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DRUG THERAPY: SPECIAL CONSIDERATIONS IN DIALYSIS PATIENTS

Considerations for Systemic Anticoagulation in ESRD

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ABSTRACT

In the setting of end-stage kidney disease, the incidence and risk for thrombotic events are increased and use of anticoagulants is common. The incidence of bleeding, however, is also a frequent issue and creates additional challenges in the management of anticoagulation therapy. Patients with end-stage renal disease are typically excluded from large clinical trials exploring the use of anticoagulants, which limits our knowledge of optimal management approaches. Furthermore, varying degrees of renal failure in addition to conditions that alter the pharmacokinetics of various anticoagulants or pharmacodynamic response may warrant alternative approaches to dosing. This review will explore systemic chronic anticoagulation therapy in the setting of chronic kidney disease where hemodialysis is required. Agents discussed include vitamin K antagonists, low-molecular-weight heparins, fondaparinux, oral factor Xa antagonists, and direct thrombin inhibitors. Clinical challenges, approaches to dosing regimens, and tools for measuring responses and reversal will be explored.

Stroke, in the setting of atrial fibrillation (AF) or venous thromboembolism (VTE), can occur more commonly in the setting of end-stage renal disease (ESRD) (1–4). There are several drivers for thrombosis in chronic kidney disease (CKD): higher levels of procoagulant factors, concomitant use of erythropoietin stimulating agents, decline in fibrinolytic activity, and decreased endogenous anticoagulants (5–7). Thus, systemic anticoagulation therapy is commonly indicated in hemodialysis (HD) patients (2). In addition, anticoagulants may also be used to prevent recurrent clotting of access grafts or thrombosis in the extracorporeal dialysis circuit.

In contrast, the risk and incidence of bleeding events can also be greater in advanced CKD. Bleeding rates of 40–50% have been reported in patients with CKD or on HD (5). Maintaining adequate hemoglobin levels is critical in ESRD, and acute or chronic blood loss can create challenges in achieving and sustaining goals. Factors driving bleeding include platelet dysfunction from uremia or shear wall stress via the dialysis circuit (8,9). In addition, platelet-mediated functions that influence hemostasis may be impaired (5).

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Initiating and Maintaining Anticoagulation Therapy

In the setting of HD, little is known about how to adjust initial or maintenance doses for anticoagulation. Dialyzable agents, such as dabigatran, may not be optimal choices as maintenance therapy would have to account for dialysis removal, and elimination may vary between patients. Anticoagulation regimens may be more conservative for prophylaxis or more aggressive for thromboembolism. For thrombosis prophylaxis, some agents may require reduced dosing strategies. However, in ESRD treatment dosing regimens may be closer to prophylactic regimens for some agents. In selected situations such as the presence of mechanical heart valves or AF with a high risk for stroke, more aggressive "treatment" levels of anticoagulation may be preferred due to the thromboembolic risks involved. In others, the presence of ESRD may be associated with decreased benefits of anticoagulation therapy. A recent report and review of the literature suggested that the use of warfarin in the setting of AF may not be beneficial in reducing stroke, but may be associated with increased

bleeding (10). Decisions to withhold anticoagulation therapy should weigh the risk of both bleeding and thrombosis, especially if the stroke risk in this case is very high.

Maintaining anticoagulation therapy also requires appropriate monitoring. Measuring the level of anticoagulation in ESRD patients is often recommended; however, several assumptions may not be accurate. A single laboratory observation may not alone describe the risks for thrombosis and bleeding in ESRD because other drivers (e.g., plasminogen activator 1, uremic platelets), not typically expressed in normal kidney function, may now influence observed outcomes. Commonly used assays and their associated target ranges may not have been validated in ESRD; they can vary between different laboratories and with the reagents used which can further reduce confidence in applying results to clinical decisions. Some assays such as the antifactor Xa activity have not been validated as a predictor for bleeding or thrombosis, let alone for making dosing adjustments in the setting of ESRD. In addition, measured values in the first days of therapy may be reduced in ESRD when drug accumulation occurs over time (e.g., enoxaparin). Since patients with severe renal disease and HD have been excluded from comparative clinical trials, most of the available insights have been based on smaller postmarketing and single center experiences. Thus, clinicians should consider these limitations as well as the altered balance between bleeding and thrombosis when deciding on which anticoagulant to use, the dose, and monitoring procedures.

Anticoagulant Agents

Unfractionated Heparin

Unfractionated heparin (UFH) is a hepatically eliminated anticoagulant administered subcutaneously for VTE prophylaxis and as a continuous infusion for the management of systemic thrombosis or dialysis circuit patency. UFH is typically preferred in ESRD as there is no need to adjust dosing for renal function. However, antithrombin concentrations may be reduced in ESRD, potentially decreasing the patient's response to UFH (11). In the setting of acute thrombosis, a loading dose may be given followed by a continuous infusion and a delay in measuring the activated partial thromboplastin time (aPTT) considered to allow the bolus effect to dissipate (e.g., 6–8 hours post any bolus and rate change). In situations where there is no need for immediate anticoagulant effect, such as acute stroke, stroke prevention for AF, or history of a VTE, a bolus dose may not be necessary and the aPTT can be measured sooner (e.g., 4 hour post rate changes). The anticoagulation effects may be measured via aPTT or antifactor Xa activity. For higher doses and level of anticoagulation during selected procedures, one of the 2 heparin intensity ranges measured by activated clotting time (low range and high range) may be used.

Low-Molecular-Weight Heparin

While UFH may be preferred in ESRD, low-molecular-weight heparins (LMWH) have been administered intravenously prior to HD to sustain circuit patency (12–14). Since LMWH are primarily eliminated renally, dosing reductions are necessary as renal function declines in order to avoid excessive anticoagulation and bleeding complications (15). For dalteparin and tinzaparin, the dose is not adjusted if the creatinine clearance (CrCl) is ≥20 ml/minute (16). However, enoxaparin dosing is reduced by 50% if the CrCl <30 ml/minute (17). Although not part of the prescribing information, it has been suggested to reduce the enoxaparin dose by 25%, or the next lower syringe size, if CrCl is between 30 and 60 ml/minute (17). Individuals with a serum creatinine >2.5 mg/dl were typically excluded from the clinical trials, and therefore the dosing recommendations do not reflect patients with CrCl values <20 ml/minute or those who are dialysis dependent. The approach to HD also influences the elimination of LMWH as high-flux membrane dialyzers can remove more LMWH compared with low-flux dialyzers (18).

There is limited evidence regarding adjusted dose LMWH for systemic anticoagulation in HD. In an analysis of tinzaparin 175 units/kg/day and dalteparin 200 units/kg/day for periprocedural bridging in HD, accumulation of measured antifactor Xa activity was observed (19). This suggests that even short periods of LMWH therapy may lead to higher than desired effects. Previous analyses have also noted higher bleeding rates with enoxaparin as renal function declines (20). Using observations that suggested a reduction in bleeding without changing thrombosis rates by lowering doses of 31–60 mg enoxaparin to 30 mg enoxaparin, one single center retrospective study explored a revised dosing strategy with the temporary use of enoxaparin for systemic treatment levels of anticoagulation and subsequent bridge to warfarin (21). Subcutaneous enoxaparin 0.7 ± 0.2 mg/kg/day (range 0.4–1) was given in 82 HD patients for a mean of 3.3 ± 4.2 days. Antifactor Xa activity was not measured. Using a matched cohort of 82 patients receiving UFH, patients receiving enoxaparin had a shorter length of hospital stay, a slight but not statistically lower incidence in bleeding, and no episodes of thromboembolism (21).

Fondaparinux

Fondaparinux is a renally eliminated factor Xa antagonist that carries a contraindication when the CrCl is <30 ml/minute (22). One potential advantage of fondaparinux is as an alternative anticoagulant in the setting of heparin-induced thrombocytopenia (HIT) because of lower reactivity with platelets (23). Experience with fondaparinux in ESRD is limited. In HD with measured antifactor Xa activity, doses of 0.05 mg/kg or 2.5 mg provided adequate anticoagulation but with drug accumulation observed

(24–26). Concurrent use of high-flux polysulfone membranes has been associated with increased clot formation compared with low-flux dialyzers (27). In the setting of HIT and ESRD, doses of 1.5 mg daily or 2.5 mg every other day have been proposed based on case reports (26,28–30).

Measuring Anti-Xa Activity

Measuring antifactor Xa levels in ESRD has been used in hopes of maximizing thrombosis prevention while minimizing bleeding. An anti-Xa level of 1.05 IU/ml for dalteparin and 0.85 IU/ml for tinzaparin has been suggested 4 hours post administration (31). For enoxaparin administered twice daily, ranges of 0.6–1.0 IU/ml measured 4 hours after a dose for treatment levels have been proposed (31). This can help detect potential accumulation, especially given that the elimination half-life of enoxaparin measured on day 1 and then day 4 increased from 7.3 to 15.9 hours (32). Dalteparin and tinzaparin appear to have different responses with less accumulation observed and more rapid elimination in ESRD compared with enoxaparin (33–37). Other observations have suggested that accumulation of dalteparin and tinzaparin can occur in ESRD (38,39). For fondaparinux, correlation with dose and antifactor Xa activity has been observed, but phase II trials in the setting of VTE or ACS have not shown a dose–response relationship between serum concentrations and bleeding or thrombosis (40,41).

Clinicians should exercise caution in measuring anti-Xa activity and adjusting dosing in the setting of ESRD as improved outcomes have not been demonstrated. Furthermore, discordance between observed anti-Xa activity and thrombin generation in HD has been reported (42). Considerable variability may also occur between laboratories due to differences in assay reagents and equipment (43). Poor correlation is seen between anti-Xa activity and estimated renal function for LMWH (44). Clinicians should keep in mind that ordered tests may create additional challenges, especially if results suggest adjustments that may not be desired.

Vitamin K Antagonists

Vitamin K antagonists such as warfarin are primarily eliminated via the liver and are commonly used for long-term anticoagulant therapy. Recent observations suggest that renal failure and uremia influence select cytochrome P450 enzymes including 2C19, a minor pathway for warfarin metabolism (45). Evaluations of warfarin use in ESRD have suggested that effective doses to achieve target goals may be 10–24% lower (46–48). In one comparative analysis of warfarin requirements in various levels of renal function, mean doses were approximately 20% lower (mean 4.3–4.8 mg/day) in CKD compared with normal renal function (mean 5.6 mg/day), but similar between stages of CKD including ESRD (mean 4.8 ± 1.9 mg) (48). Multiple factors should be considered when initiating warfarin therapy including age, function of organ systems, drug interactions, ethnic background, thrombosis risk, or bleeding risks (49). Certain drug interactions, heart failure or infections that drive a lowering in the dose may be more common in ESRD. In addition, observations suggested higher risks of bleeding and thromboembolism including stroke in AF in CKD patients requiring warfarin therapy (50–53).

Therapy is adjusted by measuring the international normalized ratio (INR), with typical targets of 2–3, but may be higher in selected indications such as mechanical mitral valve replacements. In general, INR values during chronic therapy just below (e.g., down to 1.8) or above the target (e.g., up to 3.2) may be re-assessed with a subsequent result prior to making dosing adjustments. ESRD patients have been reported to have lower overall measured time in the therapeutic INR range in addition to increased mortality, underscoring the importance of arranging close follow-up by clinicians familiar with both renal failure and anticoagulation (50,54,55). In situations where the risk for major bleeding is very high, slightly lower INR targets may be considered, but should be weighed against the consequences of a thrombotic event; however, no evidence currently supports this approach. Warfarin may also be used for thrombosis in dialysis access, where INR targets of 2–3 are typically used without much supporting data (56,57). Utilizing warfarin to preserve access function using conservative INR targets (e.g., INR 1.4–1.9) did not show any benefit (54,58).

International normalized ratio measures are drawn is by a point of care device or venipuncture. To avoid additional venipunctures INRs can be measured prior to HD on dialysis days. In one analysis, measuring the INR through the arterial port 1 hour after initiation of dialysis yielded only slightly higher values (0.2 ± 0.2) than that from venipuncture (59). Measuring INR values through catheters should carefully avoid any hemodilution, which can yield falsely elevated values. Unexpected critical INR values should be rechecked if possible or further assessment should be completed prior to making changes or reversing (if no acute bleeding) therapy, especially in patients who are at high risk for thrombosis (60).

Parenteral Direct Thrombin Inhibitors

In selected situations such as HIT or antithrombin deficiency, parenteral direct thrombin inhibitors (DTI) may be used in place of UFH when long term anticoagulation is either being held or initiated. Argatroban and bivalirudin are the most common agents used in this setting. Argatroban is primarily eliminated in the liver; however, recent observations have suggested dosing reductions in the setting of renal failure (61) (Table 2). Argatroban does not appear to be significantly removed by HD (62). Bivalirudin is

primarily removed enzymatically but is also partly removed by the kidney and during HD. Therefore, dosing reductions may be necessary for decreased renal function, but increased in continuous renal replacement therapy as bivalirudin can be removed thru HD (63). Parenteral DTI therapy outside of use during invasive cardiac procedures is typically adjusted using aPTT, with targets of 1.5–2.5 times baseline aPTT (1.5–3 for argatroban).

Non-Vitamin K Dependent Oral Anticoagulants

Dabigatran

Dabigatran is an oral DTI primarily eliminated by the kidney, and dosing reductions are necessary as renal function declines; it is not recommended in ESRD. Dabigatran is removed by HD (64), which can serve as a reversal strategy; however, a rebound effect can occur after stopping HD. Longer sessions may therefore be required depending on how much dabigatran is in the system (65,66).

Rivaroxaban

Rivaoxaban is an oral factor Xa antagonist that works independent of antithrombin for activity. It is partially eliminated by the kidney, and dosing reductions are recommended based on CrCl and indication (Table 1). Rivaroxaban is highly protein bound and not removed during HD (67). Its use in ESRD is limited and there are no reliable approaches to measuring its effects. Antifactor Xa activity has been explored, but the reliability of this test in ESRD limits its application. Rivaroxaban can also increase the INR depending on the assay reagent used. If elevated INR values are noted in patients with renal failure receiving rivaroxaban, the risk of bleeding compared with thrombosis should be re-assessed.

Apixaban

Apixaban is an oral factor Xa inhibitor that is typically administered twice daily. Patients who have any two of the following: a serum creatinine ≥1.5 mg/dl, age >80 years or weight <60 kg should have the dose reduced (68) (Table 2). The basis for ESRD dosing is a pharmacokinetic assessment of maximum plasma concentration and area under the curve in various degrees of renal impairment. In the ESRD group, HD was initiated 2 hours after a single 5 mg oral dose with a 4 hours dialysis session including a dialysis flow rate of 500 ml/minute and blood flow rate of 350–500 ml/minute. The measured dialysis clearance was approximately 18 ml/minute and a 14% decrease in exposure compared with the off dialysis period. Combined with a 17% increase in the area under the curve, no dosing modifications were recommended (69). However, this analysis is based on a single dose and did not consider tissue uptake and accumulation. In addition, apixaban is eliminated via cytochrome P450 enzymes that could be impaired in renal failure leading to higher serum concentrations over time. Thus, resulting serum levels and safety of use long term in the setting of hemodialysis is unknown.

Edoxaban

Edoxaban was recently approved in the United States for stroke prevention in AF and treatment of VTE. For stroke prevention in AF, the approved dose is 60 mg once daily with a reduction to 30 mg if the estimated CrCl is 15–50 ml/minute and avoided if lower. For treatment of VTE, endoxaban started after an initial course of 5 to 10 day course of heparin or LMWH is 60 mg once daily, reduced to 30 mg once daily if the CrCl was between 15 and 50 ml/minute or weight 60 kg or less, or concurrent use of a potent P-glycoprotein inhibitor (70). A handful of studies suggest a 50% reduction in dose may be appropriate for patients with moderate-severe renal impairment (CrCl 15–50 ml/minute) with a 15 mg daily dose being suitable for thromboprophylaxis in both AF and orthopedic surgical patients (71,72). This 15 mg dose was also evaluated in a cross-over study of 10 HD subjects who received a dose 2 hours prior to dialysis on a dialysis day and a dose on a nondialysis day (73).

TABLE 1. Pharmacokinetic properties of anticoagulants in renal failure

	Normal half-life	Half-life in renal dysfunction*	Plasma protein binding (%)	Renal excretion (%)
Heparin	1–2 hours	1–2 hours	High	10
Enoxaparin	5–7 hours	6–9 hours	High	40
Dalteparin	2–5 hours	4–8 hours	High	
Tinzaparin	1–2 hours	5 hours	High	
Fondaparinux	17–21 hours	>21 hours	94	77
Argatroban	39–51 minutes	0.5–1 hour	54	16
Bivalirudin	25 minutes	3.5 hours	None	20
Warfarin	1 week	1 week	99	92
Dabigatran	12–17 hours	28 hours	35	80
Rivaroxaban	5–9 hours	10 hours	92–95	36
Apixaban	12 hours	17 hours	87	27
Edoxaban	9–11 hours	10–14 hours	60	35

*half-life values will vary depending on the degree of renal dysfunction

TABLE 2. Dosing adjustments of anticoagulants in chronic kidney disease

Agent	Dosing in CKD		Comment
Parenteral agents			
Unfractionated heparin	No adjustment necessary		Low antithrombin activity may affect dosing requirements
Dalteparin	No adjustment for CrCl ≥ 20 ml/minute		Dosing adjustment for CrCl <20 ml/minute unclear
Enoxaparin	CrCl >60 ml/minute: no dose modification CrCl 30–60 ml/minute: 25% dose reduction Crcl 20–30 ml/minute: 50% dose reduction		Dosing adjustment for CrCl <20 ml/minute unclear
Tinzaparin	No adjustment for CrCl ≥20 ml/minute		Adjustment for CrCl <20 ml/minute unclear
Fondaparinux	Contraindicated in CrCl <30 ml/minute		Dosing adjustments for renal function are unclear
Argatroban	Renal dysfunction dose adjustment unclear Fraction of extracorporeal clearance not clinically significant		Dose reduction of 0.1–0.6 μg/kg/minute per 30 ml/minute CrCl decrease has been suggested
Bivalirudin	Eliminated enzymatically and renally; however, clearance relationship exists between CrCl and dose requirements HIT and VTE dosing: CrCl >60 ml/minute: 0.15 mg/kg/hour CrCl 30–60 ml/minute: 0.08–0.1 mg/kg/hour CrCl <30 ml/minute or RRT: 0.03–0.05 mg/kg/hour		Substantially removed during HD. Higher doses are used during cardiac interventional procedures with adjustment for renal dysfunction necessary.
Lepirudin	*CrCl (ml/minute)*	*Dose (mg/kg/hour)*	Doses as low as 0.005 mg/kg/hour have been used in renal failure requiring HD
	>60	0.1–0.15	
	45–60	0.075	
	30–44	0.045	
	15–29	0.0225	
	<15	0.02 or less	
Oral agents			
Warfarin	No adjustment necessary		
Dabigatran	*Non-valvular AF CrCl (mL/minute)*	*Dose*	
	>50	150 mg BID	Do not open capsule
	30–50	Consider 75 mg BID if also receiving P-gp inhibitor	
	<30	Avoid use (per American College of Chest Physicians)	The AHA/ACC/HRS does not recommend dabigatran for non-valvular AF in end stage chronic kidney disease
	VTE treatment CrCl (ml/minute)	*Dose*	
	>30	150 mg BID	For treatment of DVT: patients initially received either UFH or LMWH initially. Avoid coadministration with P-gp inhibitor if CrCl <50 ml/minute
	<30	No recommendations	
Rivaroxaban	*Nonvalvular AF CrCl (ml/minute)*	*Dose*	Dose adjustment depends on indication
	>50	20 mg daily	
	15–50	15 mg daily	
	<15 or on HD	Avoid use	
	VTE treatment CrCl (mL/minute)		
	≥30	15 mg BID for 21 days, then 20 mg daily	
	<30	Avoid use	
	VTE prophylaxis post orthopediac procedures	Dose 10 mg/day	
	CrCl <30	Avoid use	
Apixaban	*Nonvalvular AF*	*Dose*	
		5 mg BID	
	If patient meets two of the following: SCr ≥1.5 mg/dl, age ≥80 years, body weight ≤60 kg	2.5 mg BID	
	ESRD on HD	5 mg BID (reduce to 2.5 mg BID for age ≥80 or body weight ≤60 kg)	Hemodialysis dose is based off study of single dose administration and does not account for tissue accumulation of drug
	VTE treatment	Dose	
	CrCl >25 ml/minute or Scr <2.5	10 mg BID for 7 days, then 5 mg BID	Patients with CrCl below 25 ml/min or Scr above 2.5 were excluded in the VTE trials and no dosing recommendations are provided. After 6 months of therapy, the dose can be reduced to 2.5mg BID if continued
	VTE prophylaxis post hip and knee surgery	Dose 2.5 mg BID	Patients with CrCl <30 ml/minute were excluded

Table 2. (Continued)

Agent	Dosing in CKD		Comment
Edoxaban	Nonvalvular AF CrCl (ml/min)	*Dose*	
	>95	Warfarin preferred	
	>50–95	60 mg daily	
	15–50	30 mg daily	
	<15	Avoid use	Reduced does has not been extensively studied in end stage renal disease requiring hemodialysis
	VTE treatment		
	CrCl >50 ml/minute	60 mg once daily	VTE treatment: Endoxaban started after 5 days of UFH or LMWH
	CrCl 15–50 ml/minute or wt ≤60 kg or use with certin P-glycoprotein inhibitors	30 mg once daily	
	<15	Avoid use	

Measured area under the curve was similar without and with HD, and negligible amounts of drug were removed by HD. Despite studies suggesting reduced dose edoxaban to 15 mg daily in severe renal impairment, more robust studies are needed to determine safety and efficacy compared with more established therapies.

Routine Monitoring

Routine monitoring for bleeding or thrombosis should be a component of any anticoagulant management plan. In ESRD populations where experience and clinical trials are limited, frequent follow-up assessments may be necessary. Educating the patient on their anticoagulation therapy and when to contact their health care provider is an important part of their management. This includes indication for use, assessment of any notable bleeding, symptoms of thrombosis, new mediations that may interact and the importance of adherence. For some agents such as warfarin, routine laboratory test (INR) may be included. For dabigatran and rivaroxaban, new methods to quantify serum concentrations that are becoming available should be considered in selected situations but with notable caution. At times an unexpected laboratory result may be reported and not easy to explain. In such cases, consider a repeat test or confirm with a different test before altering the management plan. For INR's on warfarin or the aPTT on heparin, lab draws through the dialysis access port just prior to initiating HD may be considered to limit peripheral blood draws.

Planning for Procedures

The decision to continue anticoagulation therapy during invasive procedures should be influenced by various factors, including the patient's thromboembolic risk and the severity of bleeding associated with the procedure or surgery. However, despite the increased risk for stroke in ESRD and AF, renal failure is not part of the $CHADS_2$ or CHA_2DS_2-VAS_C stroke risk assessment score (74,75).

If anticoagulation is discontinued prior to an elective procedure, the duration of time to withhold therapy prior to the procedure should be based on the medication's pharmacokinetic profile. Warfarin should be stopped 5–7 days (longer hold in patients on lower doses) prior to the procedure due to its prolonged duration of action (76). The use of therapeutic bridging therapy prior to and after the procedure should be evaluated on a case-by-case basis, but is recommended for patients who have a high risk of perioperative thromboembolism. While most studies evaluating bridging therapy utilized therapeutic LMWH, IV UFH is commonly used for patients with severe renal insufficiency or on HD. It should be administered to obtain an aPTT of 1.5–2.0 times the baseline aPTT, stopped 4–6 hours prior to the procedure, then resumed without a bolus dose at the same infusion rate if no severe changes in organ function have occurred once adequate hemostasis has been achieved (76).

Low-molecular-weight heparins should be withheld at least 24 hours prior to the procedure, and potentially longer if there is concern with renal accumulation and a procedure associated with a high risk for bleeding. The duration for holding dabigatran is dependent on renal function, where doses should be held 1–2 days if CrCL ≥50 ml/minute or 3–5 days if CrCl <50 ml/minute (77). Rivaroxaban should be discontinued at least 24 hours prior (67) and apixaban should be discontinued at least 48 hours prior to an invasive procedure with a moderate to high risk of bleeding and at least 24 hours prior to a procedures with a low bleeding risk (68). Holding periods of up to 4 days may be necessary for either agent in high risk bleeding procedures including neuraxial anesthesia (78).

Reversing Anticoagulation Therapy

In emergent situations where bleeding must be stopped or an invasive procedure with high bleeding risk is required, reversal agents can be administered

in addition to supportive care. When considering various reversal agents, the benefits of anticoagulation reversal must be weighed against the potential prothrombotic risk. Warfarin therapy can be reversed with vitamin K, prothrombin complex concentrates (PCC), activated PCC, and recombinant activated factor VII (79). The anticoagulant effects of UFH and LMWH can be reversed with protamine, although the effect is only partially successful in LMWH. There are no specific reversal agents for bivalirudin and argatroban, but their effects will decrease quickly once the infusion is discontinued due to their short half-lives. Renal impairment will prolong the effects of bivalirudin and argatroban; however bivalirudin can be removed by hemofiltration.

There is limited evidence regarding reversal of dabigatran, rivaroxaban, and apixaban. Phase III clinical trials exploring the efficacy of the newer oral anticoagulants did not include patients with estimated CrCl values below 25-30 ml/min. Experiences with their use in ESRD is limited. One recent analysis with their use in atrial fibrillation and chronic ESRD requiring HD noted that both dabigatran and rivaroxaban were associated with a higher risk of hospitalization and death, including hemorrhagic death compared to warfarin (80). Endoxaban and apixaban were not available when the trial was initiated, so outcomes related to their long term use in this population compared to warfarin remains unclear. This however highlights a notable concern when using these agents in ESRD, the potential risks and bleeding complications. Dabigatran can be removed by HD, and there are case series demonstrating efficacy of this approach (77,81,82). Studies of single doses before HD probably over estimate dabigatran removal when compared with actual drug removal after prolonged therapy, where significant tissue distribution has occurred. It appears that prolonged dialysis may be necessary to capture rebound dabigatran plasma concentrations from tissue redistribution.

There are also case reports of using activated PCC to manage bleeding in dabigatran patients (83–85). Another case report described using low dose factor eight inhibitor bypass activity (FEIBA) of 8 units/kg immediately prior to successful insertion of the dialysis access catheter for emergent dabigatran removal (86). Due to its high plasma protein binding, rivaroxaban and apixaban are not significantly removed by dialysis. While there are currently no reports of successful reversal of bleeding in patients on rivaroxaban and apixaban, one study found that 4-factor PCC successfully corrected abnormal coagulation parameters in healthy patients on rivaroxaban (87). Specific antidotes to dabigatran (aDabi-Fab) and factor Xa (andexanet α) are currently in development (88,89). Use of these agents in ESRD has not been determined, and prolonged effects may impair the ability to re-initiate anticoagulants targeted by the antidote.

Conclusion

Patients with ESRD are at a higher risk for both thrombosis and bleeding, and literature is limited on describing the best approach to managing anticoagulant therapy in this population. Decisions on the approach to anticoagulation therapy frequently depend on balancing the risk of bleeding and thrombosis, with monitoring and education necessary to improve management. Experiences with the use of anticoagulation in ESRD continues to expand providing helpful insights on their value and limitations.

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