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REVIEW OF THE EFFICACY AND SAFETY OF DIRECT ORAL ANTICOAGULANTS IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE AND ATRIAL FIBRILLATION

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Abstract

The prevalence of atrial fibrillation (AF) in the population is very high and continues to increase. According to available statistics, its prevalence reaches about 2%, which is twice as high as was thought in the last decade. The prevalence of AF in patients with chronic kidney disease (CKD) ranges from 11 to 22% (other reports range
from 15 to 20%) and increases with age, much higher than in the general population in all age groups [1]. The vast majority of patients with AF require anticoagulant treatment to prevent ischaemic stroke and systemic thromboembolism. However, in the case of the combination of AF and CKD, in addition to an increased incidence of stroke and thromboembolic complications, the incidence of major bleeding is also significantly increased, making the choice of adequate anticoagulant therapy in this situation much more difficult. For many years, vitamin K antagonists were the only representatives of the class of anticoagulants for long-term therapy of patients with AF. Their well-known disadvantages (narrow therapeutic window, the need for frequent laboratory monitoring, numerous drug and dietary interactions, unpredictability of pharmacodynamics and pharmacokinetics in individual patients) contributed to the search for new, more convenient to use drugs. Direct oral anticoagulants have been easier to use and, according to the results of major studies, have been as good as or better than warfarin in terms of the balance of efficacy and safety. However, they have not been studied specifically in patients with reduced renal function. This

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review considers the features of modern anticoagulant therapy in elderly patients with AF and CKD.

Keywords: Anticoagulant therapy, advanced age, atrial fibrillation, chronic kidney disease.

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Introduction

Atrial fibrillation (AF) and chronic kidney disease (CKD) are increasingly common conditions that affect millions of people worldwide, leading to significant morbidity and healthcare costs [1,2]. The prevalence of AF is notably high in patients with CKD: approximately 18% to 20% in those with CKD not undergoing dialysis [3,4] and 15% to 40% in dialysis-dependent patients [5,6]. AF and CKD often coexist, mutually influencing and exacerbating one another [7,8]. Patients with CKD and concomitant AF experience worse clinical outcomes [9,10]. Furthermore, a meta-analysis revealed that AF is associated with increased mortality, allograft loss, and stroke after kidney transplantation [11]. Among patients with coexisting AF and CKD, the risks of stroke and bleeding escalate as renal function declines [12,13]. A previous study [14] demonstrated that patients with AF and advanced CKD had a 49% higher risk of stroke or systemic thromboembolism compared to patients with AF without CKD; the highest risk was observed in those with end-stage CKD undergoing dialysis. Additionally, patients with AF on dialysis often require routine heparin anticoagulation during dialysis procedures, further increasing bleeding risks. Thus, balancing thromboembolic and bleeding risks is a critical aspect of managing AF in CKD patients. Recent studies have suggested that warfarin may provide benefits for patients with AF and CKD [14-16].Elderly patients (aged ≥65 years) with CKD face a significantly higher risk of developing AF [5]. This demographic constitutes 60% to 80% of all AF and CKD cases [14]. The incidence of stroke and bleeding among AF patients tends to increase with age [17,18]. However, the efficacy and safety of anticoagulant therapy in individuals with coexisting AF and CKD remain uncertain. Recent investigations [19-25] into anticoagulant therapy in this population have yielded inconsistent results. Accordingly, the present study aims to evaluate the efficacy and safety of anticoagulant therapy in elderly patients with AF and CKD.

Analysis of Current Publications

Anticoagulant therapy is recommended for patients with AF with CKD and patients on dialysis according to guidelines [29, 30]. However, the role of anticoagulant therapy in elderly patients with AF and CKD has not yet been clearly defined.Society guidelines recommend anticoagulant therapy for patients with AF who have an increased risk of stroke, such as a history of stroke, transient ischemic attack (TIA), or a CHA_2DS_2-VASc score exceeding 1 point. This scoring system accounts for factors such as congestive heart failure, arterial hypertension, age 64–74 years (1 point), age over 75 years (2 points), diabetes, prior stroke/TIA/thromboembolism (2 points), vascular disease, and female sex. However, questions remain regarding the optimal choice of anticoagulant therapy for patients with CKD.Warfarin was the cornerstone of oral anticoagulant therapy for many years until the development of direct oral anticoagulants (DOACs). However, data on the use of warfarin in CKD remain limited, as earlier studies either did not quantify CKD

patient subgroups or included only small numbers of such patients [10–15]. The use of warfarin in terminal renal failure (TRF) is particularly controversial due to conflicting evidence. Moreover, patients with severe CKD or TRF were excluded from most large-scale trials supporting the use of NOACs. For the prevention of thromboembolism, combined guidelines from the American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Rhythm Society (HRS) recommend either warfarin or a NOAC of equivalent efficacy (class I recommendation) [9]. However, the European Society of Cardiology (ESC) [16] and the Canadian Cardiovascular Society (CCS) [17] favor NOACs over warfarin. Additionally, patients with CKD are at a particularly high risk of off-label NOAC usage. Overdosing has been associated with increased mortality, whereas underdosing has been linked to a rise in hospitalizations for cardiovascular conditions [18].

In general, studies of warfarin in patients with CKD are retrospective and observational, but most support its use in patients with mild to moderate CKD. The Stroke Prevention in Atrial Fibrillation III trial was a randomized controlled study that compared dose-adjusted warfarin, aspirin, and fixed low-dose warfarin. Among patients with stage 3 CKD, the use of dose-adjusted warfarin led to a 76% reduction in the relative risk of ischemic stroke and systemic embolism [15]. A large observational multicenter study in Sweden, which included more than 24,000 patients with CKD, demonstrated a lower incidence of combined death, myocardial infarction (MI), and ischemic stroke across all CKD categories without an increased risk of bleeding associated with warfarin use. Several other small studies have also shown a reduced incidence of stroke in patients taking warfarin compared to those who were not [4, 21, 22]. A meta-analysis of 11 cohorts of patients with CKD and AF, involving more than 48,000 individuals (including over 11,000 taking warfarin), found a 30% lower risk of ischemic stroke and thromboembolism among patients with non-end-stage CKD taking warfarin [23]. Another meta-analysis revealed similar results regarding the reduction of thromboembolic complications in non-end-stage CKD but also showed that NOACs were superior to warfarin in this regard [3].

Each of the four major NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) has been evaluated in large randomized controlled trials that included patients with mild to moderate CKD. These studies demonstrated either comparable efficacy or superiority of NOACs over warfarin in preventing stroke and thromboembolism. Patients with a creatinine clearance (CrCl) of at least 25 ml/min were included in the ARISTOTLE trial, while those with CrCl ≥30 ml/min were included in the remaining studies.

In the RE-LY study, dabigatran at a dose of 110 mg twice daily was found to be non-inferior to warfarin in preventing stroke and systemic embolism, with a lower risk of major bleeding. The FDA-approved dosage of 150 mg BID showed a lower risk of thromboembolism while maintaining a similar overall bleeding profile, though it was associated with a higher incidence of gastrointestinal and life-threatening bleeding [24]. Notably, there have been case reports of renal damage associated with dabigatran, raising concerns particularly for CKD patients [25].

The ROCKET-AF trial compared two dosing regimens of rivaroxaban: 20 mg daily for patients with CrCl ≥50 ml/min and 15 mg daily for those with CrCl between 30–49 ml/min. Rivaroxaban was non-inferior to warfarin in preventing strokes, without an increased incidence of major bleeding events [26].

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In the ARISTOTLE trial, apixaban was assessed at doses of 5 mg BID for most patients, with a reduced dose of 2.5 mg BID for those meeting two of the following criteria: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. Overall, apixaban outperformed warfarin in stroke and embolism prevention while demonstrating a lower risk of bleeding. The reduced dose (2.5 mg BID) was non-inferior to warfarin, but the number of patients in this subgroup was relatively small [27].

The ENGAGE trial evaluated edoxaban in two dosing groups: a high dose of 60 mg and a low dose of 30 mg. The edoxaban dose in both groups was halved for patients with CrCl between 30–50 ml/min, body weight ≤60 kg, or when drug-drug interactions were anticipated based on pharmacokinetic modeling. Edoxaban was non-inferior to warfarin in preventing thromboembolism, with a lower incidence of bleeding and cardiovascular mortality [28].

Several further studies of NOACs (Non-Vitamin K Antagonist Oral Anticoagulants) in patients with mild to moderate CKD (Chronic Kidney Disease) confirmed the results obtained in clinical trials. A pre-specified 2014 RE-LY analysis showed that the incidence of stroke or systemic embolism, major bleeding, and all-cause mortality increased as renal function declined. The incidence of stroke or systemic embolism was lower with dabigatran at a dose of 150 mg and similar with 110 mg twice daily compared with warfarin, with no significant difference in subgroups defined by renal function. However, the study grouped all patients with an eGFR (estimated Glomerular Filtration Rate) <50 mL/min and did not include patients with an eGFR <30 mL/min [29]. Another study comparing patients receiving dabigatran 110 mg twice daily with a CrCl (creatinine clearance) of 50 mL/min or higher to patients with a CrCl of 30 to 49 mL/min showed no difference in overall bleeding between the two groups, demonstrating the safety of the low dose in moderate CKD with respect to bleeding risk [30].

Rivaroxaban is excreted by the kidneys to approximately 33% [54], and is not removed by haemodialysis [55, 56]. A 10 mg dose of rivaroxaban has been shown to produce similar drug levels in dialysis patients as a 20 mg dose in healthy volunteers [55]. A 15 mg dose in dialysis patients also exhibits pharmacokinetics and pharmacodynamics similar to those observed in patients with moderate to severe renal impairment who are not on dialysis [56]. These pharmacological studies suggest the potential use of rivaroxaban in this population, but it has not been studied for stroke prevention, and one study raised concerns about the increased risk of bleeding and mortality in dialysis patients taking rivaroxaban compared to warfarin [57]. In the same study, dabigatran was shown to increase the risk of death and bleeding and was found to be effectively removed by dialysis [58, 59]. As mentioned earlier, case reports of dabigatran-induced renal damage should also be noted [25]. Thus, dabigatran is less likely to be used in dialysis patients and may be considered safe, but more patient-level data are needed given concerns about bleeding risk.

Apixaban at a dose of 5 mg twice daily was compared with aspirin in patients with stage 3 CKD in the AVERROES trial and significantly reduced the risk of stroke without increasing major bleeding [31]. Compared with warfarin in the ARISTOTLE analysis, apixaban remained more effective and safer regardless of renal function. In fact, the reduction in the relative risk of major bleeding was greatest in patients with a calculated glomerular filtration rate (eGFR) ≤ 50 mL/min. Patients with an eGFR <50 mL/min were included in one group, and patients with an eGFR <30

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mL/min were not included [32]. Another analysis from ARISTOTLE in 2016 also showed that the benefits of apixaban persisted regardless of renal function. Once again, patients with an eGFR <30 mL/min were not included, and those with an eGFR <50 mL/min were considered as one group [33]. Apixaban is the least excreted by the kidneys of all NOACs (estimated at 25%) [27]. A recent review supported its use in dialysis patients at a reduced dose of 2.5 mg twice daily [60]. A small pharmacological study comparing eight patients with terminal renal failure (TRF) on dialysis and eight patients with normal renal function showed that 5 mg apixaban resulted in only a small increase in apixaban exposure in the absence of haemodialysis (compared with normal patients) and was minimally eliminated by haemodialysis. This suggests that apixaban can be used in patients with TRF on dialysis [61]. An analysis of the ENGAGE trial, which compared edoxaban and warfarin, showed that the reduction in risk of stroke and systemic embolism with edoxaban was maintained in all renal function groups in patients with CrCl of at least 30 mL/min. The analysis considered CrCl <50 ml/min as one group [34].

In addition, multiple meta-analyses have demonstrated the overall superiority of NOACs over warfarin. The 2014 meta-analysis of the four major NOAC trials mentioned earlier showed that, as a class, NOACs are superior to warfarin in stroke prevention, especially in haemorrhagic stroke, with reduced mortality and intracranial haemorrhage, but with an increase in gastrointestinal bleeding. However, the increased incidence of gastrointestinal bleeding may be primarily attributed to dabigatran and rivaroxaban, rather than apixaban or edoxaban [35]. As noted earlier, another meta-analysis of large NOAC trials also demonstrated the superiority of NOACs over warfarin in patients with non-end-stage CKD in reducing thromboembolic complications [3]. A meta-analysis of patients with mild-to-moderate CKD in major NOAC trials again demonstrated the superiority of NOACs as a class compared to warfarin overall, with dabigatran 150 mg BID showing the greatest efficacy, and apixaban and edoxaban demonstrating a reduction in major bleeding events compared to warfarin [36].

In summary, NOACs have been shown in large clinical trials as well as in meta-analyses to be at least as effective as, if not superior to, warfarin. These results have been confirmed in several studies of patients with mild to moderate CKD.

In patients with severe CKD, guidelines favor warfarin or lack specific recommendations. The AHA/ACC/HRS guidelines note that NOAC dose reduction may be considered, but lack information on safety and efficacy (class IIb, LOE C) and therefore recommend warfarin as the anticoagulant of choice [9]. The CCS guidelines recommend warfarin rather than NOAC for patients with eGFR between 15 and 30 mL/min [17]. The ESC guidelines note that anticoagulants can be safely prescribed in moderate to severe CKD, but do not specifically mention NOACs [16]. Evidence for the use of NOACs in severe CKD is limited, and dosing recommendations are based on small pharmacological studies that lack rigorous clinical endpoints. RE-LY excluded patients with CrCl less than 30 mL/min; however, prescribing guidelines allow a dosage of 75 mg twice daily for patients with CrCl between 15 and 30 mL/min [24], based on pharmacological modeling showing that 75 mg BID in patients with CrCl between 15 and 30 mL/min achieved similar NOAC plasma levels as 150 mg BID in patients with CrCl greater than 30 mL/min [37]. In ROCKET-AF, patients with CrCl between 15 and 30 mL/min were not studied, but FDA labeling indicates that based on the pharmacodynamic study, rivaroxaban at a dose of 15 mg daily is expected to produce

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similar effects as 20 mg daily in patients with normal renal function [38]. Apixaban 2.5 mg twice daily is recommended if patients have two of the following conditions (age at least 80 years, body weight at least 60 kg, or serum creatinine at least 1.5 mg/dL), but patients with CrCl less than 25 mL/min in ARISTOTLE have not been studied [27].

Thus, data on warfarin and NOACs in severe CKD are limited. However, studies of warfarin support its use, while studies of NOACs are limited to pharmacological modeling with no clinical endpoints.

Atrial fibrillation (AF) is the most common arrhythmia in patients with CKD. In many patients, AF and CKD overlap because these conditions share a common pathophysiology and a number of similar risk factors. Elderly individuals are associated with an increased risk of thromboembolism and bleeding; therefore, elderly people are included in both the CHA2DS2-VASc score [31] and the HAS-BLED score [32]. Moreover, elderly patients with CKD may easily discontinue anticoagulants for safety reasons [18]. The benefit-risk profiles of anticoagulant therapy remain unclear in elderly patients with AF and CKD.

In the general population, prevention of thromboembolic events in patients with atrial fibrillation (AF) with oral anticoagulant therapy (OAT) follows strict guidelines.

Without a doubt, substantial evidence from large-scale randomized trials supports the view that almost all patients with ≥1 risk factor for stroke or systemic embolism (defined as a CHA2DS2-VASc score ≥1 in men and ≥2 in women) should receive OAT, as the benefit of stroke prevention clearly exceeds the risk of bleeding in the general population.

In contrast, the prevention of stroke and systemic embolism is more challenging and much less justified in patients with advanced chronic kidney disease (CKD), especially when they reach terminal renal failure. No adequately powered randomized controlled trial has analyzed the efficacy (i.e., prevention of thromboembolic complications) and safety (i.e., absence of major bleeding) of vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs) in advanced stages of CKD (e.g., in patients with a glomerular filtration rate [GFR] <30 mL/min per 1.73 m^2 or on dialysis).

With regard to less advanced CKD, a retrospective subgroup analysis from one randomized controlled trial found significantly fewer strokes in patients with stage G3a/G3b CKD receiving adjusted-dose warfarin than in patients receiving low-dose warfarin in combination with aspirin [1].

This lack of evidence is noteworthy because AF is more likely to develop in patients with advanced CKD, and patients with CKD and AF experience thromboembolic complications more frequently than patients with AF and preserved renal function [3].

Thus, theoretically, patients with AF and CKD should benefit more from oral anticoagulant therapy (OAT) in terms of risk prevention than patients with AF and preserved renal function. Unfortunately, the risk of side effects from anticoagulant therapy is also increased in patients with CKD, who are particularly at higher risk of bleeding events, including intracerebral hemorrhage. The complexity of this issue is further compounded by the fact that traditional OAT with vitamin K antagonists (VKAs) is thought to promote and accelerate vascular calcification, a condition common in CKD and presumably associated with adverse cardiovascular events and progression of CKD [5].

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Compared with non-anticoagulant therapy, anticoagulant therapy had a comparable risk of ischemic stroke/TIA in elderly patients with AF and CKD, regardless of dialysis status. Elderly patients with AF and CKD have an increased risk of thromboembolic complications. In addition, the risk of thromboembolism increases with the progression of worsening renal function. The most frequently used anticoagulant in most patients was warfarin. As an important inhibitor of endogenous calcification, the synthesis of matrix protein Gla depends on vitamin K; thus, warfarin may promote vascular calcification through the carboxylation of matrix protein Gla [33, 34]. Moreover, older patients with CKD tend to have the highest burden of vascular calcification, which may lead to a higher incidence of ischemic stroke or lacunar infarctions. The effect of warfarin on atherosclerosis may negate the benefits of anticoagulation in elderly patients with AF and CKD. Lacunar infarcts generally have a better clinical prognosis and may explain the observed lower all-cause mortality in patients prescribed anticoagulants [35]. Anticoagulant therapy may improve stroke severity but not stroke risk itself, resulting in a lower risk of all-cause mortality.

Studies show that anticoagulant therapy increases the risk of bleeding in patients with AF on dialysis but not in patients without dialysis. In patients with CKD, the risk of bleeding increases with the progressive deterioration of renal function [13, 36]. Both impaired renal function and advanced age are risk factors for bleeding [32]. Elderly patients with CKD are particularly susceptible to bleeding, especially those on dialysis. Several factors may increase the risk of bleeding in patients with CKD, including elevated vascular prostaglandin I2 levels, chronic inflammation, and abnormal platelet adhesion and aggregation [37, 38]. Moreover, the presence of uremic toxins is thought to increase the risk of bleeding in dialysis patients [39]. In addition, elderly patients on dialysis require routine heparin anticoagulant therapy during dialysis, which may further increase the risk of bleeding. These factors may explain why anticoagulant use was not associated with a lower risk of ischemic stroke/TIA in dialysis patients but rather with an increased risk of bleeding.

Conclusions

The combination of AF and CKD creates a therapeutic dilemma due to the increased risks of both thromboembolism and bleeding. With the introduction of NOACs, treatment options have expanded and can now be selected based on the degree of CKD. Warfarin and NOACs are suitable for treating mild to moderate CKD, with NOACs demonstrating superior efficacy and safety. Limited data suggest that warfarin remains effective in severe CKD. FDA-approved dose reductions for NOACs are based on pharmacological studies, but there is a lack of clinical data in patients. In individuals with end-stage renal failure (ESRF) and those on dialysis, existing evidence indicates no significant benefit from warfarin, alongside an increased risk of bleeding. Although data on NOACs are limited, recent retrospective studies of apixaban suggest its safety and efficacy. Further research through well-designed prospective controlled trials is required to evaluate the efficacy and safety of warfarin and apixaban in patients with ESRF and on dialysis.

In elderly patients not undergoing dialysis, anticoagulants reduced the risk of all-cause mortality compared to non-anticoagulants, while maintaining comparable risks for ischemic stroke, transient ischemic attack (TIA), and bleeding. Among elderly dialysis patients, anticoagulants increased the risk of bleeding compared to non-anticoagulants, but showed similar risks for ischemic stroke/TIA

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and death. Compared to non-anticoagulant therapy, anticoagulants were associated with a reduced risk of death in elderly patients with non-dialysis AF, although they carried an increased risk of bleeding in elderly dialysis patients.

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