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Role of Direct Oral Anticoagulants in Patients with Kidney Disease

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Abstract

The anticoagulation field is experiencing a renaissance that began with regulatory approval of the direct thrombin inhibitor, dabigatran, a Direct Oral Anticoagulant (DOAC) in 2010. The DOAC medication class has rapidly evolved to include the additional approval of four direct factor Xa inhibitors. Commensurately, DOAC utilization has grown and collectively account for the majority of new anticoagulant prescriptions. Despite exclusion of moderate-to-severe kidney disease patients from most DOAC pivotal trials, DOACs are increasingly utilized in this setting. An advantage of DOACs is similar or improved antithrombotic efficacy with less bleeding risk (when compared to traditional agents). Several post-hoc analyses, retrospective studies, claims data studies, and meta-analyses suggest that these benefits extend to kidney disease patients. However, the lack of randomized controlled trial data in specific kidney disease settings, with their unique pathophysiology, should be a call-to-action for the kidney community to systematically study these agents; especially since early data suggest that DOACs may pose less risk of anticoagulant-related nephropathy than vitamin K antagonists. Most DOACs are renally cleared and are significantly protein bound in circulation, thus the pharmacokinetics of these drugs are influenced by reduced renal function and proteinuria. DOACs are susceptible to altered metabolism by P-glycoprotein inhibitors and inducers, including drugs commonly utilized for management of kidney disease co-morbidities. We summarize the currently available literature on DOAC use in kidney disease and illustrate knowledge gaps which represent important opportunities for prospective investigation.

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Keywords

Anticoagulation; Chronic Kidney Disease; End-Stage Kidney Disease; Nephrotic Syndrome; Lupus Nephritis; Dialysis; Atrial Fibrillation; Venous Thromboembolism

INTRODUCTION

Kidney disease patients are at increased risk for both thrombotic disease and bleeding events, thus requiring careful clinical attention to hemostatic balance.[1–4] Arterial thromboembolic disease arises primarily from co-morbid atherosclerosis and its management in kidney disease patients has been recently reviewed in this journal and elsewhere.[1, 5–10] With the exception of stroke prevention in patients with co-morbid atrial fibrillation (AF), arterial thrombosis is primarily managed with antiplatelet agents, although recent data support the use of low-dose rivaroxaban (2.5 mg twice daily) in combination with antiplatelet therapy for coronary or peripheral artery disease.[11, 12] In addition to other reviews, antiplatelet agent use in kidney disease scenarios has been a recent Cochrane review subject.[13–16] Meanwhile, there have been significant advancements in oral anticoagulant medications for primary stroke prevention in AF and secondary prophylaxis in venous thromboembolic (VTE) disease. This review will focus on the use of oral anticoagulant medications for kidney disease patients with an emphasis on the Direct Oral Anticoagulants (DOACs).

The prevalence of AF in chronic kidney disease (CKD) patients is 2–3–fold higher than in the general population and an estimated 7–20% of end-stage kidney disease (ESKD) patients have AF.[17–24] In a large Danish case-control study, the odds ratio (OR) for VTE in adults with kidney disease was 1.41–2.89.[2] Our group recently analyzed United States claims data demonstrating ~1:200 children with chronic renal disease suffer from VTE complications (vs. ~1:10,000 in the general pediatric population).[3, 25] Nephrologists are likely to encounter patients requiring anticoagulation for these or other indications during routine practice.

Whereas vitamin K antagonists (VKA) and heparins served as the mainstays of anticoagulation for decades, the field is evolving rapidly. Five DOACs have received regulatory approval and additional novel anticoagulant approaches are presently in clinical trials. We will thus review the pharmacology of approved anticoagulants and their use in various kidney disease contexts.

ANTICOAGULATION PHARMACOLOGY

Heparins are indirect anticoagulants that potentiate the enzymatic activity of antithrombin (AT; Figure).[26] This activity is dependent upon interaction of a specific heparin pentasaccharide sequence with AT. Whereas standard (unfractionated) heparin effectively inhibits both thrombin and factor Xa, low molecular weight heparins (LMWH; e.g. enoxaparin, dalteparin) are less potent thrombin antagonists, exerting their effects predominantly via factor Xa inhibition. The synthetically produced pentasaccharide (fondaparinux) is factor Xa selective. Heparinoids (e.g. danaparoid) are mixtures of heparan, dermatan, and chondroitin sulfates that primarily antagonize factor Xa with less prominent

inhibition of other coagulation factors. Heparins, pentasaccharides, and heparinoids are administered either intravenously (standard heparin) or subcutaneously (all compounds). Standard heparin is eliminated by non-renal metabolism, whereas LMWHs and heparinoids are cleared renally and non-renally. While standard heparin needs no dose adjustment for renal insufficiency, the others should be dose adjusted.

VKAs (e.g. warfarin, acenocoumarol) are indirect anticoagulants which inhibit vitamin K epoxide reductase complex 1 (VKORC1). Consequently, the reduced form of vitamin K becomes depleted and unavailable to facilitate post-translational γ-carboxylation of factors II (prothrombin), VII, IX, and X. Because factor VII has the shortest half-life, the greatest effects are seen on the prothrombin time (PT) and VKAs are thus monitored with the PT-derived international normalized ratio (INR). Clearance is via hepatic metabolism primarily involving CYP2C9. The VKA therapeutic window is narrow and requires careful monitoring and frequent dose adjustment.[27] Patients with chronic kidney disease tend to require lower maintenance doses than other patients and experience more volatile INRs, requiring more intense monitoring.[28]

Several parenteral direct anticoagulants have been clinically available since ~2000.[29, 30] Argatroban is a competitive thrombin inhibitor.[30] It is cleared hepatically via CYP3A4/5 metabolism and has a short half-life requiring continuous intravenous administration. Bivalirudin (a synthetic oligopeptide mimetic of the naturally occurring medicinal leech venom anticoagulant, hirudin) is a selective, reversible thrombin antagonist.[31] Similar to argatroban, its short half-life requires continuous intravenous infusion. Desirudin, a recombinant hirudin analog is suitable for intermittent subcutaneous injection.[32] Both bivalirudin and desirudin are predominantly cleared renally (50% as unchanged drug) and may require dose adjustment for renal impairment.

Originally referred to as “new,” “novel,” or “non-VKA oral anticoagulants” (NOACs), the preferred international consensus nomenclature for oral anticoagulants that directly inhibit a single molecular target is “direct oral anticoagulant” (DOAC).[33] These agents have received regulatory approval on the basis of clinical trials demonstrating improved safety and non-inferiority, usually in comparison to warfarin. These agents have similar or improved efficacy in primary or secondary thromboprophylaxis and, perhaps more importantly, they generally have a superior safety profile (less clinically relevant major and non-major bleeding). The improved safety profile may be due to their more predictable pharmacokinetics over indirect anticoagulants (esp. VKAs) or result from their direct mechanisms of action. The first DOAC (dabigatran) received FDA approval in 2010. DOACs have since captured a growing share of anticoagulant prescriptions, recently surpassing warfarin in the United States and United Kingdom.[34, 35]

Dabigatran etexilate mesylate is an orally bioavailable prodrug requiring metabolism by both plasma and hepatic esterases to dabigatran, the active drug.[36, 37] Dabigatran is currently the only clinically-approved direct thrombin inhibitor which binds reversibly to the active site of thrombin (Figure). Its clearance is predominantly renal (80% as dabigatran or active metabolites; Table 1).[37–40] In contrast, there are currently four approved factor Xa-antagonist DOACs: rivaroxaban, apixaban, edoxaban, and betrixaban. These drugs all bind

reversibly to the factor Xa active site and dampen downstream thrombin and fibrin generation.[41] However, these compounds vary considerably in their pharmacokinetics, metabolism, and renal clearance (Table 1).[38] Rivaroxaban has the shortest half-life (5–9 h), apixaban and edoxaban are intermediate (10–14 h), and betrixaban the longest (19–27 h). Rivaroxaban and apixaban undergo hepatic metabolism (primarily CYP3A4/5) to inactive metabolites whereas edoxaban and betrixaban undergo minimal hepatic metabolism. Rivaroxaban excretion is predominantly urinary (66% by active tubular excretion; 36% as unchanged drug). Apixaban is also excreted in urine (27% as parent drug). Edoxaban is about 50% renally cleared (primarily as unchanged drug) whereas betrixaban is predominantly (85%) excreted in the feces.

Dabigatran is dialyzable (~57% removed over 4 hours), but rivaroxaban, apixaban, and edoxaban are not (betrixaban has not yet been studied). Reversal agents for the DOACs have recently been approved (Table 1). Idarucizumab, a monoclonal antibody fragment, binds dabigatran with an affinity 350-fold higher than thrombin, neutralizing the drug within minutes.[42] Andexanet alfa, a recombinant, enzymatically inert mutant factor Xa molecule, competes with endogenous factor Xa for binding of factor Xa DOACs.[43] Andexanet also restores hemostasis within minutes, but reversal may be incomplete in a substantial portion of patients. Moderate renal impairment (creatinine clearance (CrCl) 30–60 mL/min) modestly increases the half-life of idarucizumab which is excreted in the urine whereas andexanet has no measurable renal elimination.[44] Renal dose adjustments are not recommended for either antidote.

ANTICOAGULATION SCENARIOS IN KIDNEY DISEASE

Kidney disease has been identified as a risk factor for both VTE and AF, two common indications for anticoagulation.[1–3, 17–24] Although CKD patients were excluded from the pivotal, phase 3 DOAC trials. Data on their use, efficacy and side effects in various kidney diseases and levels of renal function are emerging from post-marketing studies. Below, we describe common causes of kidney disease and particular scenarios which might warrant anticoagulation (Table 2).[45]

Nephrotic Syndrome

VTE is a well-recognized nephrotic syndrome (NS) complication.[46–48] In the aforementioned Danish registry, adult NS patients had the highest risk for VTE (OR 2.17 [95% CI 1.68–2.80]). Similarly our United States claims data analysis demonstrated that children with NS have the highest VTE prevalence (2% vs. 0.4%).[2, 3] Reported NS-associated VTE prevalence varies dependent upon how VTE was ascertained and underlying pathology. In studies employing active VTE screening in adults with NS, the prevalence of renal vein thrombosis (RVT) was as high as 24% and highest in those with membranous nephropathy (MN), approaching 37%.[47] In childhood NS, the overall prevalence is much lower (~3%), although the majority of these studies reported clinically evident VTE.[47] Among children, those with MN and similar pathology demonstrated the highest VTE occurrence.[49]

In a cohort of 1,313 glomerular disease patients (MN, focal segmental glomerulosclerosis [FSGS], and IgA nephropathy [IgAN]), the MN group had the highest VTE risk, after disease severity adjustment (proteinuria and hypoalbuminemia), with a hazard ratio (HR) of 10.8 (vs. IgA nephropathy).[50] Patients with FSGS were at intermediate risk (HR 5.9). Serum albumin was an independent VTE risk factor. In a pooled analysis of two registries including 898 MN patients, clinically evident VTE was noted in ~7%, and VTE risk increased with worsening hypoalbuminemia (highest when albumin <2.8 g/dL).[51] Most VTE occurred within 2 years of diagnosis, consistent with other data suggesting that VTE is most likely early in the course of NS (sometimes prior or simultaneous to diagnosis).[50, 51]

Based on similar data, the 2012 KDIGO guidelines recommend consideration of prophylactic warfarin therapy for MN if serum albumin is <2.5 g/dL and additional thrombosis risk factors are present (grade 2C evidence).[52] Based on the above data, a clinical guidance tool was developed to guide prophylactic warfarin use in MN patients while accounting for bleeding risk (https://www.med.unc.edu/gntools/).[53] Generally, this tool suggests anticoagulation for MN patients with low bleeding risk and albumin <3 g/dL. However, this tool has limitations including a lack of validation studies. Because bleeding risk calculations in this algorithm are derived from warfarin safety data, the tool should only be applied to warfarin prophylaxis in adult MN cases. Optimal VTE prophylaxis for NS remains unclear as many studies have included heterogeneous causes of NS in which risk varies as described above. LMWH has been evaluated in an uncontrolled study in which no VTE events were noted among patients in the LMWH group.[54] Another observational study compared 44 patients receiving prophylactic LMWH or warfarin to 35 control patients.[55] Four VTEs were observed in the control group compared to none in the prophylaxis group. Two major bleeding events were reported in the prophylaxis group, both of whom were taking concomitant aspirin. There is no consensus on prophylaxis duration; however, most data suggest that hypercoagulopathy improves with NS remission.[52] Thus, discontinuation of prophylaxis may be reasonable once sustained complete remission is achieved and after contemplating other patient-specific thrombotic and bleeding risks.

Data on DOAC use in NS are beginning to emerge. Apixaban use was recently described for two NS patients.[56] One had minimal change disease and was treated with prophylactic apixaban until remission. The second had MN with a remote history of VTE and received apixaban prophylaxis for 3 months until resolution of NS. Neither patient experienced VTE, and the first had a minor epistaxis episode. Five additional case reports have described: two patients with recurrent VTE while on therapeutic warfarin successfully treated with rivaroxaban and edoxaban, respectively; one patient successfully treated with dabigatran after developing warfarin-related hepatotoxicity, and two patients treated with rivaroxaban (1 had recurrent VTE on rivaroxaban; the other discontinued drug after one week and subsequently developed intra-cardiac thrombosis). A small, open-label randomized trial compared dalteparin to rivaroxaban in 16 NS patients with VTE and AT deficiency. The primary outcome was >90% resolution of thrombus at 4 weeks.[57] Outcomes were similar in both groups suggesting similar rivaroxaban efficacy to LMWH. We recently reported an MN case with recurrent VTE on full-dose apixaban, but with sub-optimal peak drug levels.[58] While DOAC safety and efficacy in NS patients awaits systematic prospective study,

carefully selected DOACs may be a reasonable alternative for patients suffering recurrent VTE while on therapeutic warfarin (see Dosing Considerations).

Diabetic Nephropathy

Diabetes mellitus is not a strong independent VTE risk factor.[59] However, diabetic nephropathy (DN) may confer increased VTE risk. The aforementioned Danish study demonstrated that DN was associated with higher adjusted VTE odds (OR 1.43 [95%CI 1.28–1.61]) compared to controls.[2] Presently, no published data support specific anticoagulants for use in DN. However, a study of DOACs in type 2 diabetes demonstrated no differences in 2-hour pharmacokinetics or pharmacodynamics compared to non-diabetic controls for rivaroxaban, apixaban, or dabigatran.[60] Data from the *Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation* (ARISTOTLE) trial demonstrated similar benefit for both diabetic and non-diabetic participants, suggesting diabetes itself did not influence efficacy[61]. However, DN patients with nephrotic-range proteinuria and/or hypoalbuminemia could exhibit altered DOAC metabolism. Cardiovascular events and cerebrovascular events are well known complications of diabetes. In patients with NS secondary to diabetes, arterial events were far more likely than VTE.[62]

Antiphospholipid Syndrome and Lupus Nephritis

Suggested primary prophylaxis (prior to first thrombosis) for patients with antiphospholipid antibodies (irrespective of SLE or LN status) is low-dose aspirin.[63] Antiphospholipid syndrome (APS; antiphospholipid antibodies plus a thrombotic event) may be primary (without an underlying systemic autoimmune disorder) or may occur secondarily to a broader rheumatic disease.[64] APS imparts a major predisposition to both arterial and venous thrombosis.[65] Recommended therapy for patients with APS is long-term VKA with goal INR 2–3.[63, 64, 66, 67] DOACs are generally not recommended for patients with APS. Most data regarding the management of APS coincident with kidney disease are in relation to lupus nephritis (LN). Systemic lupus erythematosus (SLE) patients are at increased VTE risk, but it is unclear if LN imparts additional VTE risk. One study examining renal outcomes in 66 patients with membranous LN (Class V LN) noted VTE in 15 (23%) patients over mean follow-up of 6.9 years.[68] Most (93%) of these patients had secondary NS at the time of VTE. SLE patients may also develop antiphospholipid antibodies and secondary APS. The *Rivaroxaban in Antiphospholipid Syndrome* (RAPS) study evaluated rivaroxaban vs. warfarin in patients with APS (11% of whom had SLE).[69] Over 6 months, no new thrombotic events were seen in either group. Triple positive APS (positive lupus anticoagulant plus both anti-cardiolipin and anti-β2 glycoprotein I antibodies) patients are at highest thrombotic risk and 28% of RAPS patients were triple positive. However, failure of rivaroxaban to prevent recurrent VTE has been reported in APS patients with and without triple positivity.[70, 71] A systematic review of DOACs in APS identified 122 patients treated with DOACs, the majority (89%) of whom were treated with rivaroxaban (11% dabigatran; and one apixaban patient).[72] Recurrent thrombotic events occurred in 19 patients and triple positivity was associated with 3.5-fold OR for recurrent thrombosis. The recently completed *Trial on Rivaroxaban in AntiPhospholipid Syndrome* (TRAPS) study, examined the non-inferiority of rivaroxaban vs. warfarin in recurrent VTE prevention in triple positive APS patients.[73] TRAPS was concluded prematurely due to a higher incidence of the composite

outcome (thromboembolic events, major bleeding, and vascular death) in the rivaroxaban group. A recently published non-inferiority study evaluated rivaroxaban versus VKA for secondary thromboprophylaxis in 190 patients with APS.[74] Rivaroxaban did not meet the non-inferiority criteria and trended toward an increased risk of recurrent thrombotic events. Additional reports noted failure of dabigatran to prevent recurrent APS-associated VTE, not all of whom had triple positivity.[75, 76] A current ongoing study is evaluating apixaban versus warfarin to prevent recurrent VTE in patients with APS (NCT02295475).[77] Considering these data, DOACs are not recommended for APS as first-line therapy. Some authors suggest that DOACs may be considered for patients who fail warfarin therapy, but we suggest that LMWH may be a better option.[63] DOACs should be avoided in triple positive APS patients. Management of childhood APS is largely derived from adult data, thus these principles are generally applied to children.[78, 79]

ANCA Vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA) vasculitis patients are known to be at high-risk for VTE. Data from cohort studies and clinical trials suggest that 8–16% of ANCA vasculitis patients develop VTE.[80–83] In the *Wegener's Granulomatosis Etanercept Trial* (WGET), 29 (16%) of 180 patients experienced VTE; 13 events occurred prior to enrollment.[81] While this heightened VTE risk was initially reported primarily in granulomatosis with polyangiitis (GPA) ANCA patients, a study from the Netherlands reported the opposite, observing fewer events among PR3-positive patients.[81, 84] Data from the European Vasculitis Study group suggested no difference in VTE risk between MPO^+ vs. $PR3^+$ patients.[85] These data also identified higher serum creatinine and cutaneous or gastrointestinal involvement as VTE risk factors. In the *Rituximab in ANCA-Associated Vasculitis* (RAVE) trial, cardiac involvement, PR3 positivity, pulmonary hemorrhage, and urinary red blood cell (RBC) casts were identified as independent VTE risk factors.[80] While most studies have focused on patients with GPA, microscopic polyangiitis or renal limited vasculitis, patients with eosinophilic granulomatosis with polyangiitis also have increased VTE risk.[86] VTE have also been reported in children with ANCA vasculitis.[87] The pathophysiology of ANCA vasculitis-associated hypercoagulopathy is likely multifactorial. Antibodies against plasminogen (inhibiting fibrinolysis) have been reported in both MPO^+ and $PR3^+$ patients.[88, 89] Generation of tissue factor-bearing microparticles from inflamed vasculature may also contribute to the hypercoagulopathy.[90, 91] Tissue factor may also be expressed within neutrophil extracellular traps (NETs) during ANCA vasculitis.[91–93]

Optimal management of thrombotic risk in ANCA vasculitis remains unknown. The majority of VTE occur during peak disease activity (even before diagnosis).[80, 81, 84, 85] These patients are at risk for disease-associated pulmonary hemorrhage (which may also increase VTE risk); thus, risks and benefits of anticoagulation must be carefully balanced. Treatment of VTE has typically been warfarin or heparin in the acute phase. Well-established reversal protocols for these agents offer some security in the event of pulmonary hemorrhage. DOACs may be reasonable once disease is less active and pulmonary hemorrhage is less likely if continued therapy is indicated. Earlier use may be reasonable if DOAC reversal agents are readily available. Leukocytoclastic vasculitis hypersensitivity reactions have been reported in association with all DOACs and could confound assessment

of vasculitis activity.[94] This rare DOAC complication should not necessarily represent a contraindication. Optimal anticoagulant duration is unknown although it is reasonable to postulate VTE risk may be lower when vasculitis is quiescent. However, ANCA patients may exhibit hypercoagulability even in remission.[95] A recent study demonstrated that peak microparticle-derived tissue factor activity (which did not necessarily correlate with disease activity) was associated with VTE.[93] Further studies are thus needed to better define potential VTE-risk biomarkers in ANCA patients to guide anticoagulation prophylaxis and treatment.

Chronic Kidney Disease and End-Stage Kidney Disease

AF and VTE are both more common in patients with CKD or ESKD than in the general population. In a pooled analysis of five prospective cohorts including almost 600,000 European and United States participants, CKD (defined as estimated glomerular filtration rate (eGFR) <60 ml/1.73m^2/min or albuminuria ≥30 mg/g creatinine) was associated with VTE (HR 1.54 [95% CI 1.15–2.06]).[62] Even modest eGFR reductions were associated with elevated VTE risk. Similarly, AF occurs at higher rates and is associated with greater stroke risk in CKD and more so in ESKD patients.[96, 97] Unfortunately, bleeding risks also increase making anticoagulation indications less clear.[97, 98] Those with advanced CKD (eGFR <30 ml/1.73m^2/min) deemed at high-risk for AF-related thromboembolic events likely benefit from warfarin anticoagulation.[96] In contrast, some studies have demonstrated a lack of warfarin benefit in patients with ESKD on dialysis and potentially more bleeding events and stroke.[99–101] Routine use of warfarin for AF in ESKD patients on dialysis is not recommended in the current KDIGO guidelines.[102] Anticoagulation has been employed to maintain hemodialysis access patency but its utility for this purpose is unclear and generally not recommended.[103]

Data on DOACs in CKD are limited and largely derived from observational studies which may be confounded. The major randomized studies leading to DOAC approvals for non-valvular AF in the general population excluded patients with eGFR <25 ml/1.73m^2/min.[104] Despite this lack of trial data, DOAC use has become fairly routine in CKD care. For example, the *Global Anticoagulant Registry in the FIELD-Atrial Fibrillation* (GARFIELD-AF; a large registry of newly diagnosed AF cases) included 2,623 patients with moderate to severe CKD (stage 3–5), of whom 45.8% were placed on DOACs.[105] Based upon these registry data and clinical trials, DOACs appear to be safe for patients with moderate CKD. A recent Cochrane review evaluated 12,545 patients with CKD across five large clinical trials who were randomized to a DOAC (apixaban, rivaroxaban, edoxaban or dabigatran).[106] Compared to warfarin, DOACs demonstrated lower combined risk for stroke and systemic embolism (RR 0.81, 95% CI 0.65 to 1.00) and a trend toward less major bleeding (RR 0.79, 95% CI 0.59 to 1.04). The authors concluded that these agents were safe in CKD patients with the caveat that these data were primarily in patients with eGFR >30 ml/1.73m^2/min. A recent retrospective, single center study included 6,412 patients with and without CKD (defined as eGFR <60 ml/1.73m^2/min) and determined DOACs had similar benefit in stroke prevention with a small increase in bleeding.[107] However, this study included few patients (N=8) with eGFR <30 ml/1.73m^2/min. A recent study from Taiwan followed a prospective cohort of 3,771 patients with stage 4 or 5 CKD (about 25% on dialysis) with newly

diagnosed AF.[108] Notably only 21% of patients received anticoagulation - median eGFR in the group receiving DOACs was 25 ml/1.73m^2/min compared to 17 ml/1.73m^2/min in the warfarin and 16 ml/1.73m^2/min in the non-anticoagulated group. DOAC and warfarin use were both associated with similar stroke risk to the non-anticoagulated group, but with higher bleeding event rates. A recent meta-analysis evaluated 45 trials of CKD or hemodialysis patients (8 trials) over a variety of indications.[103] All of the hemodialysis trials only studied VKAs, the remaining studies excluded patients with severe CKD. In these analyses, DOACs had lower risk for stroke (RR 0.79, 95% CI 0.66 to 0.93) and hemorrhagic stroke (RR 0.48, 95% CI 0.30 to 0.76) than warfarin. The benefit of DOACs on recurrent VTE or VTE-related death were less clear but in the direction of benefit (RR 0.72, 95% CI 0.44 to 1.17) with lower bleeding risk.

DOAC use in ESKD has also become more common despite ESKD patients being excluded from the pivotal drug approval trials. The United States prescribing information for rivaroxaban and apixaban provide dose guidance for patients with ESKD. For non-valvular AF, rivaroxaban 15 mg daily is suggested and apixaban is suggested at the usual dose of 5 mg twice daily (unless dose reduction is indicated by age or weight). For VTE therapy and prophylaxis, no dose adjustment is suggested for ESKD patients. The suggested doses are reported to result in similar drug concentrations as observed in non-ESKD trials. However, these doses are based solely upon pharmacodynamic studies in ESKD patients without clinical outcome data.[109] In retrospective claims analyses, rivaroxaban had an insignificantly decreased risk of ischemic stroke, but major bleeding was lower in the rivaroxaban group (HR 0.68, 95% CI 0.47–0.99) compared to warfarin.[110] The majority of ESKD experience has been with apixaban. A large retrospective study used a claims data approach to match 25,523 ESKD patients with AF starting apixaban to those starting warfarin.[111] No difference was noted in ischemic stroke risk but apixaban was associated with lower bleeding risk (HR 0.72, 95% CI 0.59–0.87). A sensitivity analysis of these data revealed that full dose apixaban (5 mg bid) was more favorable than reduced dose apixaban (2.5 mg bid) or warfarin in terms of stroke and mortality. Two other small retrospective studies demonstrated that apixaban has less bleeding-risk relative to warfarin in ESKD patients.[112, 113] These latter studies also included patients treated for VTE; one noted no difference in VTE risk and the other noted an insignificantly lower VTE recurrence risk for DOACs compared to warfarin. While the benefit of any anticoagulant for AF in ESKD patients remains unclear, these observational data suggest DOACs may be safer than warfarin. Warfarin use is also a concern in ESKD patients (and in late-stage CKD) due to its potential contribution to vascular calcification and calciphylaxis. Thus, apixaban may prove to be a better option in ESKD patients at risk for these complications.[114] Clinical trials are underway examining apixaban compared to warfarin in ESKD patients with AF (NCT02933697).

Renal Transplantation

Renal transplant recipients also have elevated VTE risk.[115] Unfortunately, little is known about DOACs in this setting. Acute changes in kidney function may occur due to acute rejection episodes, so it may be reasonable to avoid DOACs that are highly dependent on renal clearance due to the potential for wide pharmacodynamic fluctuations. However, the reversal agents may mitigate any risk associated with fluctuating drug clearance. Apixaban

and rivaroxaban are reasonable choices if dosed appropriate to kidney function (Table 2). Drug interactions between calcineurin inhibitors (CNI) and DOACs do exist (see Dosing Considerations). Thus, immunosuppressant monitoring and/or DOAC dose adjustment are important considerations.[116] Caution should be employed in this unique population due to possible polypharmacy with additional agents that may influence DOAC metabolism.

SPECIAL CONSIDERATIONS

Anticoagulant-Related Nephropathy

Anticoagulant-related nephropathy (ARN) was first described in patients on warfarin with acute kidney injury (AKI).[117] Clinical findings included hematuria and AKI in patients with supratherapeutic INRs (>3) without other known AKI causes. Kidney biopsies demonstrated dysmorphic RBCs in Bowman's space, RBC casts in dilated distal tubules, and tubular hemosiderin deposition. Hypothesized injury mechanisms are nephron obstruction by RBC casts or tubular oxidative stress from RBC-derived iron.[118] While not initially widely accepted, the association between anticoagulation and AKI has been confirmed in several additional studies and may be more common that initially thought.[119–121] For example, in one retrospective non-biopsy study, 20.5% of patients treated with warfarin with a first INR >3 developed AKI within 1 week; those with AKI had a 65% increased risk of mortality within 1 year.[122] Risk factors for ARN include CKD, older age, diabetes mellitus, hypertension, and cardiovascular disease.[122] Nonetheless, these largely retrospective studies may be subject to bias, including potential reverse causality. Accelerated progression of CKD has also been attributed to recurrent episodes of ARN. DOACs have also been associated with ARN, although with lower risk than warfarin. An early meta-analysis of ten RCTs demonstrated similar AKI risk in patients treated with dabigatran, apixaban, or rivaroxaban compared to warfarin.[123] In contrast, a large retrospective study from Taiwan demonstrated a lower risk of AKI with apixaban, dabigatran, and rivaroxaban compared to warfarin.[124] Retrospective analysis of a United States cohort similarly demonstrated lower AKI risk and lower risk of ≥30% decline in eGFR with DOAC treatment compared to warfarin.[125] Moreover, post-hoc analyses of the *Randomized Evaluation of Long Term Anticoagulant Therapy* (RE-LY) and *Rivaroxaban Once-daily Compared with Vitamin K Antagonism for Prevention of Embolism Trial in Atrial Fibrillation* (ROCKET AF) trials demonstrated slower CKD progression with dabigatran or rivaroxaban, respectively, compared to warfarin.[126, 127] Warfarin is also known to contribute to vascular calcification, which may indirectly contribute to CKD progression.[128]

Dosing Considerations

Kidney Function—All DOACs are renally excreted, varying between 11–80% (Table 1). Dose adjustments are required for reduced CrCl and based upon anticoagulant indication and regulatory agency (i.e. FDA vs. EMA; Table 2).[45] A prescription data analysis showed that 28% of CKD patients prescribed DOACs did not receive recommended dose reductions.[107] Notably, all pivotal, phase 3 DOAC trials used CrCl determined by Cockcroft-Gault to estimate kidney function rather than eGFR and excluded patients with CrCl <25–30 ml/min. Both *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI) and *Modification of Diet in Renal Disease* (MDRD) eGFR equations produce higher estimates of renal function

compared to CrCl.[129] A study of 185 consecutive patients with AF found that using the CKD-EPI formula to determine DOAC dosing would cause 48% of patients with CrCl <30 ml/min and 46% with CrCl 30–49.9 ml/min to receive treatment inconsistent with guidelines.[129] A study utilizing *National Health and Nutrition Examination Survey* (NHANES) data similarly demonstrated that substitution of MDRD eGFR for estimated CrCl can lead to higher dosing of DOACs and potentially increased bleeding rates.[130] Thus, DOAC dosing should be determined using Cockcroft-Gault CrCl for CKD patients.

Nephrotic Syndrome—Anticoagulant dosing in NS patients is complex due to altered pharmacokinetic properties associated with hypoalbuminemia and altered protein binding (Table 1), increased volume of distribution, and fluctuations in CrCl. A pharmacokinetic study of warfarin, which is highly protein bound, demonstrated threefold higher plasma clearance and twofold shorter half-life in NS patients vs. controls, frequent INR monitoring is thus recommended for NS patients.[131] Experience with DOACs in NS is limited primarily to case reports demonstrating effective primary prophylaxis with apixaban[57] and effective treatment of VTE with rivaroxaban, edoxaban, and dabigatran.[132–134] However, recurrent VTE in a patient with MN while on therapeutic dosing of apixaban has also been described.[58] The authors reported a lower peak apixaban concentration and hypothesized higher unbound drug fraction led to more rapid excretion, shorter half-life, and increased VTE risk. Among the DOACs, plasma protein binding ranges from 35–95%; NS-specific studies are thus needed for each drug to establish dosing recommendations in this population.

Drug/Drug Interactions

Polypharmacy is prevalent in CKD patients and increases risks for adverse drug interactions. Warfarin is metabolized by CYP2C9; thus CYP2C9 inhibitors (e.g. amiodarone, fluconazole, fluvastatin, isoniazid, sertraline) may increase anticoagulant effects whereas CYP2C9 inducers (e.g. rifampin) reduce them.[135] There are also important potential drug interactions relevant to DOACs.[136] Dabigatran is a substrate for P-glycoprotein, thus treatment with P-glycoprotein inducers (e.g. rifampin, phenobarbital, phenytoin) may decrease anticoagulant effects and increase risk of treatment failure. Co-treatment with P-glycoprotein inhibitors (e.g. digoxin, cyclosporine, verapamil, diltiazem, amiodarone) may increase anticoagulant effects and bleeding risk. Particular care should be taken in the CKD setting where the combination of reduced renal clearance and co-administration of P-glycoprotein inhibitors may increase bleeding risk.[137] Factor Xa DOACs also depend on the P-glycoprotein pathway for metabolism, and interactions with inducers and inhibitors have been described. Moreover, factor Xa DOACs are metabolized by cytochrome P450 and drug effectiveness may be affected by co-administration with CYP3A4 inhibitors (e.g. fluconazole, ketoconazole, itraconazole, vorconazole) or CYP3A4 inducers (e.g. rifampin, phenytoin). These drug interactions increase bleeding risk or treatment failure, respectively. An administrative database review of 91,330 patients with AF in Taiwan treated with DOACs found an increased risk of major bleeding in those co-prescribed amiodarone, fluconazole, rifampin, and phenytoin.[138] Close consultation with an experienced pharmacist may be helpful in minimizing adverse events from drug interactions.

Childhood Kidney Disease

Children with CKD have higher VTE risk than the general pediatric population.[3] Risk factors include NS, infection, recent trauma/surgery, central venous catheters, and ESKD/dialysis.[3] LMWH has been standard therapy for children with VTE for over 20 years, with dose adjustments for CrCl <30 ml/min, similar to adults.[139] DOACs are potentially attractive agents in this population due to oral administration and no need for timed lab monitoring. However, none are currently approved for pediatric use. However, phase 2 pediatric trials of rivaroxaban and dabigatran were recently published and phase 3 trials (NCT02234843 and NCT01895777, respectively) are nearing completion.[140, 141] Thus, these agents may soon be available for pediatric use. Anticoagulant dosing in children is complex due to age related hemostasis-system maturation as well as pharmacokinetic differences compared to adults.[142] Only dabigatran has published pharmacokinetic data in children showing similarities to adults with the exception of longer clotting times in children <1 year of age.[143] Pediatric pharmacokinetic data for the remainder of the DOACs is limited to *in vitro* experiments[144] and case reports that suggest possible differences compared to adults.[145] Similar to the adult studies, children with CrCl <30–50 ml/min are excluded from the aforementioned studies, making it unlikely that safety and efficacy data will be generated for childhood CKD in the near term.

CONCLUSIONS

DOACs are increasingly utilized in a variety of kidney disease settings, despite the lack of controlled trial data. The field would benefit from carefully designed trials that consider renal function, intravascular volume, plasma protein-drug binding, and interactions with commonly employed medications, in each type of kidney disease where anticoagulation is frequently indicated. While the early forms of data described in this review suggest that DOACs hold promise for improved efficacy and safety in the setting of kidney disease, this can only be confirmed through meticulous prospective study.

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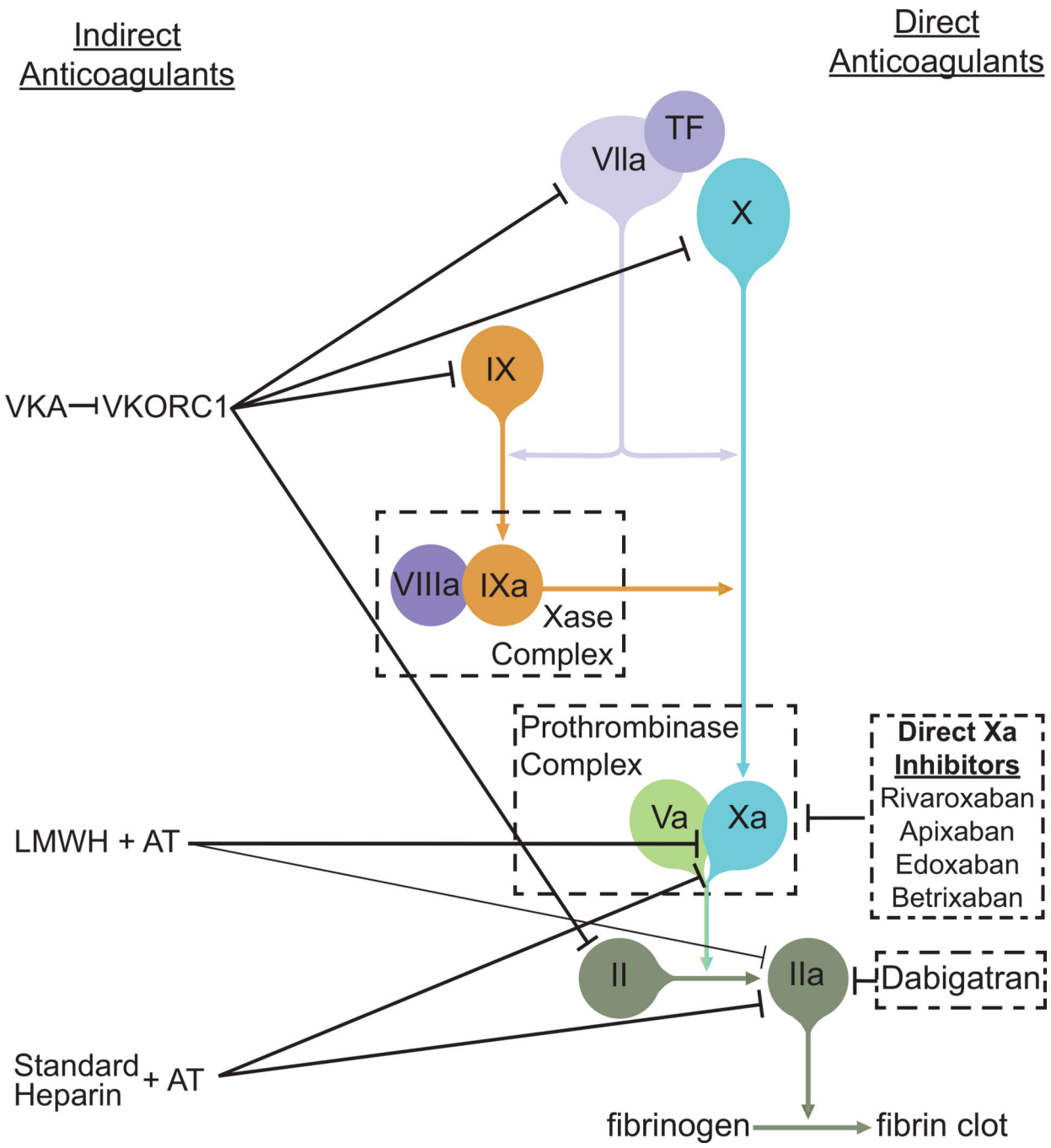

Figure:
Schematic Representation of Oral Anticoagulant Mechanisms of Action

Table 1:

Pharmacology of Direct Oral Anticoagulants[+]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa	Factor Xa
Half-Life (h)	12–17	5–9	12	10–14	19–27
Renal Excretion (%)	80[^]	66	27	50	11
Fecal Excretion (%)	Not Applicable	7	~50	50	85
Hepatic Metabolism	No	CYP3A4/5; CYP2J2	CYP3A4/5; others	CYP3A4/5 (minimal)	Minimal
Protein Binding (%)	35	92–95	87	55	60
Dialyzable	Yes[*]	No	No	No	Not Studied
Reversal Agent	Idarucizumab	Andexanet Alfa	Andexanet Alfa	Andexanet Alfa?[$]	Andexanet Alfa?[$]

[+] Data from FDA-approved package inserts and Huisman and Klok, 2018.[38]

[^] Renal excretion of intravenously administered drug.

[*] ~57% removed over 4 hours.

[$] Effectively reversed edoxaban in a rabbit model, theoretically should reverse betrixaban, not yet studied in humans.[39, 40]

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Table 2:

DOAC Dosages by Common Indications, Renal Impairment, and Regulatory Agency Labeling[†]

	United States Food and Drug Administration (FDA)		European Medicines Agency (EMA)	
Indication DOAC	**CrCl[*] 15–29 mL/min**	**CrCl[*] 30–50 mL/min**	**CrCl[*] 15–29 mL/min**	**CrCl[*] 30–50 mL/min**
Atrial Fibrillation				
Dabigatran	75 mg twice daily	150 mg twice daily	NR[^]	150 mg or 110 mg twice daily[#]
Rivaroxaban	15 mg once daily	15 mg once daily	15 mg once daily	15 mg once daily
Apixaban	5 mg twice daily[$]	5 mg twice daily[$]	2.5 mg twice daily	5 mg twice daily[$]
Edoxaban	30 mg once daily	30 mg once daily	30 mg once daily	30 mg once daily
Betrixaban	NL[α]	NL[α]	NA[β]	NA[β]
VTE Treatment				
Dabigatran	NR[^]	150 mg twice daily[+]	NR[^]	150 mg or 110 mg twice daily[#+]
Rivaroxaban	Avoid Use	15 mg twice daily x3 weeks, then 20 mg once daily	15 mg twice daily x3 weeks, then 20 mg once daily[γ]	15 mg twice daily x3 weeks, then 20 mg once daily
Apixaban	10 mg twice daily x7 days, then 5 mg twice daily	10 mg twice daily x7 days, then 5 mg twice daily	10 mg twice daily x7 days, then 5 mg twice daily	10 mg twice daily x7 days, then 5 mg twice daily
Edoxaban	30 mg once daily[+]	30 mg once daily[+]	30 mg once daily[+]	30 mg once daily[+]
Betrixaban	NL[α]	NL[α]	NA[β]	NA[β]
VTE Prophylaxis[δ]				
Dabigatran	NR[^]	150 mg once daily	NR[^]	75 mg on day 1, then 150 mg once daily
Rivaroxaban	Avoid Use	10 mg once daily	10 mg once daily	10 mg once daily
Apixaban	2.5 mg twice daily	2.5 mg twice daily	2.5 mg twice daily	2.5 mg twice daily
Edoxaban	NL[α]	NL[α]	NL[α]	NL[α]
Betrixaban[δ]	80 mg on day 1, then 40 mg once daily	160 mg on day 1, then 80 mg once daily	NA[β]	NA[β]

[†]Adapted from Parker and Thachil[45] and respective US and European prescribing information.

[*]CrCl: Creatinine clearance by the Cockcroft-Gault method.

[^] NR: Not recommended.

[#] Clinical judgement based upon individual patient bleeding vs. thrombotic risk.

[+] Following an initial 5 day period of parenteral anticoagulation.

[$] Dose adjusted to 2.5 mg twice daily if any 2 of the following criteria are met: serum creatinine >1.5 mg/dL (>133 μmol/L), weight <60 kg, or age >80 years.

[α] NL: Not Labeled for this indication

[β] NA: Not Applicable; Betrixaban is not approved by the EMA for any indication.

[γ] Consider dose reduction to 15 mg once daily.

[δ] Post-arthroplasty (Total Hip or Knee Replacement) prophylaxis for all drugs except betrixaban, which is FDA-approved for VTE prophylaxis in acutely ill medical patients.