

Direct Oral Anticoagulants in End-Stage Renal Disease

Adi J. Klil-Drori, MD¹ Vicky Tagalakakis, MD, MSc^{1,2}

¹ Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada

² Department of Medicine, McGill University, Montreal, Quebec, Canada

Address for correspondence: Adi J. Klil-Drori, MD, Center for Clinical Epidemiology, Jewish General Hospital, Montreal, QC H3T 1E2, Canada (e-mail: adi.klil-drori@mail.mcgill.ca).

Semin Thromb Hemost 2018;44:353–363.

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 m² 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 m² 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

published online
January 10, 2018

Issue Theme Recent Advances in
Thrombosis and Hemostasis – Part III;
Guest Editor: Sam Schulman, MD, PhD.

Copyright © 2018 by Thieme Medical
Publishers, Inc., 333 Seventh Avenue,
New York, NY 10001, USA.
Tel: +1(212) 584-4662.

DOI <https://doi.org/10.1055/s-0037-1621715>.
ISSN 0094-6176.

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 ratio¹⁴ 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 ESRD¹⁸ 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 ~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 arteriopathy (or calcific vasculopathy), which leads to ischemic skin necrosis.³¹ This syndrome is prevalent in ~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 arteriopathy 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 m² 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 m², while in Europe, the 110-mg dose is recommended for patients with GFR between 30 and 49 mL/min/1.73 m² 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
Mavrikanas 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
Matsushima et al 2013 ⁷²	Randomized crossover	PO edoxaban 60 mg, IV edoxaban 30 mg ± concomitant quinidine	35 healthy subjects	apixaban in dialysis patients is double that in 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
Winkelmayr 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 GFR 15–30: 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) Apixaban (n = 40)	81/39/0 32/8/0	9 8.8	7 major; 7 CRNMB 0 major; 5 CRNMB	NA NA	57.% of apixaban users had 2.5 mg BID dose
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) Warfarin (n = 73)	53/19/1 53/19/1	369 562	7 major; 13 CRNMB 13 major; 6 CRNMB	9.5 major; 17.6 CRNMB 11.6 major; 5.3 CRNMB	Rates are for severe CKD rather than ESRD alone
Chan et al 2015 ⁴²	Retrospective cohort	Warfarin (n = 8,064) Dabigatran (n = 281) Rivaroxaban (n = 244)	8,064/0/0 281/0/0 244/0/0	175 168 106	1,858 major; 4,367 minor 106 major; 153 minor 46 major; 113 minor	47.1 major; 120.6 minor 83.1 major; 58.8 minor 68.4 major; 149.4 minor	Substantially shorter follow-up on rivaroxaban Major bleeding definitions do not conform with ISTH
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 ≥ 1.5 mg/dL, age ≥ 80 , and weight ≤ 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 m² 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 m² 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 m² 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 m² 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.

References

- 1 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2012;3(01):1–150

- 2 Murphy D, McCulloch CE, Lin F, et al; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med* 2016;165(07):473–481
- 3 Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2016 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2017;69(03, Suppl 1):A7–A8
- 4 Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013;382(9888):260–272
- 5 Pippias M, Kramer A, Noordzij M, et al. The European Renal Association – European Dialysis and Transplant Association Registry Annual Report 2014: a summary. *Clin Kidney J* 2017;10(02):154–169
- 6 Lau YC, Proietti M, Guiducci E, Blann AD, Lip GYH. Atrial fibrillation and thromboembolism in patients with chronic kidney disease. *J Am Coll Cardiol* 2016;68(13):1452–1464
- 7 Reinecke H, Brand E, Mesters R, et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. *J Am Soc Nephrol* 2009;20(04):705–711
- 8 Ocak G, Lijfering WM, Verduijn M, et al. Risk of venous thrombosis in patients with chronic kidney disease: identification of high-risk groups. *J Thromb Haemost* 2013;11(04):627–633
- 9 Mahmoodi BK, Gansevoort RT, Næss IA, et al. Association of mild to moderate chronic kidney disease with venous thromboembolism: pooled analysis of five prospective general population cohorts. *Circulation* 2012;126(16):1964–1971
- 10 Nampoory MR, Das KC, Johny KV, et al. Hypercoagulability, a serious problem in patients with ESRD on maintenance hemodialysis, and its correction after kidney transplantation. *Am J Kidney Dis* 2003;42(04):797–805
- 11 Allon M, Brouwer-Maier DJ, Abreo K, et al. Recommended clinical trial end points for dialysis catheters. *Clin J Am Soc Nephrol* 2017;CJN.12011116
- 12 Holford NH. Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. *Clin Pharmacokinet* 1986;11(06):483–504
- 13 Leblond F, Guévin C, Demers C, Pellerin I, Gascon-Barré M, Pichette V. Downregulation of hepatic cytochrome P450 in chronic renal failure. *J Am Soc Nephrol* 2001;12(02):326–332
- 14 Dreisbach AW, Japa S, Gebrekal AB, et al. Cytochrome P4502C9 activity in end-stage renal disease. *Clin Pharmacol Ther* 2003;73(05):475–477
- 15 Sakaan SA, Hudson JQ, Oliphant CS, et al. Evaluation of warfarin dose requirements in patients with chronic kidney disease and end-stage renal disease. *Pharmacotherapy* 2014;34(07):695–702
- 16 Yang F, Hellyer JA, Than C, et al. Warfarin utilisation and anticoagulation control in patients with atrial fibrillation and chronic kidney disease. *Heart* 2017;103(11):818–826
- 17 Limdi NA, Beasley TM, Baird MF, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. *J Am Soc Nephrol* 2009;20(04):912–921
- 18 Bachmann K, Shapiro R, Mackiewicz J. Influence of renal dysfunction on warfarin plasma protein binding. *J Clin Pharmacol* 1976;16(10 Pt 1):468–472
- 19 Ifudu O, Dulin AL. Pharmacokinetics and dialysability of warfarin in end-stage renal disease. *Nephron* 1993;65(01):150–151
- 20 Bachmann K, Shapiro R, Mackiewicz J. Warfarin elimination and responsiveness in patients with renal dysfunction. *J Clin Pharmacol* 1977;17(5-6):292–299
- 21 Keskar V, Sood MM. Use of oral anticoagulation in the management of atrial fibrillation in patients with ESRD: con. *Clin J Am Soc Nephrol* 2016;11(11):2085–2092
- 22 McCullough PA, Ball T, Cox KM, Assar MD. Use of oral anticoagulation in the management of atrial fibrillation in patients with ESRD: pro. *Clin J Am Soc Nephrol* 2016;11(11):2079–2084
- 23 Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int* 2010;77(12):1098–1106

- 24 Tan J, Bae S, Segal JB, et al. Treatment of atrial fibrillation with warfarin among older adults with end stage renal disease. *J Nephrol* 2017
- 25 Shen JL, Turakhia MP, Winkelmayr WC. Anticoagulation for atrial fibrillation in patients on dialysis: are the benefits worth the risks? *Curr Opin Nephrol Hypertens* 2012;21(06):600–606
- 26 Schooli M, Grooteman MP, Bartels PC, Nubé MJ. Aspects of platelet disturbances in haemodialysis patients. *Clin Kidney J* 2013;6(03):266–271
- 27 Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139–1151
- 28 Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365(10):883–891
- 29 Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365(11):981–992
- 30 Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369(22):2093–2104
- 31 Hayden MR, Kolb LG, Khanna R. Calciphylaxis and the cardio-metabolic syndrome. *J Cardiometaab Syndr* 2006;1(01):76–79
- 32 Nigwekar SU, Zhao S, Wenger J, et al. A nationally representative study of calcific uremic arteriolopathy risk factors. *J Am Soc Nephrol* 2016;27(11):3421–3429
- 33 Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos* 2008;36(02):386–399
- 34 Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010;49(04):259–268
- 35 Heidbuchel H, Verhamme P, Alings M, et al; European Heart Rhythm Association. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;15(05):625–651
- 36 FDA. PRADAXA capsules for oral use. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s0071bl.pdf. Accessed Aug 16, 2017
- 37 Liesenfeld KH, Clemens A, Kreuzer J, Brueckmann M, Schulze F. Dabigatran treatment simulation in patients undergoing maintenance haemodialysis. *Thromb Haemost* 2016;115(03):562–569
- 38 Khadzhyrov D, Wagner F, Formella S, et al. Effective elimination of dabigatran by haemodialysis. A phase I single-centre study in patients with end-stage renal disease. *Thromb Haemost* 2013;109(04):596–605
- 39 Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med* 2017;377(05):431–441
- 40 Blennerhassett R, Favaloro EJ, Pasalic L. Novel (Oral) anticoagulant challenges in surgery. *Semin Thromb Hemost* 2017;43(07):706–715
- 41 Sindet-Pedersen C, Pallisgaard JL, Staerk L, et al. Temporal trends in initiation of VKA, rivaroxaban, apixaban and dabigatran for the treatment of venous thromboembolism - a Danish nationwide cohort study. *Sci Rep* 2017;7(01):3347
- 42 Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. *Circulation* 2015;131(11):972–979
- 43 Chan KE, Giugliano RP, Patel MR, et al. Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. *J Am Coll Cardiol* 2016;67(24):2888–2899
- 44 Steinberg BA, Shrader P, Thomas L, et al; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients. Factors associated with non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with new-onset atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II). *Am Heart J* 2017;189:40–47
- 45 Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol* 2017;69(23):2779–2790
- 46 Weinz C, Schwarz T, Kubitzka D, Mueck W, Lang D. Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. *Drug Metab Dispos* 2009;37(05):1056–1064
- 47 Kubitzka D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol* 2010;70(05):703–712
- 48 Dias C, Moore KT, Murphy J, et al. Pharmacokinetics, pharmacodynamics, and safety of single-dose rivaroxaban in chronic hemodialysis. *Am J Nephrol* 2016;43(04):229–236
- 49 De Vriese AS, Caluwé R, Bailleur E, et al. Dose-finding study of rivaroxaban in hemodialysis patients. *Am J Kidney Dis* 2015;66(01):91–98
- 50 Mueck W, Schwes S, Stampfuss J. Rivaroxaban and other novel oral anticoagulants: pharmacokinetics in healthy subjects, specific patient populations and relevance of coagulation monitoring. *Thromb J* 2013;11(01):10
- 51 Stampfuss J, Kubitzka D, Becka M, Mueck W. The effect of food on the absorption and pharmacokinetics of rivaroxaban. *Int J Clin Pharmacol Ther* 2013;51(07):549–561
- 52 Deal EN, Shuster JE. Balancing anticoagulation decisions in patients on dialysis with atrial fibrillation. *J Am Soc Nephrol* 2017;28(07):1957–1959
- 53 FDA. Xarelto - tablets for oral use. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202439s0171bl.pdf. Accessed Aug 16, 2017
- 54 Bayer. Xarelto - prescribing information. Available at <http://www.xarelto-info.co.uk/static/new/site-resources/pdfs/prescribing-information.pdf>. Accessed Aug 16, 2017
- 55 Fordyce CB, Hellkamp AS, Lokhnygina Y, et al; ROCKET AF Steering Committee and Investigators. On-treatment outcomes in patients with worsening renal function with rivaroxaban compared with warfarin: insights from ROCKET AF. *Circulation* 2016;134(01):37–47
- 56 Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos* 2009;37(01):74–81
- 57 Frost C, Yu Z, Nepal S, et al. Apixaban, a direct factor Xa inhibitor: single-dose pharmacokinetics and pharmacodynamics of an intravenous formulation. *J Clin Pharmacol* 2008;48(09):1132
- 58 Leil TA, Feng Y, Zhang L, Paccaly A, Mohan P, Pfister M. Quantification of apixaban's therapeutic utility in prevention of venous thromboembolism: selection of phase III trial dose. *Clin Pharmacol Ther* 2010;88(03):375–382
- 59 Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *J Clin Pharmacol* 2016;56(05):628–636
- 60 Mavranakas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. *J Am Soc Nephrol* 2017;28(07):2241–2248
- 61 Kowalski K, Nielsen J, Roy A, et al. Apixaban exposure and anti-Xa activity in nonvalvular atrial fibrillation patients: an application of population PK/PD analysis. *J Pharmacokinet Pharmacodyn* 2014;41(Suppl 1):7–101
- 62 FDA. Eliquis tablets for oral use. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s0021bl.pdf. Accessed Aug 17, 2017
- 63 FDA. ELIQUIS Supplemental Approval. Available at https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/202155orig1s0021tr.pdf. Accessed Aug 7, 2017

- 64 Heiddbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015;17(10):1467–1507
- 65 Staerk L, Fosbøl EL, Lip GYH, et al. Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study. *Eur Heart J* 2017;38(12):907–915
- 66 Hohnloser SH, Basic E, Nabauer M. Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation: a post-marketing surveillance study. *Clin Res Cardiol* 2017;106(08):618–628
- 67 Potpara TS, Lenarczyk R, Larsen TB, Deharo JC, Chen J, Dagnes N; Conducted by the Scientific Initiatives Committee, European Heart Rhythm Association. Management of atrial fibrillation in patients with chronic kidney disease in Europe. Results of the European Heart Rhythm Association Survey. *Europace* 2015;17(12):1862–1867
- 68 Sarratt SC, Nesbit R, Moye R. Safety outcomes of apixaban compared with warfarin in patients with end-stage renal disease. *Ann Pharmacother* 2017;51(06):445–450
- 69 Steuber TD, Shiltz DL, Cairns AC, Ding Q, Binger KJ, Courtney JR. A multicenter analysis of factors associated with apixaban-related bleeding in hospitalized patients with end-stage renal disease on hemodialysis. *Ann Pharmacother* 2017;51(11):954–960
- 70 Stanton BE, Barasch NS, Tellor KB. Comparison of the safety and effectiveness of apixaban versus warfarin in patients with severe renal impairment. *Pharmacotherapy* 2017;37(04):412–419
- 71 Hijazi Z, Hohnloser SH, Andersson U, et al. Efficacy and safety of apixaban compared with warfarin in patients with atrial fibrillation in relation to renal function over time: insights from the ARISTOTLE Randomized Clinical Trial. *JAMA Cardiol* 2016;1(04):451–460
- 72 Matsushima N, Lee F, Sato T, Weiss D, Mendell J. Bioavailability and safety of the factor Xa inhibitor edoxaban and the effects of quinidine in healthy subjects. *Clin Pharmacol Drug Dev* 2013;2(04):358–366
- 73 Bathala MS, Masumoto H, Oguma T, He L, Lowrie C, Mendell J. Pharmacokinetics, biotransformation, and mass balance of edoxaban, a selective, direct factor Xa inhibitor, in humans. *Drug Metab Dispos* 2012;40(12):2250–2255
- 74 Ridout G, de la Motte S, Niemczyk S, et al. Effect of renal function on edoxaba-f r pharmacokinetics (PK) and on population PK/PK-PD model. *J Clin Pharmacol* 2009;49(09):1124
- 75 Parasrampur DA, Marbury T, Matsushima N, et al. Pharmacokinetics, safety, and tolerability of edoxaban in end-stage renal disease subjects undergoing haemodialysis. *Thromb Haemost* 2015;113(04):719–727
- 76 FDA. SAVAYSA tablets for oral use. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/2063161bl.pdf. Accessed Aug 18, 2017
- 77 EMA. Lixiana - Assessment Report. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002629/WC500189045.pdf. Accessed Aug 18, 2017
- 78 Bohula EA, Giugliano RP, Ruff CT, et al. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 Trial. *Circulation* 2016;134(01):24–36
- 79 Koretsune Y, Yamashita T, Kimura T, Fukuzawa M, Abe K, Yasaka M. Short-term safety and plasma concentrations of edoxaban in Japanese patients with non-valvular atrial fibrillation and severe renal impairment. *Circ J* 2015;79(07):1486–1495
- 80 Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012;367(07):625–635
- 81 Lai HM, Aronow WS, Kalen P, et al. Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin. *Int J Nephrol Renovasc Dis* 2009;2:33–37
- 82 Phelan PJ, O'Kelly P, Holian J, et al. Warfarin use in hemodialysis patients: what is the risk? *Clin Nephrol* 2011;75(03):204–211
- 83 Kai B, Bogorad Y, Nguyen LN, et al. Warfarin use and the risk of mortality, stroke, and bleeding in hemodialysis patients with atrial fibrillation. *Heart Rhythm* 2017;14(05):645–651
- 84 Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. *Clin J Am Soc Nephrol* 2011;6(11):2662–2668
- 85 Biggers JA, Remmers AR Jr, Glassford DM, Sarles HE, Lindley JD, Fish JC. The risk of anticoagulation in hemodialysis patients. *Nephron* 1977;18(02):109–113
- 86 Vázquez E, Sánchez-Perales C, García-Cortes MJ, et al. Ought dialysis patients with atrial fibrillation be treated with oral anticoagulants? *Int J Cardiol* 2003;87(2-3):135–139, discussion 139–141
- 87 Khalid F, Qureshi W, Qureshi S, Alirhayim Z, Garikapati K, Patsias I. Impact of restarting warfarin therapy in renal disease anticoagulated patients with gastrointestinal hemorrhage. *Ren Fail* 2013;35(09):1228–1235
- 88 Wang TK, Sathananthan J, Marshall M, Kerr A, Hood C. Relationships between Anticoagulation, Risk Scores and Adverse Outcomes in Dialysis Patients with Atrial Fibrillation. *Heart Lung Circ* 2016;25(03):243–249
- 89 Yodogawa K, Mii A, Fukui M, et al. Warfarin use and incidence of stroke in Japanese hemodialysis patients with atrial fibrillation. *Heart Vessels* 2016;31(10):1676–1680
- 90 Klil-Drori AJ, Coulombe J, Nessim SJ, Tagalakis V. The risk of major bleeding with low-molecular-weight-heparins for venous thromboembolism in dialysis patients: the Q-VTE Study. *Blood* 2016;128(22):89–89
- 91 Shah M, Avgil Tsadok M, Jackevicius CA, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. *Circulation* 2014;129(11):1196–1203
- 92 Shen JI, Montez-Rath ME, Lenihan CR, Turakhia MP, Chang TI, Winkelmayer WC. Outcomes after warfarin initiation in a cohort of hemodialysis patients with newly diagnosed atrial fibrillation. *Am J Kidney Dis* 2015;66(04):677–688
- 93 Yoon CY, Noh J, Jhee JH, et al. Warfarin use in patients with atrial fibrillation undergoing hemodialysis: a nationwide population-based study. *Stroke* 2017;48(09):2472–2479
- 94 Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J* 2015;36(05):297–306
- 95 Genovesi S, Rebora P, Gallieni M, et al. Effect of oral anticoagulant therapy on mortality in end-stage renal disease patients with atrial fibrillation: a prospective study. *J Nephrol* 2017;30(04):573–581
- 96 Wakasugi M, Kazama JJ, Tokumoto A, et al. Association between warfarin use and incidence of ischemic stroke in Japanese hemodialysis patients with chronic sustained atrial fibrillation: a prospective cohort study. *Clin Exp Nephrol* 2014;18(04):662–669
- 97 Zellweger M, Bouchard J, Raymond-Carrier S, Laforest-Renald A, Quéirin S, Madore F. Systemic anticoagulation and prevention of hemodialysis catheter malfunction. *ASAIO J* 2005;51(04):360–365
- 98 Clark EG, Rodger MA, Ramsay TO, Knoll GA. Effectiveness of a computerized decision support system for anticoagulation management in hemodialysis patients: a before-after study. *Hemodial Int* 2016;20(04):530–536
- 99 Knoll F, Sturm G, Lamina C, et al. Coumarins and survival in incident dialysis patients. *Nephrol Dial Transplant* 2012;27(01):332–337
- 100 Crowther MA, Clase CM, Margetts PJ, et al. Low-intensity warfarin is ineffective for the prevention of PTFE graft failure in patients on hemodialysis: a randomized controlled trial. *J Am Soc Nephrol* 2002;13(09):2331–2337
- 101 Mokrzycki MH, Jean-Jerome K, Rush H, Zdunek MP, Rosenberg SO. A randomized trial of minidose warfarin for the prevention of late malfunction in tunneled, cuffed hemodialysis catheters. *Kidney Int* 2001;59(05):1935–1942
- 102 Traynor JP, Walbaum D, Woo YM, Teenan P, Fox JG, Mactier RA. Low-dose warfarin fails to prolong survival of dual lumen venous dialysis catheters. *Nephrol Dial Transplant* 2001;16(03):645