

The Role of Direct Oral Anticoagulants in Advanced Chronic Kidney Disease – Questions and Future directions

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Received date: July 12, 2021, **Accepted date:** July 28, 2021

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With the advent of the direct oral anticoagulants (DOACs), patients requiring anticoagulation for common conditions such as atrial fibrillation and venous thromboembolism no longer need to worry about dietary restrictions or regular monitoring of the international normalized ratio which complicated warfarin treatment. Switching from warfarin to apixaban, a DOAC, has been shown to improve patient satisfaction by reducing treatment burden [1]. The clotting factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) and the direct thrombin inhibitors (argatroban and dabigatran) have shown non-inferiority in preventing thromboembolic events and a superior safety profile in terms of bleeding in several trials when compared to warfarin [2-6]. Furthermore, apixaban and dabigatran have even shown superiority in preventing stroke or systemic embolism [3,6].

Despite these promising outcomes, there remains an important subgroup of patients who have been excluded from the initial DOAC trials: advanced chronic kidney disease (CKD stage 4-5) and hemodialysis (HD) patients. Specifically, the ARISTOTLE trial evaluating the efficacy of apixaban versus warfarin in preventing stroke or systemic embolization in patients with atrial fibrillation excluded individuals with a serum creatinine greater than 2.5 mg/mL or an estimated GFR less than 25 mL/min [7]. The AVERROES trial similarly compared apixaban to warfarin and excluded patients with renal insufficiency utilizing identical criteria to the ARISTOTLE study [8]. This population, however, having a high burden of atrial fibrillation and cardiovascular disease [9,10], is at increased risk of stroke [11], and would theoretically benefit greatly from treatment with DOACs.

Concerns regarding the use of oral anticoagulation in general and with DOACs in particular emerge from two

perspectives: that of efficacy and that of safety. Available retrospective studies both with warfarin [12-16] and with apixaban [17] have yielded conflicting results with regards to the benefit of anticoagulation in CKD patients. The differential effect of statins in CKD and non-CKD populations should serve as a warning against extrapolating the results of prospective trials that have not studied the population in question [18]. On the other side of the problem, the safety of anticoagulation in CKD and HD patients is an important one given their inherently higher propensity for bleeding (including with warfarin [15]) and the impaired clearance of renally-excreted DOACs in ESRD [19,20]. All DOACs are renally excreted to some degree and, in the setting of kidney insufficiency, even properly dosed medications may accumulate in the body which can increase the risk for major bleeding events [21]. With one of the lowest percentages of renal clearance at 27% [22], apixaban may represent one of the safest choices in CKD patients and two retrospective studies have found a significantly lower bleeding risk with apixaban compared to warfarin in the CKD population, which was not demonstrated with other DOACs [23,24]. Apixaban dosing in the setting of HD remains controversial. One pharmacokinetic study showed that a reduced dose of apixaban at 2.5 mg twice daily in HD patients was found to predictably result in equivalent drug exposure to a dose of 5 mg twice daily in patients with preserved renal function. While a full dose of 5 mg twice daily led to suprathreshold doses in HD patients [25]. The timing of administration is also likely to influence drug levels [26]. Others, however, found no increase in drug levels in HD patients [27,28].

Clinical evidence on the safety and efficacy of apixaban in CKD and HD patients remains limited as only one randomized controlled trial has been completed, but was stopped early. Decisions on DOAC use in this cohort

must rely primarily on retrospective studies, registry data, meta-analyses, one post-hoc analysis of the ARISTOTLE trial and one underpowered randomized controlled trial. Available observational data has shown a consistent trend of lower bleeding with apixaban compared to warfarin [29-31], with one large study demonstrating higher efficacy as well for the prevention of thrombotic events at doses of 5 mg twice daily [31]. Although prospective in nature, the ARISTOTLE trial did not include renal function amongst its randomization variables and any results should be interpreted as a post-hoc analysis. The study by Stanifer and colleagues found a lower incidence of bleeding with apixaban compared to warfarin in patients with creatinine clearance between 25 and 30 ml/min, with a larger effect size compared to patients with better renal function [28]. RENAL-AF, the only completed randomized controlled trial investigating the use of apixaban in HD patients was unfortunately stopped early due to lack of funding and low accrual [32]. Out of a planned 760 patients only 154 were included in the final analysis and, as such, the study remained underpowered and any interpretation of their findings must be done cautiously. It is, however, reassuring that even with this limited sample, the frequency of clinically relevant non-major bleeding was lower in patients treated with apixaban 5 mg twice daily. No differences were noted in the rates of major bleeding, intracranial bleeding or ischemic stroke between the two groups.

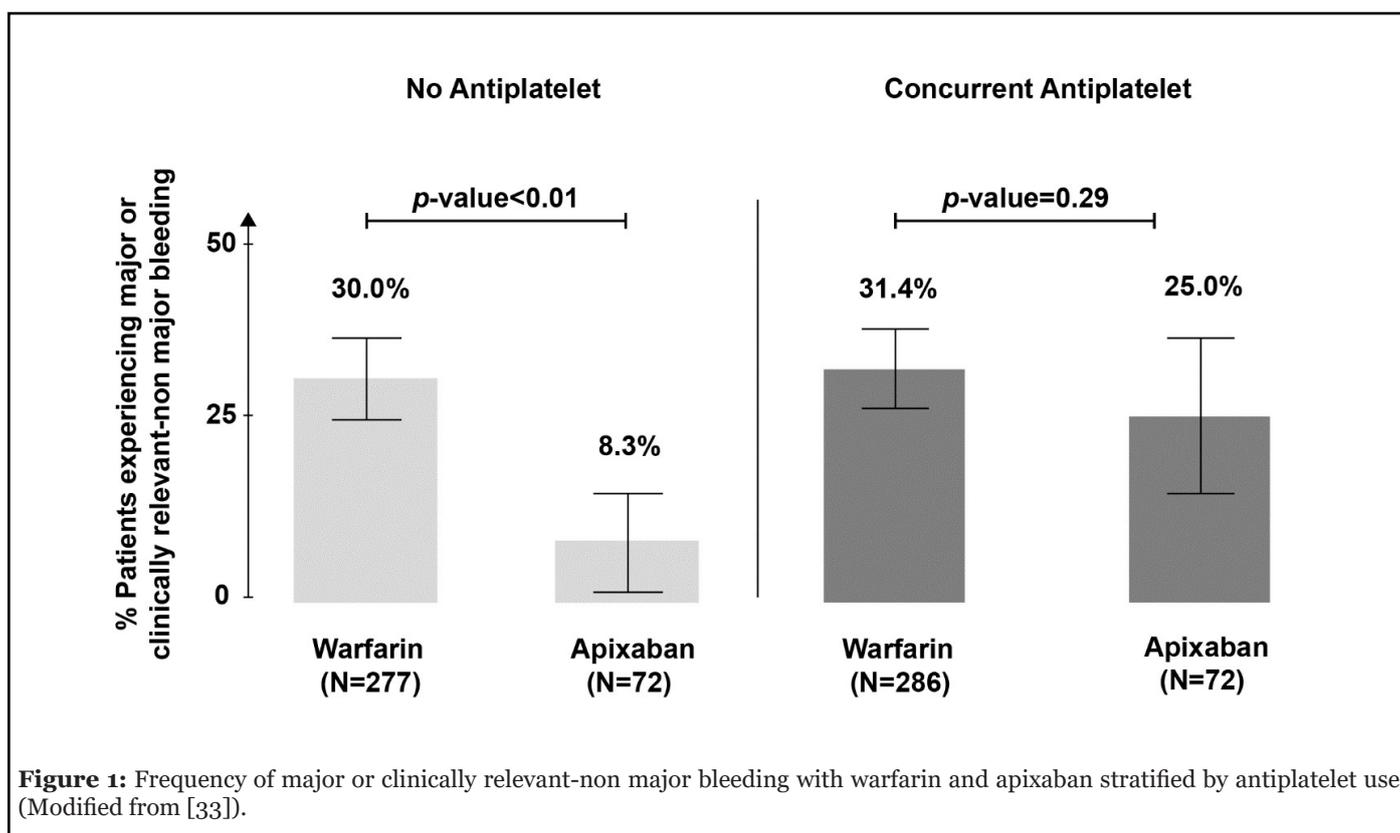
The interpretation of retrospective evidence is difficult given the substantial risk for confounding. An additional complicating issue is the inability to investigate clinical variables that may impact the safety of apixaban due to lack of quality data. Chiefly, analyses of bleeding risk with DOACs in CKD and HD patients have largely ignored the interaction of antiplatelets and anticoagulants, which has recently gained attention in the cardiovascular disease literature. As previously discussed, CKD and HD patients are underrepresented in these studies, but the importance of this issue is underscored by a high percentage of antiplatelet use (40%-50.6%) in our cohort and that of others [32,33]. In the RENAL-AF trial, the impact of antiplatelet therapy on bleeding, despite a high rate of use (40%), was not explored.

In non-HD patients, one study found that the concurrent use of any antiplatelet and apixaban increased the risk of major bleeding (adjusted odds ratio of 2.01; 95% confidence interval [95% CI] 1.29-3.11) [34]. A large retrospective study demonstrated a similarly increased bleeding risk with addition of aspirin to DOAC (hazard ratio [HR] 1.30; 95% CI 1.11-1.52) [35]. Another retrospective analysis, however, found that add-on dual or single agent antiplatelet therapy to DOAC did not influence the risk in multivariate analysis [36]. Perhaps the strongest evidence for the increased

bleeding risk with addition of antiplatelet medication comes from the AUGUSTUS study, a multicenter, randomized trial with a 2x2 factorial design which investigated the use of a P2Y12 inhibitor in combination with warfarin *versus* apixaban and aspirin *versus* placebo in patients with atrial fibrillation and acute coronary syndrome or percutaneous coronary intervention [37]. No patients on hemodialysis were included and the number of patients with a creatinine above 1.5 mg/dL was small (creatinine clearance was not reported). The analysis found an increased risk of bleeding with the use of a dual antiplatelet regimen in combination with anticoagulation compared to single antiplatelet agent combined with anticoagulation with no additional benefit. Although exploring primarily the risk profile of adding dual antiplatelet therapy compared to single antiplatelet therapy, AUGUSTUS provides compelling evidence for increased bleeding potential with concurrent use of interacting pharmacokinetic drugs.

Our group recently reported findings from a retrospective analysis of bleeding rates in HD patients treated with either warfarin or apixaban [33]. We found a significantly lower bleeding propensity with apixaban use alone compared to warfarin alone, whereas concurrent antiplatelet therapy markedly reduced the difference (Figure 1). Additionally, in a multivariate competing risk model, the use of apixaban alone was again associated with less bleeding (HR 0.24, 95% CI 0.10-0.55), but this safety advantage was not observed with concurrent use of apixaban and any antiplatelet (HR 0.93, 95% CI 0.55-1.56). It is worthwhile to note that a large database study of non-HD patients found a lower risk of major bleeding with concomitant DOAC-antiplatelet use compared to warfarin-antiplatelet (HR 0.68; 95% CI 0.51-0.91), again raising the question of whether CKD and HD patients have a different bleeding risk profile with antithrombotic combinations compared to other populations [38]. The majority of bleeding in our cohort (nearly 80% in the apixaban group and 50% in the warfarin group) originated in the gastrointestinal tract raising the question of whether the ulcerogenic activity of antiplatelets underlies the observed difference. Notably, use of proton pump inhibitors or H2 blockers did not impact the bleeding risk in our analysis, but this remains an important avenue for future research.

Important unknowns remain with regards to the use of anticoagulant and antiplatelet medication in the advanced CKD and HD populations. The fundamental question pertains to the efficacy of anticoagulation in preventing stroke or venous thromboembolism recurrence in these cohorts as available data for warfarin and DOACs is of poor quality and conflicting. One ongoing trial (NCT03987711) is actively addressing this question by inclusion of a placebo (no anticoagulation) comparison arm. Secondly, the safety of DOACs remains to be



demonstrated in a large, prospective study and two are currently ongoing (NCT02933697, NCT03987711). Importantly, with the current trend in decreasing the intensity of antithrombotic regimens in patients with coronary artery disease, antiplatelet therapy should be included among the randomization criteria of prospective studies as preliminary findings suggest that their addition may minimize safety benefits without a concomitant decrease in thrombotic events. Lastly, with the advent of betrixaban, a newer DOAC with the lowest documented renal clearance (15%) [39], it remains to be determined if this new medication represents a more attractive option for advanced CKD and HD patients compared to apixaban.

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