Chronic kidney disease and anticoagulation: from vitamin K antagonists and heparins to direct oral anticoagulant agents

CHRONIC KIDNEY DISEASE AND ANTICOAGULATION: FROM VITAMIN K ANTAGONISTS AND HEPARINS TO DIRECT ORAL ANTICOAGULANT AGENTS

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Short Title: Anticoagulation in CKD patients

Key words:

chronic kidney disease, anticoagulation, heparins, direct anticoagulant agents, rivaroxaban, apixaban, dabigatran etexilate, thrombosis, factor Xa inhibitor, thrombin inhibitor

Word count Abstract: 153

Word count Manuscript: 2521

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Abstract:

Background

Anticoagulation in patients with impaired kidney function can be challenging since drugs' pharmacokinetics and bioavailability are altered in this setting. Patients with chronic kidney disease (CKD) treated with conventional anticoagulant agents [vitamin K antagonist (VKA), low-molecular weight heparin (LMWH) or unfractionated heparin (UFH)] are at high risk of bleeding events (both non-major and major clinically relevant bleeding). While anticoagulation reduces the risk of thromboembolic events, the co-existing bleeding risk and the fact that the most commonly used anticoagulation agents are eliminated via the kidneys pose additional challenges. More recently, two classes of direct oral anticoagulant agents (DOACs) have been investigated for the prevention and/or management of venous thromboembolic events: the direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban, and the direct thrombin inhibitor dabigatran.

Purpose of the review

In this review we discuss the complex challenges and the practical considerations associated with the management of anticoagulation treatment in patients with CKD, with a special focus on DOACs.

Introduction

Renal impairment has been associated with altered drug binding to plasma proteins and changes in volume of distribution, potentially leading to drug toxicity or ineffective therapy[1]. Anticoagulation in patients with impaired kidney function and chronic kidney disease (CKD) can be challenging since pharmacokinetics and bioavailability are altered in this setting.

Furthermore, patients with renal failure treated with conventional anticoagulant agents (such as vitamin K antagonist (VKA), low-molecular weight heparin (LMWH) or unfractionated heparin (UFH)) have a higher risk of major or non-major clinically relevant bleeding when compared to those subjects with normal renal function[2].

Vitamin K Antagonists

VKAs are mostly metabolized in hepatocytes via a monooxygenase, cytochrome P450 2C9 (CYP2C9), resulting in inactive products[3]; nevertheless, patients with impaired renal function require frequent monitoring to ensure therapeutic anticoagulation with VKAs because of their unpredictable pharmacokinetics [4–7].

VKA's activity is measured and monitored with the international normalized ratio (INR). CKD has been associated with anticoagulant instability, meaning that closer INR monitoring and VKA dosing adjustments are required in these patients compared to patients with a normal renal function (adjustments required in 22% vs. 12% of visits,

respectively). Moreover, the time in therapeutic INR range is reduced significantly in patients with CKD vs. others (62% vs. 74%, respectively)[8].

Over-anticoagulation (e.g. INR>4.0) with a subsequent increase in bleeding (both non major and major clinically relevant bleeding) has been estimated to be four times more likely in patients with CKD. The risk of bleeding is further increased in subjects with severe CKD compared to those with moderate CKD[4, 8].

Limdi and coworkers [4] evaluated the influence of kidney function on warfarin dosage, anticoagulation control, and risk for hemorrhagic complications in prospective cohort of 578 patients treated with VKA. Over-anticoagulation (INR >4) was more frequently encountered among patients with severe CKD, (estimated GFR <30 ml/min per 1.73 kg/m2) as compared with patients with moderate CKD (incidence rate ratio [IRR] 1.8, 95% CI 1.4 to 2.3; $p< 0.0001$). Likewise, patients with moderate CKD had a higher incidence of over-anticoagulation compared to those with no or mild CKD (IRR 1.20; 95% CI 1.10 to 1.46; $p = 0.007$). The overall incidence of clinically relevant major bleeding was 8.4 (95% CI 6.5 to 10.7) per 100 patient-years. Patients with severe CKD had a higher incidence of clinically relevant major bleeding compared to those with moderate CKD (IRR 3.7; 95% CI 1.8 to 7.2; p=0.0003) and those with no or mild CKD (IRR 4.9; 95% CI 2.6 to 9.1; P < 0.0001). The incidence of clinically relevant major bleeding was not significantly different among patients with moderate CKD compared with those with no or mild CKD (IRR 1.30; 95% CI 0.74 to 2.40; p=0.31). Severe CKD was associated with a two-fold higher risk for

major hemorrhage (p = 0.027) after adjustment for clinical and genotypic variables and correction for dependence[4].

A report from the Danish national patient registry examined the risk reduction of stroke and systemic thromboembolism among patients with atrial fibrillation (AF) with chronic kidney diseases (CKD) on or off anticoagulation over a 12 year period [9]. They found that treatment with VKA increased the risk of bleeding in CKD patients (HR 1.36, 95% CI 1.17-1.59; p< 0.001). In another large retrospective study consisting of 1626 patients with AF and with end-stage CKD, of whom 756 patients were prescribed VKA, and the reminder were not, it was found that the patients on VKA had a 44% increased bleeding risk[10].

Managing VKA treatment to prevent thromboembolism among haemodialysis patients is still challenging[11]. The absence of a standardized protocol for anticoagulant use in haemodialysis patients with AF is reflected in the heterogeneous treatment approaches adopted by clinicians internationally. Although some studies reported a significantly worse outcome with VKAs[12, 13] others suggested a clear benefit [14]. Of note, Genovesi and co-workers found that a higher time in therapeutic range (TTR) was associated with a reduced bleeding risk (HR 0.09, CI 0.01-0.76, P = 0.03) in haemodialysis patients with atrial fibrillation receiving VKAs[15].

A recent meta-analysis analysed data from 4,010 hemodialysis patients receiving VKA, from twelve retrospectives and a prospective study. Treatment with VKA was associated with a nonsignificant reduction of the risk of ischemic stroke (HR 0.74; 0.51-1.06), a significant increase regarding the bleeding risk (HR 1.21; 1.03-1.43), and a non-significant

correlation with mortality (HR 1.00; 0.92-1.09)[16]. Furthermore, in another recent meta-analysis, Dahl and colleagues analysed >48,500 total patients with >11,600 warfarin users [17]. In patients with AF and non-end-stage CKD, warfarin resulted in a lower risk of ischemic stroke/thromboembolism (HR, 0.70; 0.54-0.89) and mortality (HR, 0.65; 0.59-0.72; but had no effect on major bleeding (HR, 1.15; 0.88-1.49). In patients with AF and end-stage CKD, warfarin had no effect on the risks of stroke (HR, 1.12; 0.69-1.82) and mortality (HR, 0.96; 0.81-1.13), but increased the risks of major bleeding (HR, 1.30; 1.08-1.56). On the other hand, several recent studies describe a reduction of mortality in hemodialysis patients treated with VKAs, however it does not seems not to be associated with a decreased rate of thromboembolic events [18, 19].

Low-molecular Weight Heparins and Unfractionated Heparins

LMWHs are excreted by the kidneys[2, 20] leading to plasma accumulation in patients with reduced renal function. The extent as to which plasma accumulation takes place depends on the type of LMWH and the proportion of the substance cleared by the kidneys[21]. Bioaccumulation may not only result in an excessive anticoagulant effect but also in an increased bleeding risk when using standard LMWH doses[2, 22]. In a meta-analysis including 18 randomized controlled trials (RCTs) (15 studies using enoxaparin, two using tinzaparin, and one using dalteparin) a higher rate of bleeds was reported in patients with severe renal impairment (estimated creatinine clearance [eCrCl] <30 mL/min) receiving

LMWH for VTE when compared to patients with eCrCl ≥30 mL/min [5% and 2.45%, odds ratio, 2.25 (95% CI, 1.19 to 4.27); p=0.013][23].

Patients with renal impairment and acute VTE treated with UFH are at higher risk of death compared to patients treated with LMWH[24], and patients with eCrCl <30 mL/min have a two-fold higher mortality rate when compared to patients with normal renal function[24]. Trujillo-Santos J et al[24]reported registry data from the Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) evaluating the 15-day outcome in 38,531 patients treated LMWH or UFH for venous thromboembolism. Propensity score-matched groups of patients with creatinine clearance levels >60 mL/min (n = 1598 matched pairs), 30 to 60 mL/min (n = 277 matched pairs), and <30 mL/min (n = 210 matched pairs) showed an increased 15-day mortality for unfractionated heparin compared with low-molecular-weight heparin (4.5% vs 2.4% [p = 0.001], 5.4% vs 5.8% [p= not significant], and 15% vs 8.1% [p = 0.02], respectively), an increased rate of fatal pulmonary embolism (2.8% vs 1.2% [p = 0.001], 3.2% vs 2.5% [p= not significant], and 5.7% vs 2.4% [p = 0.02], respectively), and a similar rate of fatal bleeding (0.3% vs 0.3%, 0.7% vs 0.7%, and 0.5% vs 0.0%, respectively)[24].

Overall, studies comparing UFH with LMWH in the treatment of VTE and acute coronary syndromes report a similar efficacy without an increased rate of bleeding for LMWH[25, 26]. In their meta-analysis of RCTs, Antman et al[27]. reported that the rate of bleeding (especially major events) was similar in patients treated with LMWH (enoxaparin) compared to those treated with UFH (1.3% and 1.1%, respectively, p= not significant).

Based on these observations, LMWHs have been increasingly prescribed in patients with renal impairment especially for thromboprophylaxis where only small doses are required. Interestingly, there are more studies investigating the use of LMWH for anticoagulation in haemodialysis than there are on patients with stage III or IV kidney disease (reviewed above [2]). The predictable pharmacokinetic profile of LMWH makes them easy to use. However, whether all these advantages can be directly extrapolated to recommend the use in patients with renal failure is still under debate.

Direct Anticoagulants Agents

Taken together, these data show that a fixed degree of systemic anticoagulation, ideally obtained with a fixed-dose oral anticoagulant would offer significant practical and clinical advantages over the currently available treatments. Needless to say that these advantages would be particular for frail patients such as those with renal impairment [28–31]. Currently, two classes of direct anticoagulants agents (DOACs) have been investigated for VTE management and thromboembolism prevention in non-valvular AF: The direct factor Xa inhibitors (rivaroxaban, apixaban and edoxaban), and the direct thrombin inhibitor dabigatran. The main recommendations for the use in patients with CKD are summarized in Table 1. Due to their rapid onset of action and predictable pharmacokinetics DOACs are given at fixed doses without the need for routine laboratory monitoring[32]. Moreover fewer drug to drug interactions have been reported for DOACs compared to VKAs, which is highly relevant in patients with chronic longstanding conditions at risk of polypharmacy[32].

Similarly to the VKA-induced risk of haemorrhage, an increased likelihood of bleeding has been observed when administering DOACs concomitantly with agents that interfere with haemostasis (e.g. anti-aggregant therapies).In a phase II trial in patients with acute coronary syndromes on dual antiplatelet therapy, dabigatran was found to increase the risk of bleeding in a dose-dependent manner [hazard ratio (HR) 1.77 (95% CI 0.70, 4.50) for 50 mg; HR 2.17 (0.88, 5.31) for 75 mg; HR 3.92 (1.72, 8.95) for 110 mg; and HR 4.27 (1.86, 9.81) for 150 mg). However, the risk was not increased when comparing patients with normal kidney function to those with mild/moderate CKD[33]. Similar bleeding rates were observed in the APPRAISE[34] and ATLAS studies[35]. On top of dual antiplatelet treatment, there was a 2.6 times relative increase and 7.9% absolute rate with a 10 mg daily dose of apixaban (p=0.001) in the APPRAISE trial[34]. In the ATLAS study[35], rivaroxaban associated to dual antiplatelet treatment versus placebo increased major bleeding (2.2% vs. 0.6%, $p < 0.001$) and intracranial haemorrhage (0.6% vs. 0.1%, $p = 0.015$).

Dans and co-workers[36] analysed the use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) and showed that the concomitant use of a single antiplatelet seemed to increase the risk of major bleeding (HR, 1.60; 95% CI, 1.42–1.82). Additional dual antiplatelet therapy seemed to increase this even more (HR, 2.31; 95% CI, 1.79–2.98)[36].

Very recently, Gibson and colleagues [37] in the PIONEER study, randomly assigned 2124 participants with nonvalvular atrial fibrillation who had undergone percutaneous coronary

intervention with stenting to receive either low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 months (group 1), very-low-dose rivaroxaban (2.5 mg twice daily) plus dual antiplatelet therapy (DAPT) for 1, 6, or 12 months (group 2), or standard therapy with a dose-adjusted VKAs (once daily) plus DAPT for 1, 6, or 12 months (group 3). In this study, the administration of either low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than was standard therapy with a VKAs plus DAPT for 1, 6, or 12 months. The three groups had similar efficacy rates, although the observed broad confidence intervals diminish the surety of any conclusions regarding efficacy. Other drug–drug interactions are limited to agents that directly affect DOAC metabolism, as detailed in table 2[38–42].

The direct factor Xa inhibitors rivaroxaban and apixaban are metabolised by the cytochrome P450 (CYP) system (including both the 2J2 and 3A4 group of enzymes) for degredation [39, 43]. As a consequence, plasma concentrations of DOACs will be reduced or elevated in the presence of strong inducers or inhibitors of CYP3A4, respectively. Furthermore, the elimination of direct factor Xa inhibitors is dependent on P-glycoprotein (P-gp) and this should be kept in mind when rivaroxaban or apixaban are given concomitantly with other medications affecting the P-gp system[39, 40, 43, 44].

Dabigatran is mainly eliminated by the kidneys, but unlike direct factor Xa inhibitors, CYP3A4 is not involved in the elimination of dabigatran [42]. Edoxaban is also a substrate of P-gp, although to a lesser degree [39, 43]. Hence, plasma concentrations of both

edoxaban and dabigatran may change when these agents are concomitantly prescribed with drugs whose metabolism is dependent on P-gp, potentially leading to increased plasma concentration in case of P-gp inhibitors or decreased plasma concentration in case of P-gp inducers[39, 43].

The role of DOACs in preventing thromboembolism in non-valvular AF and in managing VTE (treating acute DVT/PE and the secondary prevention of VTE) has been investigated in several phase III non-inferiority RCTs[45–52]. When pooled together, the results of these RCTs show that DOACs are no less effective and have a similar or even better safety profile when compared to conventional anticoagulation[45–52]. In a large meta-analysis of RTCs comparing the efficacy and safety of DOACs with VKAs in patients with AF, DOACs were found to significantly reduce stroke or systemic embolic events by 19% compared with warfarin (RR 0,81, 95% CI 0,73-0,91; p<0,0001) and all-cause mortality (0,90, 0,85-0·95; p=0,0003)[53]. Similar results were observed when assessing the efficacy of DOACs in treatment and secondary prevention of VTE[54]. DOACs were equally effective as VKAs in preventing recurrent symptomatic VTE (RR 0.89, 95% CI 0.75-1.05), reducing VTE recurrence rates to 1.32% (vs. 7.24% with placebo, p <0.00001). Sardar P. and coworkers[55]demonstrated in a pooled analysis of fifty trials including 155,537 patients treated with DOACs for all indications, that there was no significant difference risk of clinically relevant major bleeding between DOACs and comparators (OR 0.93, 95% CI 0.79-1.09).

Similar results were observed for individual DOACs: There was no significant difference in the risk of clinically relevant major bleeding for patients treated with rivaroxaban, apixaban or dabigatran compared to pharmacologically active comparators or VKA[55].

In a recent meta-analysis, Del-Carpio and colleagues [56] included the randomized clinical trials that compared efficacy and safety (e.g. major bleeding) outcomes of DOACs compared to warfarin for the treatment of nonvalvular atrial fibrillation and had available data on renal function. In their study, the pooled relative risk of stroke/systemic embolism and major bleeding were higher in subjects with renal impairment compared to normal renal function, independent of type of anticoagulant therapy. In subjects with normal renal function, no difference in the risk of stroke/systemic embolism was observed, whereas the risk of major bleeding was slightly lower for subjects taking DOACs (RR 0.87, 95% confidence interval [CI] 0.76 to 0.99). In subjects with mild or moderate renal impairment, DOACs were associated with a reduced risk of stroke/systemic embolism (RR 0.75, 95% CI 0.66 to 0.85 and RR 0.80, 95% CI 0.68 to 0.94, respectively) and major bleeding (RR 0.87, 95% CI 0.79 to 0.95 and RR 0.80, 95% CI 0.71 to 0.91, respectively) compared to warfarin. However, some practical aspects, such as the use of DOACs in the specific settings of patients with CKD require further consideration. As previously mentioned, available DOACs are at least partially eliminated by renal clearance (dabigatran 80%, rivaroxaban 35%, and apixaban 25%) [57–59]. Previous analyses reported an increase in plasma concentration defined as the area under the curve and/or peak plasma concentration for dabigatran, rivaroxaban and apixaban in patients with impaired renal

function[59–61]. On the basis of these observations, modified dosing regimens were adopted in patients with renal insufficiency in most RCTs in order to investigate the safety and efficacy of DOACs. In the ‘Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation’ (ROCKET-AF) trial, a 15 mg daily dose of rivaroxaban was administered to patients with eCrCl 30-49 mL/min instead of the 20-mg daily dose prescribed to patients with renal function eCrCl>50mL/min[45]. In trials investigating the use of apixaban, a reduced dose regimen (2.5 mg twice daily rather than 5-mg twice per day dose) was adopted in patients with serum creatinine >133 m mol/L, over the age of 80 years or who weighed <60 kg[47].

However, extrapolation of the results obtained in phase III RCTs to frail sub-populations, such as patients with CKD, might be subject to some limitations. In fact, although the fixed-dose regimen of DOACs offers a clear practical advantage, physicians are likely to question the safety of fixed-dose administration in frail subgroups of patients. In line with these observations, among others, Molteni and co-workers, when reviewing available evidence on the use of dabigatran in patients with CKD and in the elderly, pointed out that that despite in patients with no contraindication to its use, the clinical benefit of dabigatran versus VKAs is independent of renal function, some physicians still perceive mild-to-moderate renal impairment as a relative contraindication to DOAC’ use[62].

To date, evidence supporting the use of DOACs in patients on dialysis is scarce, conflicting and challenging to interpret.

In a recent study, when analysing apixaban pharmacokinetics in seven hemodialysis patients at steady state, Mavrakanas and colleagues [63] found that drug concentration with 2.5 mg twice daily resulted in drug exposure comparable with that of the standard dose (5 mg twice daily). Similarly, De Vriese and colleagues[64] analysed the pharmacokinetics and pharmacodynamics of rivaroxaban in 18 maintenance hemodialysis patients. In their study, they found that a 10 mg dosage of rivaroxaban in hemodialysis patients resulted in a comparable drug dose of 20 mg for healthy volunteers from published data.

However, very recently, Chan and co-workers[65] investigated the use of dabigatran or rivaroxaban in haemodialysis patients using the Fresenius Medical Care North America (FMCNA) ESRD database from October, 2010 to October, 2014. After regression analysis, dabigatran (rate ratio 1.48; 95% CI, 1.21-1.81; p=0.0001) and rivaroxaban (rate ratio 1.38; 95% CI 1.03-1.83; p=0.04) were associated with an incresead risk of hospitalization or death from bleeding when compared with VKAs. This analysis highlighted the potential for risk when DOACs and especially dabigatran are used in dialysis patients in whom kidney failure impairs the clearance of the agent, leading to drug bioaccumulation and a potentially increased risk of severe bleeding.

To date, a recommendation for the use of DOACs in haemodialysis patients cannot be made on the basis of the currently available data.

Conclusion

In conclusion, patients with CKD are at a higher risk for both thrombosis and bleeding, and evidence based medicine is limited on describing the best approach to managing anti-coagulant therapy in this population. To date, the management depend on balancing the risk of bleeding and thrombosis for each patient, with monitoring and education necessary to improve outcomes. Experiences with the use of anticoagulation in patients with impaired renal function continue to expand providing helpful insights on their value and limitations.

Acknowledgments: None

Disclosure of Conflicts of Interest: None declared

Funding: None declared

Table 1

Main recommendations for DOAC use in patients with CKD of European Medicines Agency and Food and Drug Administration.

European Medicines Agency				
	Stages 1,2 and 3a CKD	**Stage 3b CDK**	**Stage 4 CDK**	**Stage 5 and 5D CDK**
Dabigatran	150 mg b.i.d.	150 or 110 mg b.i.d.a	None	None
Rivaroxaban	20 mg o.d.	15 mg o.d.	15 mg o.d.	None
Apixaban	5 mg b.i.d.	2.5 mg b.i.d. in presence of two of following: age >80 years, body weight 1.5 mg/dL	2.5 mg b.i.d.	None
Edoxaban	60 mg o.d.	30 mg o.d.	30 mg o.d.	None
Food and Drug Administration				
Dabigatran	150 mg b.i.d.	150 mg b.i.d.	75 mg b.i.d.	None
Rivaroxaban	20 mg o.d.	15 mg o.d.	15 mg o.d.	15 mg o.d.
Apixaban	5 mg b.i.d.	2.5 mg b.i.d. in presence of two of following: age >80 years, body weight 1.5 mg/dL	2.5 mg b.i.d. in presence of two of following: age >80 years, body weight 1.5 mg/dL	2.5 mg b.i.d. in presence of age >80 years or body weight 1.5 mg/dL
Edoxaban	60 mg o.d.	30 mg o.d.	30 mg o.d.	None

Table 2. Main Drug-Drug Interactions of DOAC with P-gp and CYP3A4 Inhibitors and Inducers

Drug	CYP3A4	P-gp	Change in Plasma Concetrantion (%)				Comments*
			Rivaroxaban	Apixaban	Edoxaban	Dabigatran	
Amiodarone		Inhibitor/ Competitor	Minor effect		+40	+50	Dabigatran: consider dose reduction
Antiacids (H2B, PPI, Al-Mg-hydroxide)						-12-30	
Atorvastatin	Inhibitor	Competitor				+18	
Carbamazepine	Inducer	Inducer					
Clarithromycin	Inhibitor	Inhibitor	+50			+15	Dabigatran and Rivaroxaban: consider dose reduction
Cyclosporin		Competitor	+50				Rivaroxaban: consider dose reduction
Diltiazem	Inhibitor	Weak Inhibitor	Minor effect	+40			Apixaban: consider dose reduction
Dronedarone	Inhibitor	Inhibitor			+80	+80	Contraindicated/not recommended (scarse data on Rivaroxaban and Apixaban)
Erythromicin	Inhibitor	Inhibitor	+30		+80	+15	Dabigatran and Rivaroxaban: consider dose reduction
Itraconazole	Inhibitor	Inhibitor					Contraindicated/not recommended
Fluconazole	Moderate Inhibitor		+40				Rivaroxaban: consider dose reduction
Ketoconazole	Inhibitor	Inhibitor	+160	+100	+80	+140	Contraindicated/not recommended
Lopinavir		Inhibitor					
Phenytoin	Inducer	Inducer					
Quinidin		Inhibitor/ Competitor	+50		+75	+50	Consider dose reduction (scarse data on apixaban)
Rifampicin	Inducer	Inducer	-50	-50		-60	Dabigatran and Apixaban: contraindicated/not recommended. Rivaroxaban and Edoxaban: consider dose reduction
Ritonavir	Inhibitor	Inhibitor	+50-150	Strong increase			Contraindicated/not recommended
Tacrolimus		Competitor	+50				
Verapamil	Weak Inhibitor	Inhibitor/ Competitor	Minor effect		+50	Variable (+12-180)	Dabigatran and Edoxaban: consider dose reduction
Voriconazole	Inhibitor						

CYP, cytochrome; P-gp, permeability glycoprotein; H2B, H2-blockers; PPI, proton-pump inhibitors. *Based on ref [38]

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