Direct Oral Anticoagulants in End-Stage Renal Disease

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Abstract

Patients with end-stage renal disease (ESRD) were excluded from pivotal clinical trials with oral anticoagulants. While such patients are at an increased risk of venous and arterial thromboembolism, their risk of bleeding is also elevated. It is thus of little surprise that stroke prevention with vitamin K antagonists (VKAs) in ESRD patients with atrial fibrillation is controversial, with observational evidence ranging from beneficial to harmful. This uncertainty extends to the less studied use of VKAs for venous thromboembolism in ESRD. The direct oral anticoagulants (DOACs) apixaban and rivaroxaban have now permissive labeling in the United States for atrial fibrillation in patients with ESRD; this expanded labeling has not yet occurred either in Europe or for venous thromboembolism. This review summarizes the current evidence for the pharmacology of DOACs in ESRD as well as their utilization and safety in patients with ESRD and atrial fibrillation.

Keywords
- anticoagulants
- renal dialysis
- kidney failure
- chronic
- venous thrombosis
- stroke

Chronic kidney disease (CKD), usually defined as glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for at least 3 months,[1] affects ~7% of adults in the United States.[2,3] Estimates of CKD prevalence vary by country and region and are associated with population aging and economic status.[4] CKD is caused by four conceptual mechanistic pathways: glomerular diseases (e.g., diabetic nephropathy), tubulointerstitial diseases (e.g., myeloma), vascular diseases (e.g., hypertension), and cystic/congenital diseases (e.g., renal dysplasia).[1] A decline of GFR to < 15 mL/min/1.73 m^2 defines kidney failure, or end-stage renal disease (ESRD), which is an indication for renal replacement therapy (RRT; dialysis or renal transplantation). By 2014, more than a million individuals in the United States and Europe combined were receiving RRT, representing a marked increase in the prevalence of ESRD.[3,5] Patients with ESRD and atrial fibrillation (AF) have an increased risk of stroke, compared with less severe renal impairment.[6] Furthermore, the prevalence of AF in the hemodialysis population is 13 to 27%, or 10- to 20-fold higher than in the general population.[7] The risk of venous thromboembolism (VTE) is also positively correlated with CKD, suggesting ESRD is a hypercoagulable state.[8,9] Such thrombotic risk could be explained by various factors, including inherited thrombophilia,[10] vascular access-related problems,[11] and increased concentrations of procoagulant factors.[6] Thus, patients with ESRD have multiple indications for the use of oral anticoagulants. Nonetheless, data on oral anticoagulant use for VTE in patients with ESRD are scarce; thus, studies reviewed below are primarily in the AF population.

Search Strategy

Published studies and conference proceedings in English were searched using PubMed, EMBASE, and the Cochrane database. Search terms included: dialysis, end stage renal disease, vitamin K antagonists (VKAs), apixaban, dabigatran, rivaroxaban, edoxaban, atrial fibrillation, venous thromboembolism, and bleeding. In addition, reference lists of narrative and systematic reviews were manually searched for peer-reviewed publications. Where multiple publications

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existed from the same data source, the most recent was reviewed. Finally, abstracts from international conferences were manually searched for relevant publications.

Vitamin K Antagonists

Pharmacology in ESRD

Vitamin K antagonists (VKAs), including warfarin, reflect the mainstay of treatment and prevention of thromboembolic disease in ESRD. Warfarin has a near 100% bioavailability, and reaches peak concentration within 4 hours of absorption. Elimination of warfarin is almost entirely via metabolism, and renal clearance is negligible.[12] However, in patients with ESRD, nonrenal clearance is diminished through downregulation of cytochrome P450 gene expression.[13] A consequent increase in the S/R enantiomer ratio[14] is the putative explanation for three important observations in ESRD patients: (1) reduced warfarin dose requirements;[15] (2) diminished time in therapeutic range regardless of international normalized ratio (INR) intensity;[16] and (3) increased time with excessive INR.[17] Nonetheless, decreased protein binding in ESRD[18] probably accounts for the 31% drop in warfarin concentration following hemodialysis, owing to partial filtration of unbound warfarin.[19] Further, reduced protein binding is the likely cause of the shortened half-life of warfarin in patients with CKD, which is 30 hours compared with 45 hours in subjects with normal kidney function (►**Table 1**).[20]

Utilization Patterns in ESRD

The effectiveness and safety of VKA among patients with ESRD and AF is highly debated,[21,22] as reflected in the wide variability of VKA use among patients with ESRD in different high-income countries.[23] Similarly, studies from the United States preceding market availability of the direct oral anticoagulants (DOACs) report a 15.5 to 62.3% prevalence of VKA use in patients on dialysis with incident AF.[16,24] One further concern with VKA use for stroke prevention is low persistence over time, or early discontinuation.[25] Indeed, almost half of dialysis patients with AF initiated on VKA were found to discontinue the drug within less than 9 months of use and without switching to DOACs.[24]

Safety in ESRD

The presence of ESRD confers a bleeding diathesis independent of oral anticoagulation, manifesting as major, but also as nonmajor bleeding events.[17] In hemodialysis patients, repetitive activation of platelets is thought to lead to platelet "exhaustion" and consequent dysfunction.[26] Several studies have been published on bleeding risk with VKA among patients with ESRD (►**Table 2**). While differing in study design and methodology, most of the larger (>100 VKA users) studies reported major bleeding rates of 10 per 100 person-years or higher. In comparison, the pivotal clinical trials with DOACs, which excluded patients with severe CKD or ESRD, reported bleeding rates of $\sim$3 per 100 person-years in the VKA arm.[27–30] This comparison emphasizes the bleeding diathesis in ESRD rather than the comparative risk of bleeding with VKA versus no use, which varies with reports.

A further safety concern with VKA use in ESRD is increased risk of calcific uremic arteriolopathy (or calcific vasculopathy), which leads to ischemic skin necrosis.[31] This syndrome is prevalent in $\sim$4% of hemodialysis recipients and is associated with a case–fatality rate of 27% at 6 months and 45% at 12 months.[32] In a cohort of 1,030 patients on hemodialysis, the incidence rate of calcific uremic arteriolopathy was 6.24 versus 3.35 per 1,000 person-years in VKA users and nonusers, respectively.[32]

Dabigatran

Pharmacology in ESRD

Dabigatran, a direct thrombin inhibitor, is the active metabolite of the prodrug dabigatran etexilate. Renal clearance is appropriately estimated with intravenous infusion; after such infusion, 81% of the dose is recovered in urine, with 80% renal contribution to the total clearance.[33] Thus, dabigatran has the highest renal clearance among DOACs (►**Table 1**). Exposure to dabigatran is negatively correlated with renal function, and the area under the plasma concentration-time curve (AUC) is 6.3-fold higher in patients with severe CKD after a single oral dose, compared with healthy subjects.[34] Accordingly, 150- or 110-mg dabigatran are not indicated in Europe in patients with severe CKD or ESRD (►**Table 3**).[35] The Food and Drug Administration (FDA) has approved the use of a 75-mg dose in patients with GFR between 15 and 30 mL/min/1.73 m^2 based on pharmacokinetic studies, but offers no dosing recommendations for ESRD.[36] Of note, a simulation study suggested that a 75- or 110-mg dose taken once daily would result in therapeutic exposure to dabigatran in hemodialysis patients.[37] Dabigatran is dialyzable, and 50 to 60% of central compartment dabigatran can be removed by a single 4-hour dialysis.[38] Whether this remains a viable option for dabigatran removal in urgent bleeding or need for urgent procedure (where anticoagulation should be stopped abruptly) following idarucizumab approval remains to be seen.[39] Hemodialysis for dabigatran removal has been suggested when idarucizumab is not available, and caution should be exercised for a resumed anticoagulant effect at the end of the dialysis session.[40]

Utilization Patterns in ESRD

Dabigatran was approved by the FDA for use in AF in October 2010, reaching this mark first among the DOACs. In the United States, the 75-mg dose is recommended in patients with GFR between 15 and 30 mL/min/1.73 m^2, while in Europe, the 110-mg dose is recommended for patients with GFR between 30 and 49 mL/min/1.73 m^2 and high risk for bleeding (►**Table 3**).[35] As noted previously, dabigatran is not approved in Europe for patients with severe CKD.

Prescription pattern analysis from Europe suggests CKD is a predictor for preferring VKA over DOACs for VTE, with dabigatran in either dose not prescribed at all in severe CKD.[41] In the United States, the 75-mg dose was used in up to 3% of dialysis patients with AF who were being anticoagulated shortly after its approval.[42] However, the

Table 1 Pharmacokinetic studies of vitamin K antagonists and direct oral anticoagulants with relevance to renal dysfunction

Study	Design	Drug	Population	Findings	Comments
Ifudu and Dulin 1993[19]	Single-arm	PO warfarin 10 mg	1 hemodialysis patient	31% drop in plasma warfarin concentration after dialysis	
Bachmann et al 1977[20]	Single-arm	PO warfarin 0.75 mg/kg	5 healthy subjects, 4 patients with GFR< 50 (2 ESRD)	Half-life of warfarin was 44.8 vs 29.9 hours in healthy subjects and renal patients, respectively	
Blech et al 2008[33]	Single-arm	Single-dose PO Dabigatran etexilate 200 mg; IV dabigatran 5 mg	10 healthy males	77% unchanged dabigatran after IV infusion and 4% glucuronic derivatives, accounting to 81% renal contribution to elimination	
Stangier et al 2010[34]	Single-arm, parallel group	Single-dose, PO dabigatran etexilate 150 mg (non-ESRD) and 50 mg (ESRD)	6 healthy, 23 renal impairment (GFR 51–80, 31–50, and ≤ 30), 6 hemodialysis	AUC was increased 1.5-, 3.2-, and 6.3-fold in renal impairment; in ESRD twofold increase	
Khadzhynov et al 2013[38]	Single-arm, multiple dosing	PO dabigatran etexilate: 150 mg postdialysis, then 110 and 75 mg	7 hemodialysis patients	48.8% elimination with "catheter setting" dialysis and 59.3% with "shunt setting" dialysis	Experimental dose very high-flow dialysis session for 4 hours
Weinz et al 2009[46]	Single- arm	PO rivaroxaban 10 mg	4 healthy subjects	66% of rivaroxaban excreted in urine (36% unchanged)	Renal clearance was not measured with intravenous infusion
Kubitza et al 2010[47]	Single-arm, parallel group	PO rivaroxaban 15 mg	8 healthy, 8 GFR 50–79, 8 GFR 30–49. 8 GRF < 30	AUC 1.33-, 2.16-, and 2.44-fold increased across renal impairment strata	Steady-state AUC differences may have been larger
Frost et al 2008[57]	Randomized crossover	PO and IV apixaban at various doses	8 healthy male subjects	Renal clearance accounted for 17–30% of total clearance	
Leil et al 2010[58]	Population pharmacokinetics from a phase II randomized trial	PO apixaban (multiple dosing regimens)	1,298 hip and knee replacements patients	Minimal concentration increased and AUC in steady-state increased by 67 and 70% with moderate renal impairment, respectively	
Wang et al 2016[59]	Single-arm, parallel group	PO apixaban 5 mg before and after dialysis	8 healthy subjects and 8 hemodialysis patients	Postdialysis AUC decreased by 14%; AUC in dialysis was 36% increased vs. healthy subjects	Single-dose study
Mavrakanas et al 2017[60]	Single-group crossover	PO apixaban 2.5 and 5 mg	7 hemodialysis patients	Steady-state AUC with apixaban 2.5 in dialysis patients mg is < 10th percentile of 5 mg apixaban in healthy subjects; steady-state AUC with 5 mg	The effectiveness of the 2.5-mg dose in atrial fibrillation is unclear

(*Continued*)

Table 1 (*Continued*)

Study	Design	Drug	Population	Findings	Comments
				apixaban in dialysis patients is double that in healthy subjects	
Matsushima et al 2013[72]	Randomized crossover	PO edoxaban 60 mg, IV edoxaban 30 mg ± concomitant quinidine	35 healthy subjects	48.6% of IV dose was excreted in urine	
Ridout et al 2009[74]	Single-dose, parallel group	PO edoxaban 15 mg	8 healthy, 8 GFR 50–80, 8 GFR 30–49, 8 GFR< 30, 8 peritoneal dialysis	AUC increased 1.32-, 1.74-, 1.72-, and 1.93-fold, respectively	
Parasrampuria et al 2015[75]	Randomized crossover	PO edoxaban 15 mg 2 hours before or between dialysis sessions	10 hemodialysis patients	On-dialysis and off-dialysis AUC < 5% different	Dialysis does not remove edoxaban efficiently

Abbreviations: AUC, area under the curve; ESRD, end-stage renal disease; GFR, glomerular filtration rate; IV, intravenous; PO, oral route.

prevalence of dabigatran use in dialysis patients has subsequently dropped, reaching 0.3% in late 2015.[43] Results from the Outcomes Registry for Better Informed Therapy for Atrial Fibrillation reflect this trend as well.[44]

Safety in ESRD

In the setting of a closely monitored phase-I study, three doses of dabigatran (150, 110, and 75 mg once) in hemodialysis patients were associated with only one minor bleeding.[38] Data from shortly after the approval of dabigatran in the United States indicate very high rates of major and nonmajor bleeding with its use in hemodialysis patients (►**Table 4**).[42] While these data may reflect erroneous, early use, current data still suggest 39.4% of dabigatran users for AF who had a renal indication for dose reduction were still receiving the standard dose.[45] However, as dabigatran remains contraindicated in ESRD and is seldom used off-label in this population, it is unlikely that more population-based safety data on dabigatran in ESRD will be published.

Rivaroxaban

Pharmacology in ESRD

Rivaroxaban, a factor Xa inhibitor, has a renal clearance of 66% after oral ingestion. Nevertheless, 36% of ingested rivaroxaban is excreted unchanged in the urine, indicating the renal clearance contribution out of total clearance (►**Table 1**).[46] In patients with mild, moderate, and severe CKD, the AUC was augmented by 44, 52, and 64%, respectively, representing significant drug accumulation.[47] Among eight patients receiving maintenance hemodialysis, a single 15-mg oral dose of rivaroxaban resulted in a 56% increase in post-dialysis AUC, compared with healthy subjects.[48] This was concluded by the authors to reflect 35% decreased clearance in ESRD patients, which recapitulates the findings in patients with moderate CKD.[48] A further study conducted on 18 patients with maintenance hemodialysis confirmed that rivaroxaban was not appreciably removed by dialysis.[49] Further, this study examined a clinical steady state achieved after 7 days of rivaroxaban at 10 mg daily and demonstrated trough levels which were on par with those observed in patients with moderate CKD in the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial who received 15 mg daily.[50] Lastly, the AUC with 10 mg of rivaroxaban in ESRD patients in steady state was comparable to that seen in healthy subjects receiving 20 mg.[51] Of note, this study has been criticized for large interpatient variability,[43] due to the wide range of trough levels of rivaroxaban (4.1–93.4 µg/L in six subjects).[49]

Utilization Patterns in ESRD

Rivaroxaban was approved by the FDA in April 2011 for prevention of stroke and systemic embolism in AF. The above pharmacokinetic studies have led to a change in the FDA labeling of rivaroxaban in August 2016, such that the 15-mg dose pharmacokinetic study was cited with the addition that

Table 2 Cohort studies reporting bleeding events with vitamin K antagonists in patients with end-stage renal disease

Study	Study design	Exposure (*n*)	Indication (AF/VTE/Other)	Follow-up, mean (d)	Exposed events	Incidence rate (per 100 PY)	Conclusions/ Limitations
Olesen et al 2011[80]	Retrospective cohort	Warfarin ($n = 178$) Warfarin + aspirin ($n = 45$)	223/0/0	725	243 major (all RRT)	8.9 (all RRT)	Person-time for exposure is nontransparent
Lai et al 2009[81]	Retrospective cohort	Warfarin ($n = 78$)	78/0/0	930	8 major	4.0	Event number in ESRD unclear
Phelan et al 2011[82]	Retrospective cohort	Warfarin ($n = 141$)	71/45/25	738	31 major	10.8	
Kai et al 2017[83]	Retrospective cohort	Warfarin ($n = 989$)	989/0/0	767	126 GIB 22 ICH	5.4 GIB 0.9 ICH	Potential exposure misclassification Immortal time bias
Winkelmayer et al 2011[84]	Retrospective cohort	Warfarin ($n = 249$)	249/0/0	552 GIB 646 ICH	48 GIB 11 ICH	13.4 GIB 2.6 ICH	Discrepancy between GIB and ICH results
Biggers et al 1977[85]	Retrospective cohort	Warfarin ($n = 48$)	0/0/48	715	50 major	53.2	Not time-to-event Prevention of circuit clotting
Vázquez et al 2003[86]	Retrospective cohort	Warfarin ($n = 29$)	7/14/8	600	13 major	26.0	Bleeding definition not compatible with ISTH
Khalid et al 2013[87]	Retrospective cohort	Warfarin ($n = 34$)	34/0/0	365	26 recurrent GIB	NA	Potential exposure misclassification Confounding by indication
Wang et al 2016[88]	Retrospective cohort	Warfarin ($n = 59$)	59/0/0	1242	22 events	9.1	Potential exposure misclassification Underpowered
Yodogawa et al 2016[89]	Retrospective cohort	Warfarin ($n = 30$)	30/0/0	1410	3 major	2.6	Potential exposure misclassification Bleeding definition unclear
Klil-Drori et al 2016[90]	Retrospective cohort	Warfarin ($n = 467$)	0/467/0	132	20 major	11.8	
Shah et al 2014[91]	Retrospective cohort	Warfarin ($n = 756$)	756/0/0	662	149 major	10.9	
Shen et al 2016[92]	Retrospective cohort	Warfarin ($n = 1,838$)	1,838/0/0	497 GIB 533 ICH	153 GIB 29 ICH	5.9 GIB 1.0 ICH	Differences between ITT and AT approaches
Yoon et al 2017[93]	Retrospective cohort	Warfarin ($n = 2,921$)	2,921/0/0	477	215 GIB 89 ICH	5.6 GIB 2.3 ICH	
Friberg et al 2015[94]	Retrospective cohort	Warfarin ($n = 164$)	164/0/0	767	61	17.7	

(*Continued*)

Table 2 (*Continued*)

Study	Study design	Exposure (*n*)	Indication (AF/VTE/Other)	Follow-up, mean (d)	Exposed events	Incidence rate (per 100 PY)	Conclusions/ Limitations
Genovesi et al 2017[95]	Prospective cohort	Warfarin ($n = 134$)	134/0/0	1461	55 events	17.0	Underpowered
Wakasugi et al 2014[96]	Prospective cohort	Warfarin ($n = 28$)	28/0/0	700	3 major	5.3	Only prevalent use Underpowered Potential exposure misclassification
Zellweger et al 2005[97]	Prospective cohort	Low-intensity warfarin ($n = 35$)	0/0/35	126	0 major	NA	Prevention of catheter malfunction Half with inadequate TTR
Clark et al 2016[98]	Prospective cohort	Warfarin ($n = 42$)	23/11/8	207	5 major	21.0	Pharmacist-led intervention did not improve TTR
Knoll et al 2012[99]	Prospective cohort	Warfarin ($n = 46$)	30/6/10	1,037	4 major (2 on treatment, 2 before treatment)	1.1	
Limdi et al 2009[17]	Prospective cohort	Warfarin ($n = 52$)	29/23/0	730	32 major	30.5	47/52 hemodialysis
Crowther et al 2002[100]	RCT	Low-intensity warfarin ($n = 56$)	0/0/56	199	5 major	16.4	Target INR 1.5–1.9 Graft patency not improved vs. placebo
Mokrzycki et al 2001[101]	RCT	Minidose warfarin ($n = 41$)	0/0/41	< 365	1 event	NA	Bleeding event probably not compatible with ISTH criteria Graft patency not increased with warfarin 1 mg/d
Traynor et al 2001[102]	RCT	Minidose warfarin ($n = 10$)	0/0/10	188	0 major	NA	Open label, small, and with crossover due to unclear reasons

Abbreviations: AF, atrial fibrillation; AT, as-treated; GIB, gastrointestinal bleeding; ICH, intracranial hemorrhage; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; ITT, intention-to-treat; NA, not available; PY, person-years; RCT, randomized controlled trial; RRT, renal replacement therapy; TTR, time in therapeutic range; VTE, venous thromboembolism.

Table 3 Renal dosing recommendations for oral anticoagulants in the United States and Europe

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Nonvalvular atrial fibrillation					
United States	No renal dosing	GFR > 30: 150 mg BID GFR15–30: 75 mg BID ESRD: contraindicated	GFR > 50: 20 mg QD GFR 15–50: 15 mg QD ESRD: 10–15 mg QD	At least 2/3: SCr ≥ 1.5 mg/dL, age ≥ 80, weight ≤ 60 kg: 2.5 mg BID Otherwise: 5 mg BID ESRD: 5 mg BID (age < 80 and weight > 60 kg)	GFR > 95: C/I GFR 51–95: 60 mg QD GFR 15–50: 30 mg QD ESRD: C/I
Europe	No renal dosing	GFR > 50: 150 mg BID GFR 30–50: 110 mg BID if high bleeding risk GFR < 30: contraindicated	GFR >50: 20 mg QD GFR 15–50: 15 mg QD GFR < 15: contraindicated	GFR > 30: SCr ≥ 1.5 mg/dL and ½ (age ≥ 80, weight ≤ 60 kg): 2.5 mg BID; Otherwise: 5 mg BID GFR ≤ 30: 2.5 mg BID ESRD: C/I	GFR 15–50 OR weight ≤ 60 kg OR P-gp inhibitors: 30 mg QD Otherwise: 60 mg QD ESRD: C/I
Venous thromboembolism (treatment)					
United States	No renal dosing	Same as NVAF	GFR ≥ 30: 15 mg BID for 21 d, then 20 mg QD GFR < 30: C/I	10 mg BID for 7 d, then 5 mg BID No dose adjustments	GFR > 50: 60 mg QD GFR 15–50 OR weight ≤ 60 kg OR P-gp inhibitors: 30 mg QD
Europe	No renal dosing	Same as NVAF	Same as US	GFR > 15: same as US ESRD: C/I	Same as for NVAF

Abbreviations: BID, twice daily; C/I, contraindicated; ESRD, end-stage renal disease; GFR, glomerular filtration rate; NVAF, nonvalvular atrial fibrillation; P-gp, p-glycoprotein; QD, once daily; US, United States.

Table 4 Cohort studies reporting bleeding events with direct oral anticoagulants in patients with end-stage renal disease

Study	Study design	Anticoagulant (*n*)	Indication (AF/VTE/Other)	Follow-up (d)	Exposed events	Incidence rate per 100 PY	Conclusions/ Limitations
Sarratt et al 2017[68]	Inpatient cohort	Warfarin (*n* = 120)	81/39/0	9	7 major; 7 CRNMB	NA	57.% of apixaban users had 2.5 mg BID dose
		Apixaban (*n* = 40)	32/8/0	8.8	0 major; 5 CRNMB	NA	
Steuber et al 2017[69]	Inpatient cohort	Apixaban (*n* = 114)	75/39/0	6.2	7 major; 5 CRNMB	NA	Prevalent users
Stanton et al 2017[70]	Retrospective cohort	Apixaban (*n* = 73)	53/19/1	369	7 major; 13 CRNMB	9.5 major; 17.6 CRNMB	Rates are for severe CKD rather than ESRD alone
		Warfarin (*n* = 73)	53/19/1	562	13 major; 6 CRNMB	11.6 major; 5.3 CRNMB	
Chan et al 2015[42]	Retrospective cohort	Warfarin (*n* = 8,064)	8,064/0/0	175	1,858 major; 4,367 minor	47.1 major; 120.6 minor	Substantially shorter follow-up on rivaroxaban Major bleeding definitions do not conform with ISTH
		Dabigatran (*n* = 281)	281/0/0	168	106 major; 153 minor	83.1 major; 58.8 minor	
		Rivaroxaban (*n* = 244)	244/0/0	106	46 major; 113 minor	68.4 major; 149.4 minor	
Koretsune et al 2015[79]	Prospective study	Edoxaban (*n* = 50)	50/0/0	98	0 major; 10 minor	NA	Patients with severe CKD and not ESRD

Abbreviations: AF, atrial fibrillation; BID, twice daily; CKD, chronic kidney disease; CRNMB, clinically relevant non-major bleeding; ESRD, end-stage renal disease; ISTH, International Society on Thrombosis and Haemostasis; NA, not available; PY, person-years; VTE, venous thromboembolism.

no clinical effectiveness data have been published in ESRD patients.[52,53] Thus, there is some uncertainty whether the appropriate dose in ESRD patients is 10 or 15 mg daily. The explicitly recommended doses are presented in ►**Table 3**.

In Europe, rivaroxaban is contraindicated in ESRD.[54] As of late 2015, rivaroxaban use was prevalent in 0.8% of dialysis patients on anticoagulants for AF in the United States.[43] Similar to dabigatran, 41.3% of the non-ESRD patients with renal indication for dose reduction were overdosed.[45] However, the large majority of rivaroxaban users with ESRD were receiving a 15-mg dose.[42] Finally, in patients with severe CKD there has been a marked increase in the use of rivaroxaban in the United States.[43]

Safety in ESRD

Very sparse information exists regarding the safety of rivaroxaban in ESRD patients, and no data on the 10-mg dose. The single study that examined the use of the 15- and 20-mg doses had a very short mean follow-up of 106 days (►**Table 4**).[42] Likely due to inappropriate use, a major bleeding rate of 68.4 per 100 person-years was recorded in this population.[42] This rate is more than 18-fold higher than the rate observed in patients who experienced worsening renal function during the ROCKET-AF trial.[55]

Apixaban

Pharmacology in ESRD

Between 24.5 and 28.8% of the parent drug apixaban, a factor Xa inhibitor, is recovered in the urine after oral ingestion (►**Table 1**).[56] After intravenous infusion, renal clearance contributes 17 to 30% of the total drug clearance.[57] Renal function is an important predictor of steady-state drug exposure, which occurs after 3 to 4 days. Thus, patients with moderate renal impairment are likely to have a 70% higher AUC at steady state at any apixaban dose.[58] In a study with eight hemodialysis patients receiving a single 5-mg dose, the AUC of apixaban was increased by 36% compared with healthy subjects. Further, dialysis has been found to have a marginal effect on apixaban exposure, reducing the maximal concentration by 13%.[59] Thus, significant accumulation of apixaban at steady state was demonstrated in a subsequent study with six hemodialysis patients who received 2.5 mg apixaban twice a day for 7 days.[60] This study is important in that it showed that the steady-state AUC and minimal concentration of apixaban at 2.5 mg twice a day taken by hemodialysis patients were well within the range in healthy subjects taking the 2.5-mg dose.[58,61] However, the effectiveness of such a regimen may be questioned, as these values fall below the 10th percentile of the 5 mg twice a day dose in normal subjects. Finally, the same six hemodialysis patients underwent a washout period and then received 5 mg apixaban twice a day for 7 days with a consequent AUC and minimal concentration which were more than twice those seen in healthy subjects.[60]

Utilization in ESRD

Apixaban was first approved by the FDA for AF in December 2012. The original label recommended dose reduction to 2.5 mg twice a day for patients with at least two factors out of: serum creatinine $\geq$ 1.5 mg/dL, age $\geq$ 80, and weight $\leq$ 60 kg.[62] Following the single-dose pharmacokinetic study mentioned above, the label was changed in January 2014 such that the 5-mg twice a day dose was recommended in ESRD patients who are not older adults or underweight (►**Table 3**).[63] Of note, in direct reference to the findings from the steady-state study, a recommendation has been made to reconsider the 5-mg dose in hemodialysis patients.[52] Concurrently, the use of apixaban is not approved in ESRD patients in Europe.[64]

A large retrospective cohort study from the United States that excluded patients with ESRD has demonstrated that among patients with AF receiving apixaban with a renal indication for dose reduction, overdosing was very common at 48.5%; importantly, overdosing was associated with doubling of major bleeding rates.[45] Further, among patients without renal indication for dose reduction, 16.5% were underdosed; such underdosing was associated with an increased risk of stroke (hazard ratio, 4.87; 95% confidence interval, 1.30–18.26).

Apixaban has been adopted very rapidly in the United States among patients with hemodialysis and AF, and has reached a point prevalence of 10.5% in this population in October 2015.[43] There is currently paucity of information on utilization of off-label DOACs in the severe CKD or ESRD population in Europe. Nonetheless, among the DOACs, it appears that a larger proportion of apixaban users with AF have baseline CKD.[65,66] In a survey among European electrophysiology centers, apixaban was indicated as the preferred anticoagulant in moderate CKD, and the lack of data on patients with severe CKD and/or RRT was emphasized.[67]

Safety in ESRD

Bleeding risk with apixaban in ESRD has been assessed in three studies to date (►**Table 4**). Two of these studies included only inpatient follow-up.[68,69] With limited follow-up and selection of only events during admission, any rates of major bleeding in these studies are not comparable to clinical trials. In the third study, matched cohorts of patients with severe CKD who used apixaban or VKA were followed for major and clinically relevant nonmajor bleeding; each cohort comprised 73 patients (27 ESRD).[70] Apixaban users received 2.5 mg twice a day primarily (61.6%) and were followed for 369 days. There were 9.5 major bleeding events per 100 person-years, which is 3.5-fold higher than the rate in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial where most of the study population received 5 mg twice a day.[29] In ARISTOTLE, major bleeding rates in patients with GFR$<$ 50 and $>$ 80 mL/min/1.73 m^2 were 3.15 and 1.33 per 100 person-years, respectively.[71] Thus, there is a suggestion for excessive bleeding with reduced-dose apixaban in patients with severe CKD or ESRD compared with full-dose apixaban in patients with nonsevere CKD or ESRD.

Edoxaban

Pharmacology in ESRD

Edoxaban, a factor Xa inhibitor, has a 50% renal clearance out of total clearance.[72] After a single dose of 60 mg, 35.4% of edoxaban is recovered in urine (►**Table 1**).[73] With renal

impairment, edoxaban exposure increases and is assessed as 1.93-fold higher in recipients of peritoneal dialysis than in healthy subjects.[74] Edoxaban is not dialyzable and no supplemental dose is needed following a hemodialysis session.[75]

Utilization in ESRD

Edoxaban (sold in the United States as Savaysa) was approved for use in AF by the FDA in January 2015. The recommended dose in patients with GFR 15 to 50 mL/min/1.73 m^2 is 30 mg once a day with no recommendation for ESRD.[76] In Europe (where it is sold as Lixiana), there are similar recommendations (►**Table 3**).[77] These recommendations by the two regulatory authorities were based on population pharmacokinetic data only, as very few participants with GFR $<$ 50 mL/min/1.73 m^2 were included in the ENGAGE-AF TIMI 48 trial.[78] To date, there are few reports on the utilization of edoxaban in the ESRD population, and, by late 2015, it was probably negligible in the United States.[43]

Safety in ESRD

A clinical trial in Japan reported on 50 patients with GFR 15 to 30 mL/min/1.74 m^2 who used edoxaban 15 mg daily in a nonrandomized fashion (►**Table 4**).[79] No major bleeding occurred during a 100-day follow-up.[79]

Conclusion

VKAs are the most widely used oral anticoagulant among AF patients with ESRD. However, there are abundant reports on excessive bleeding risk associated with its use, as well as challenges in attaining therapeutic anticoagulation. These may have triggered rapid adoption of DOACs among ESRD patients in the United States, which initially may have led to inappropriate dosing and excessive bleeding. While apixaban and rivaroxaban have to date expanded labeling which allows use in ESRD, the dosing is based on single-dose studies which may have underestimated drug accumulation and foreseeable harm. Subsequently, steady-state studies have indicated in both cases a reduced dose. While recommending these doses for use in ESRD patients would align with current safety data, their effectiveness in preventing stroke in AF and recurrent VTE remains to be established. Nevertheless, it is very likely that with further increased use of DOACs in ESRD, more population-based safety and effectiveness data will allow informed dosing and choice of oral anticoagulant.

Conflicts of Interest

Dr. Tagalakis reports an investigator initiated grant from Sanofi, and consulting and speaker bureau fees from Pfizer, Bristol Myers Squibb, Bayer, and Servier outside the submitted work. Dr. Klil-Drori reports personal fees from Bristol-Myers-Squibb, outside the submitted work.

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