, 0.70–1.16). Worsening renal function itself was associated with an increase in both stroke and systemic embolism and with bleeding. The results from this meta-analysis suggest that despite the renal excretion of NOACs, fears of increased bleeding events are irrational in moderate and mild renal impairment.

Another meta-analysis of the five randomized clinical trials by Ando et al.[34] assessed the relative efficacy and safety of the NOACs and warfarin in patients with moderate CKD using treatment hierarchy and concluded that dabigatran in the dose regimen of 150 mg was with the highest probability of ranking first for efficiency (96%), followed by apixaban (67%), while for major bleeding only apixaban and the high-dose edoxaban regimen (60/30 mg) were associated with a significant reduction compared to warfarin. It is important to note that dabigatran had the highest possibility to rank last for safety (18%). Apixaban reached a significant reduction of major bleeding compared to the other NOACs with the exception of high-dose edoxaban, where the difference was not significant. The conclusion of the authors was that in the investigated population of moderate CKD, apixaban and the high-dose regimen of edoxaban were the two balanced

choices for both efficacy and safety over the other NOACs, but different characteristics of the patients enrolled in the respective randomized clinical trials have to be taken into account with edoxaban being tested in a population with a higher CHADS2 score and in an older population with a higher prevalence of heart failure. Nonetheless, all full- or single-dose NOACs (dabigatran 150 mg, rivaroxaban, apixaban, and edoxaban high dose) proved better than warfarin for both efficacy and safety in that population.

A large study[35] based on US administrative claim database with available laboratory data for nearly 35,000 new users of anticoagulants (warfarin, apixaban, dabigatran, and rivaroxaban; edoxaban was excluded due to a small number of cases) with nonvalvular AF and eGFR ≥15 mL/min/1.73 m^2 showed an inverse association between the use of NOACs and the decline in renal function, with the prevalence of NOAC use being 75% in eGFR ≥90 mL/min/1.73 m^2 and falling to 45.0% in the eGFR 15–30 mL/min/1.73 m^2 group. In the overall specter of eGFR, compared to warfarin, all three NOACs were associated with a lower risk of major bleeding and mortality, while apixaban and rivaroxaban additionally reduced the risk for stroke, but dabigatran did not. There was a non-significant trend for lower cases of stroke in the eGFR 15–30 mL/min/1.73 m^2 group with the use of apixaban and rivaroxaban compared to warfarin, but the registered cases of stroke were very few. In the eGFR 30–45 mL/min/1.73 m^2 group and the eGFR 60–90 mL/min/1.73 m^2 group, apixaban use significantly reduced the occurrence of stroke, while the other two NOACs were comparable to warfarin. In patients with eGFR 45–60 mL/min/1.73 m^2 and >90 mL/min/1.73 m^2 there was no statistical difference in the occurrence of stroke between the anticoagulants used. Apixaban showed a significant reduction in major bleeding and gastrointestinal bleeding in the groups with eGFR between 30 and 45 mL/min/1.73 m^2, between 45 and 60 mL/min/1.73 m2, and between 60 and 90 mL/min/1.73 m^2; as well as for intracranial bleeding in the groups with eGFR between 30 and 45 mL/min/1.73 m^2 and between 45 and 60 mL/min/1.73 m^2. Dabigatran was associated with a significant reduction of gastrointestinal and major bleeding in the eGFR 60–90 mL/min/1.73 m^2 group compared to warfarin.

NOACS IN PATIENTS ON HEMODIALYSIS

The results from three randomized clinical trials investigating the use of NOACs in people on hemodialysis have been published so far, attempting to correct the insufficient knowledge in this particularly vulnerable population of patients. Observational data is also available from several registry-based studies.

The first completed randomized trial on the topic of hemodialysis and NOACs in AF was the Valkyrie study,[36] which compared three groups on therapy with 10 mg of rivaroxaban, 10 mg of rivaroxaban plus vitamin K2 2,000 µg three times weekly, and warfarin with INR between 2 and 3 in 132 recruited participants followed initially for 18 months and later on for an additional 18 months. Dephosphorylated uncarboxylated matrix G protein levels were elevated in all groups, and were increased by the use of vitamin K antagonists but decreased in the other two groups, more pronounced in the vitamin K2 group. However, this did not lead to significant changes in the calcium scores of the coronary arteries, the thoracic aorta, and the cardiac valves, or the pulse wave velocity at 18 months. In the next 18 months part of the trial, 77 of the initial patients were followed-up with a median of 1.88 years, and it was found that fatal and nonfatal CVD events occurred significantly less in both of the rivaroxaban groups compared to warfarin, but did not differ between the two rivaroxaban groups. Life-threatening and major bleedings were also significantly less frequent in both of the rivaroxaban groups (reduction with a mean of 61% for rivaroxaban and with a 52% in the rivaroxaban and vitamin K2 group) compared to warfarin, but the risk for minor or gastrointestinal bleeding did not differ between the three groups.

The randomized RENAL-AF trial (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation)[37] was unable to include the pre-planned number of patients on hemodialysis and was underpowered with 154 recruited participants out of 762 pre-planned. It confirmed the presence of a high risk of major or clinically relevant non-major bleeding in this population regardless of the type of anticoagulant used (32% with apixaban and 26% with warfarin, HR 1.20, 95% CI 0.63–2.30) and illustrated the difficulty of achieving adequate time in the therapeutic interval in patients on warfarin, of only 44%. The incidence of stroke or systemic embolism at the 1-year follow-up was 3% in apixaban and 3.3% in warfarin users, which is strikingly lower compared to the bleeding incidence. The pharmacokinetic sub-study of the aforementioned trial managed to include the 50 pre-planned participants and revealed that the 12-h area under the curve (AUC) did not differ between the patients on the 5-mg apixaban dose on hemodialysis from the RENAL-AF trial when compared to the patients from the ARISTOTLE trial with estimated creatinine clearance (eCrCl, Cock-

roft-Gault) between 45 and 59 mL/min, between 30 and 44 mL/min, and between 15 and 29 mL/min, but was significantly higher than in those with eCrCl ≥90 mL/min. For the 2.5 mg dose of apixaban in patients on hemodialysis, the AUC did not differ from the ARISTOTLE trial patients with eCrCl between ≥15 and <90 mL/min.

The AXADIA-AFNET 8 Study[38] was a German prospective randomized multi-site study that randomized 97 hemodialysis patients on either apixaban 2.5 mg twice daily or the vitamin K antagonist phenprocoumon with a median follow-up of 429 days and discovered no difference as far as safety and efficiency were concerned in this population. It is important to note that the mean CHA_2DS_2-VASc score was 4.5, and the primary efficacy outcome (defined as a composite of ischemic stroke, all-cause death, myocardial infarction, and deep vein thrombosis or pulmonary embolism) was quite common and occurred in 20.8% of the patients on apixaban and in 30.6% of patients on phenprocoumon, while major bleeding occurred in 10.4% and 12.2% of patients, respectively, with a mean HAS-BLED score of 4.2 in the investigated population.

A retrospective cohort study[39] that included beneficiaries of the Medicare insurance in the USA on hemodialysis over a period of 5 years, of which 2.351 patients were on apixaban (either the 5-mg twice-daily dose in 44% or the 2.5-mg twice-daily dose in 56%) and were matched with 7,053 patients on warfarin, found that there was no difference in the risk of stroke or systemic embolism between the groups, but apixaban use led to a reduction of the risk of bleeding with a mean of 28%. The 5-mg dose of apixaban was also associated with a lower risk of stroke or systemic embolism and death compared to both the 2.5-mg dose and to warfarin. The study did not include users of the other NOACs as their number was too small in this population.

Rivaroxaban use in 1,896 patients versus 4,848 warfarin users with stage 4 and 5 CKD or undergoing hemodialysis was assessed by analyzing data from IBM's MarketScan over a period of 5 years. The NOAC did not differ from warfarin in terms of efficiency, but significantly reduced major bleeding by 32% in this population. It is important to note that in this study only 38.7% of the patients on rivaroxaban received the recommended reduced dose of 15 mg for CrCl <50 mL/min.[40]

A recent 2023 Swedish national cohort study[41] compared the use of DOACs and warfarin with an adequate mean time in therapeutic range (TTR) of 67% in 2,453 patients with CKD stages 3 to 5, including patients on dialysis, based on high-quality data from national registries. No kidney transplant patients were included. DOACs were associated with a 29% lower bleeding risk, no difference in ischemic stroke but a 24% higher mortality risk, which the authors did not deem to be due to the use of DOACs itself, but rather due to confounders, as it did not correspond to findings from other studies or to the lower rates of bleeding in this study.

To summarize, in the populations with severe, end-stage renal failure and on hemodialysis, where the risk of bleeding and stroke is particularly high, there is still a significant lack of adequate research and large randomized trials that would ensure the same level of care as their normal or mild-to-moderately reduced kidney function counterparts. Evidence for the efficiency and safety of both vitamin K antagonists and DOACs in patients with severe renal impairment (CrCl between 15 and 30 mL/min) is limited to mostly observational studies and small randomized trials. The use of a lower dose of the DOACs (except dabigatran) in severe renal failure is allowed by both European and American guidelines, but it is based on pharmacological rather than clinical data.[42]

Going one step further, the FDA has approved the use of both dose regimes of apixaban (5 mg twice daily, reduced to 2.5 mg twice daily if at least one additional condition is fulfilled: age ≥80 years or body weight ≤60 kg)[43] and the 15-mg dose of rivaroxaban[44] for patients with end-stage renal disease (CrCl <15 mL/min) on hemodialysis based on pharmacokinetic and pharmacodynamic studies, but has clarified that there are not enough clinical data for stroke reduction and bleeding risk in those patients. None of the NOACs is currently approved for use in Europe in patients with CrCl <15 mL/min or on hemodialysis.[2]

KIDNEY FUNCTION DECLINE AND ANTICOAGULANTS

In a 2017 study, Yao et al.[45], using a large US administrative medical insurance database with laboratory results, aimed to compare apixaban, dabigatran, rivaroxaban, and warfarin in patients with non-valvular AF for the outcomes of ≥30% decline in eGFR, doubling of the serum creatinine level, acute kidney injury (AKI), and kidney failure. Renal decline was common in the studied population that consisted of 9,769 patients at the 2-year follow-up, but dabigatran use had lower risks of ≥30% decline in eGFR and AKI; rivaroxaban had a lower risk of ≥30% decline in eGFR, doubling of serum creatinine, and AKI; and apixaban did not differ from warfarin. The pooled use of NOACs led to a significant 27% risk reduc-

tion for ≥30% decline in eGFR, 38% for doubling of serum creatinine, and 32% for AKI compared to warfarin. The risk for adverse renal outcomes was higher in warfarin treatment with supratherapeutic INR.

Inohara et al.[46] analyzed the decline in kidney function over a period of 2 years in 6,682 patients with AF from 220 sites enrolled in the ORBIT II registry. The absolute values of creatinine clearance declined in all patients with an average of 6 mL/min from the baseline, with no difference between the use of warfarin or a NOAC (rivaroxaban, dabigatran, apixaban or edoxaban). However, when analyzing the reduction of the creatinine clearance by more than 20%, by more than 30%, and an absolute increase of creatinine >0.3 mg/dL from the baseline, all endpoints were significantly worse with warfarin compared to the use of a DOAC. Additionally, the authors found that dose reduction for the NOACs (edoxaban excluded due to a low number of cases) was indicated for 3.7% of all patients but was done in only 20.1% of the indicated ones, and the lack of recommended dose reduction was associated with a significant increase in bleeding.

Coleman et al.[47] analyzed the US MarketScan claims data of more than 72,000 new non-valvular AF patients on either rivaroxaban or warfarin, excluding patients in CKD stage 5 or on hemodialysis at baseline. They found that rivaroxaban led to a significant 19% reduction of AKI and additionally to an 18% less chance of progression to stage 5 CKD or hemodialysis compared to warfarin and sought the explanation in the decrease of protease-activated receptor (PAR)-mediated vascular inflammation that NOACs inhibiting factor Xa provide, alongside the lack of vitamin K inhibition. Similar results from the IBM MarketScan data were reported by Hernandez et al.[48] in patients with diabetes mellitus and non-valvular AF, but the authors again excluded CKD stage 5 and patients on hemodialysis. When compared to warfarin, rivaroxaban showed lower risks for AKI, progression to CKD stage 5, and hemodialysis.

A multicenter Italian observational cohort study[49] that included 1,667 patients with both normal eGFR and all stages of CKD on either a vitamin K antagonist or dabigatran, rivaroxaban, and apixaban, showed that patients on dabigatran and apixaban more rarely reached eGFR <50 mL/min/1.73 m^2. Significantly more patients on a vitamin K antagonist had eGFR class worsening compared to the NOACs (29.1% for vitamin K antagonists, 20.6% for apixaban, 20.1% for rivaroxaban, and 22.9% for dabigatran). However, unlike in the Coleman et al. study, they found that the presence of diabetes reduced the favorable renal effect of the NOACs.

EFFECTS OF DOACS ON INFLAMMATION, OXIDATIVE STRESS, AND ENDOTHELIAL FUNCTION

Further research of NOACs, mostly using animal experimental models, has revealed a possible additional favorable effect on inflammation reduction and endothelial function as opposed to the outcomes being related to the simple replacement of vitamin K antagonists. A possible mechanism for the beneficial effect of NOACs might be the inhibition of thrombin by dabigatran and of factor Xa by the other three NOACs. There is growing evidence that the two aforementioned factors have effects outside of coagulation, as they are known to activate the G-protein coupled PARs located in smooth muscle cells, myocytes, endothelial cells, and platelets. PAR-1 (activated by thrombin and factor Xa) and PAR-2 (activated by factor Xa) are proven to directly participate in atherosclerosis and atrial remodeling by promoting endothelial dysfunction and vascular inflammation, thus accelerating the aforementioned processes.[50,51] It is possible that this targeted inhibition of factors II and Xa has pleiotropic vasculoprotective effects[52] potentially contributing to a reduction of cardiovascular events.

In a microarray experiment on human umbilical vein endothelial cells[53] aimed to assess and compare the ability of rivaroxaban and dabigatran to inhibit pro-inflammatory gene expression (ELAM-1, ICAM-1, VCAM-1, IL-8, MCP-1, CXCL1, CXCL2, and TF) in endothelial cells, Ellinghaus et al. discovered that both rivaroxaban and dabigatran exhibited a significant and dose-dependent suppression of all tested genes that correlated to thrombin activity reduction. At lower concentrations however, dabigatran had a pro-inflammatory effect. Rivaroxaban was also proven to lower urine albumin excretion and attenuate glomerular hypertrophy, mesangial matrix expansion, effacement of the podocyte foot process, and thickened glomerular basement membrane in hypertensive mice overexpressing renin.[54] The NOAC inhibited the FXa-dependent renal expression of PAR-2 in both mice and in human podocytes, in the latter of which the expression was induced by angiotensin II stimulation and therefore the authors concluded that rivaroxaban could reduce renin-angiotensin-mediated hypertensive damage to the kidneys and potentially prevent nephrosclerosis.

Using a mouse model with a unilateral ureteral obstruction-induced renal injury, Saifi et al.[55] discovered that dabigatran significantly reduced tubulointerstitial fibrosis by inhibiting the thrombin-dependent PAR-1 and the TGF-β signaling pathway, which is also involved in fibrosis, and in addition, it reduced the proinflammatory

cytokines IL-1β and TNF-α as well as nitrite levels. The treatment with dabigatran resulted in an improvement of the histoarchitecture of the obstructed kidney with less tubular atrophy and dilation. The effect of apixaban on mesangial damage was assessed in human kidney cells by Ishibashi et al.[56] Apixaban inhibited plasma-elicited oxidative stress generation in the tested mesangial cells as well as the pro-inflammatory molecules MCP-1 and ICAM-1 mRNA via the suppression of the thrombin-PAR-1 system. MCP-1 and ICAM-1 are known to be involved in the early phase of kidney damage and are associated with albuminuria in humans, which led the authors to speculate about a possible renoprotective effect of the NOAC based on the results of this study. They also noted that the peak plasma concentration in the experiment corresponded to the one achieved by the standard dose of 5 mg apixaban twice daily.

Edoxaban use was shown to reduce albuminuria and plasma urea nitrogen levels as well as intraglomerular microembolism and tubulointerstitial fibrosis in a mouse model of subtotal nephrectomy. It was also associated with the reduction of fibrosis markers (collagen I, collagen III, and transforming growth factor [TGF] β1), epithelial-mesenchymal transition markers (α–smooth muscle actin [SMA], N-cadherin, and vimentin), inflammatory markers (tumor necrosis factor [TNF] α and monocyte chemoattractant protein [MCP] 1) and oxidative stress markers (gp91phox, p47phox, and p67phox) in proximal renal tubular cells.[57]

CONCLUSION

The choice of oral anticoagulants has the potential to influence kidney function in patients with AF, in which if indicated, anticoagulant treatment is lifelong. There is growing evidence of the more favorable effects on kidney function by the NOACs compared to the vitamin K antagonists. NOACs also appear to be a promising alternative to vitamin K antagonists with a possible better safety profile even in severe and end-stage CKD, with further research needed on the topic.

CONFLICT OF INTEREST

Nothing to declare.

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