Systemic Anticoagulation Considerations in Chronic Kidney Disease

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Anticoagulation therapy is commonly required in patients with chronic kidney disease for treatment or prevention of thromboembolic disorders. Anticoagulant management plans can involve use of a single agent, or in some cases, a combination of agents to meet both short- and long-term goals. Systemic anticoagulation in the setting of renal insufficiency poses unique challenges secondary to renal failure-associated hypercoagulable conditions and increased risks for bleeding. Evidence supporting dosing regimens and monitoring approaches in the setting of severe renal impairment or hemodialysis is limited because this population is typically excluded in clinical trials. This review explores concepts of systemic anticoagulation in the chronic kidney disease setting with warfarin, unfractionated heparin, low-molecular-weight heparin, fondaparinux, direct thrombin inhibitors, and anticoagulants in advanced stages of development. Potential strategies for anticoagulant reversal are also briefly described.

Key Words: Hemodialysis, Chronic kidney disease, Anticoagulation, Warfarin, Low-molecular-weight heparin, Heparin, Direct thrombin inhibitors

Patients with chronic kidney disease (CKD) are at high risk for venous thromboembolism (VTE) and hospitalization.[1,2] The increased risk of VTE frequently necessitates anticoagulation therapy for prophylaxis or treatment. Anticoagulants may also be used for challenges unique to CKD such as prevention of recurrent clotting of grafts or maintaining the extracorporeal dialysis circuit. Using anticoagulation therapy in the setting of CKD creates several challenges for the clinician and patient. The implementation of anticoagulation therapy can result in several barriers such as frequent blood draws required for anticoagulant monitoring, uncertain safety and efficacy of renally eliminated anticoagulants, influences of hemodialysis on coagulation and anticoagulant pharmacokinetics, and increased risk of bleeding or thromboembolism. Decisions for anticoagulation therapy, including the agent selected, duration, dose, and approaches to monitoring, should balance the risks of bleeding to thromboembolic-related outcomes. However, presence of CKD is frequently an exclusion criteria in clinical trials, with dosing insights gained through postmarketing experiences. This review will explore selected anticoagulant agents and considerations with their use in CKD, independent of maintaining the dialysis circuit.

Influences of CKD on Coagulation

The patient with CKD is at risk for clot formation, with VTE and stroke occurring more frequently as compared with their age-matched counterparts.[1,3] In the presence of CKD, several conditions unique to this population influence the risk for thrombosis. The mechanisms for increased coagulation are multifactorial. Patients with CKD are known to have increased levels of procoagulant factors.[4] Simultaneously, decreases in endogenous anticoagulants and fibrinolytic activity might occur.[5] Commonly used medications, such as erythropoietin stimulating agents, can also increase the risk of thromboembolism.[6]

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Thrombosis of vascular access can be increased depending on the location, graft material, surgical technique, and the patients' own coagulable state. The degree of hypercoagulability can increase as renal function declines, and continues to increase during concurrent anticoagulation therapy.[7,8]

In contrast, patients with CKD are also at increased risk of bleeding.[1,3] Platelets can become dysfunctional secondary to uremic-related toxin exposure and can have further adhesion defects as a result of shear wall stress alterations during hemodialysis.[9,10] Blood loss and lower hemoglobin values can be a concern for dialysis efficiency in addition to providing adequate tissue oxygenation in a population prone to anemia. This may be most critical in comorbid conditions such as asthma or coronary artery disease. Concurrent coagulopathy, secondary to hepatic dysfunction, can also alter elimination of selected anticoagulants, with dosing strategies in hepatorenal failure individualized to the patient's clinical presentation.

Treatment Versus Prophylaxis Dosing

In general, risk of drug accumulation and bleeding for renally eliminated anticoagulants in patients with CKD is higher with treatment doses compared with prophylactic doses, necessitating appropriate dosage adjustment and close monitoring when treating VTE. Prophylaxis using low-dose unfractionated heparin (UFH) at 5,000 units subcutaneously 3 times daily does not require any dose modifications in CKD; moreover, the presence of CKD is not a reason to avoid pharmacological thromboprophylaxis when indicated. Dosing of other agents becomes less clear, with consideration given sometimes to the reduction in the dose (Table 1). Data supporting the optimal prophylactic dose of low-molecular-weight heparins (LMWH), direct thrombin inhibitors, and fondaparinux in CKD are unclear, but potentially lower than that used in patients with a creatinine clearance (CrCl) over 30 mL/min. International normalized ratio (INR) target ranges with warfarin therapy do not require any adjustment solely because of the presence of CKD.

Selected Agents

Warfarin

Vitamin K antagonists including warfarin are typically used for long-term anticoagulation, and are hepatically eliminated, suggesting limited need to adjust dosage in renal failure. This class of anticoagulants reduces the hepatic-mediated vitamin K-related carboxylation to form activated clotting factors II, VII, IX, and X. In general, warfarin is eliminated hepatically using cytochrome P450 2C9. Renal dysfunction and uremia have the potential to modify the minor 2C19-mediated elimination, prolonging some of the effects of warfarin.[11] The risk of bleeding and thromboembolic complications is increased when using warfarin in the CKD population, and depends on the INR target, incidence of values outside of the target, or other comorbid conditions.[12] Therefore, warfarin dosing requirements tend to be lower as renal function declines.[12] Multiple factors including concurrent drug interactions and acute medical problems such as heart failure or infections warranting more frequent monitoring can influence the dose response initiation of warfarin.[13] INR should be measured by venipuncture before dialysis. However, other approaches may be considered to preserve venous access for patients in whom venipuncture is difficult or when venous preservation is desired. One comparative analysis of patients receiving warfarin noted that sampling from the arterial port 1 hour after initiation of dialysis yielded only slightly higher INR values (0.2 ± 0.2) compared with venipuncture.[14] Samples drawn from catheter lines locked with heparin, saline, or citrate can sometimes be hemodiluted resulting in spurious elevations in the INR. Because of the complexity of managing warfarin, and increased risk of adverse outcomes in the CKD setting, warfarin management should be deferred when possible to dedicated anticoagulation services.[15]

Heparin

UFH is a large, heterogeneous compound of approximately 45 saccharide units that indirectly binds to and increases the enzymatic activity of antithrombin (AT) against activated

Table 1. Suggested Dosing Adjustments of Parenteral Anticoagulants in CKD for VTE Treatment

Agent	Dosing in CKD	Comment
Unfractionated heparin	No adjustment necessary	Low antithrombin activity may affect dosing requirements.
Dalteparin	No adjustment for CrCl ≥20 mL/min	Dosing adjustment for CrCl <20 mL/min unclear.
Enoxaparin	CrCl >60 mL/min: no dose modification CrCl 30-60 mL/min: 25% dose reduction CrCl 20-30 mL/min: 50% dose reduction	Dosing adjustment for CrCl <20 mL/min unclear.
Tinzaparin	No adjustment for CrCl ≥20 mL/min	Adjustment for CrCl <20 mL/min unclear.
Fondaparinux	Contraindicated in CrCl <30 mL/min.	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/min per 30 mL/min decrease in CrCl has been suggested.
Bivalirudin	Eliminated enzymatically and renally; however, clearance relationship exists between CrCl and dose requirements. HIT and VTE dosing: CrCl >60 mL/min: 0.15 mg/kg/h CrCl 30-60 mL/min: 0.08-0.1 mg/kg/h CrCl <30 mL/min or hemodialysis: 0.03-0.05 mg/kg/h	Substantially removed during HD. Higher doses are used during cardiac interventional procedures with adjustment for renal dysfunction necessary.
Lepirudin	CrCl (mL/min) — Dose (mg/kg/h) >60 — 0.1-0.15 45-60 — 0.075 30-44 — 0.045 15-29 — 0.0225 <15 — 0.02 or less	Doses as low as 0.005 mg/kg/h have been used in renal failure requiring hemodialysis.

factors II and Xa through the active pentasaccharide unit. Because UFH is primarily metabolized in the liver and endothelium, little adjustment in the dose is necessary in the setting of CKD. In acute thromboembolic events, an intravenous (i.v.) bolus dose of up to 80 units/kg may be administered to rapidly reduce the activity of clotting factors that may in theory encourage expansion of an acute thrombosis. In the setting of acute coronary syndromes (ACSs), a lower bolus dose of 60 units/kg i.v. is typically used. In the absence of an emergent need for anticoagulation or high bleeding risk situations, such as in embolic strokes, the bolus dose may be omitted and just a continuous infusion may be initiated. This has the advantage of establishing anticoagulation more gradually, thereby limiting the risk of bleeding and removing the influences of the bolus on early (<6 hours) measures of intensity (ie, activated partial thromboplastin time, or aPTT) used to adjust the infusion rate. Initial UFH continuous infusion rates do not require special adjustment because of CKD alone and goal aPTT ranges should be targeted to the indication for anticoagulant therapy. If i.v. access is not available, weight adjusted subcutaneous (SC) UFH may be a suitable option.[16]

Low-Molecular Weight Heparin

Generally, UFH is the preferred option for initial parenteral anticoagulation in patients with CKD and VTE. However, an LMWH may be considered in selected situations such as no i.v. access, inability to monitor the aPTT, or desire to treat in the ambulatory setting. The LMWHs more specifically inhibit the activity of Xa, with lower affinity and effect on factor IIa. These agents are primarily eliminated renally and dosing adjustments are needed as renal function declines. The incidence of bleeding with LMWH varies, with higher rates observed in renal failure, especially when the dose was not adjusted for renal dysfunction.[17] For the LMWHs, most of the studies evaluating VTE treatment do not include the severe renal disease or hemodialysis populations. For dalteparin and tinzaparin,

dosing adjustments are not necessary when the estimated CrCl is >20 mL/min.[18] However, enoxaparin is more sensitive to renal dysfunction, requiring a dosing adjustment when the CrCl drops below 30 mL/min. Some authors have suggested a 25% reduction in the enoxaparin dose when used with CrCl levels of 30 to 60 mL/min, and a 50% reduction in dose in patients with severe renal insufficiency (CrCl <30 mL/min).[19] This would combine CKD stages IV and V into 1 dosing category. The data used to determine this are primarily driven by ACS trials involving short-term therapy with patients having serum creatinine measurements <2.5 mg/dL, but calculated CrCl <30 mL/min. The CKD stage V population was excluded from clinical trials. During hemodialysis, elimination may increase, and observed anti-Xa activity may drop when using high-flux membranes compared with low-flux.[20] Since discordance between anti-Xa activity and thrombin generation time has been reported,[21] questions have arisen as to the correlation between LMWH pharmacokinetics and pharmacodynamic response in patients receiving dialysis therapies As such, the dosing of enoxaparin when the CrCl is <20 mL/min, along with the other LMWHs, remains unclear.

Most of the data exploring the use of LMWH in the setting of CKD requiring hemodialysis focus on maintaining the dialysis circuit, with the LMWH being administered i.v. predialysis. Observations in this setting suggest that dalteparin doses of 39 units/kg in intermittent hemodialysis and 20 to 40 units/kg/h plus an initial load in continuous renal replacement therapy and enoxaparin (0.7 mg/kg and 3.5-4.2 mg/h for intermittent hemodialysis and continuous renal replacement therapy, respectively) may be effective in preventing thrombosis of the dialysis circuit.[22-24] Prolonged filter survival with the use of LMWH was observed in some reports, but not in other assessments.[22,23]

Fondaparinux

Fondaparinux is an anti-Xa-specific agent that is renally eliminated with a long elimination half-life requiring only once daily dosing. Fondaparinux is currently contraindicated in patients with a CrCl <30 mL/min.[25] Because of its small size, it does not have the same potential to cause heparin induced-thrombocytopenia (HIT) as UFH or LMWHs, and has actually been considered as an optional anticoagulant.[26] In the setting of HIT, fondaparinux may be considered in patients with CKD when direct thrombin inhibitors (DTIs) or warfarin therapy are not feasible options. The appropriate fondaparinux dose and frequency in such situations are unclear, and could range from once daily in mild renal impairment to every other day or longer dosing intervals in more severe renal dysfunction. No clear dose-response relationship between 2.5 to 10 mg has been observed in phase II trials for VTE or ACS, suggesting a lower dose may be an option.[27,28] A recent study in patients with a CrCl of 20 to 50 mL/min demonstrated that fondaparinux 1.5 mg once daily was effective and safe for prevention of VTE.[29] Another strategy is 2.5 mg every other day.[30] In hemodialysis patients, fondaparinux 0.05 mg/kg administered before each dialysis session provided adequate anticoagulation, but a significant increase in predialysis anti-Xa activity was demonstrated after only 9 consecutive hemodialysis sessions, indicating fondaparinux accumulation.[31]

In the setting of CKD, UFH or potentially LWMH are still preferred over fondaparinux for systemic anticoagulation, and DTIs are preferred in the presence of acute HIT. The decision to use fondaparinux in CKD will depend on an assessment of the risk of thrombosis and bleeding, and the ability to provide close monitoring and follow-up.

Direct Thrombin Inhibitors

In the setting of HIT or AT deficiency, DTIs may be options for anticoagulation. Currently, DTIs are only available in i.v. form and are administered either by continuous infusion or subcutaneous injection. The 3 DTIs commonly used are argatroban, bivalirudin, and lepirudin. Recognition of HIT in patients with CKD can sometimes be difficult secondary to lower baseline platelet counts. When a 50% drop in platelet count with current or recent heparin or LMWH therapy occurs, especially if unexpected clotting of the dialysis

apparatus occurs (which can occur before the 50% drop), HIT may be one of the considerations. Tools to diagnosis HIT have been previously reviewed, and this article will focus on anticoagulation management in the setting of CKD. The first goal in HIT management is to eliminate all exposure to heparin including heparin flushes and bathing the dialysis filter in heparin. Clinical trials for the DTIs did not recognize the effect of renal insufficiency, with current dosing recommendations influenced by postmarketing observations.[26]

Argatroban is hepatically eliminated, and it has been suggested that no adjustment in dosing is required for renal insufficiency or hemodialysis. In clinical trials, the mean doses in HIT was 1.6 μg/kg/min, targeting aPTT values 1.5 to 3 times control. Postmarketing observations of acutely ill patients with renal failure have suggested lower dosing requirements, with dose reductions of approximately 0.1 to 0.6 μg/kg/min noted for each 30 mL/min decrease in the CrCl.[32,33] In at least one observation, the mean argatroban dose to reach target ranges was 0.8 μg/kg/min with a CrCl <30 mL/min, 1.2 μg/kg/min if CrCl was 31 to 60 mL/min, and 2.2 μg/kg/min if the CrCl was above 60 mL/min.[33]

In comparison with argatroban and bivalirudin, lepirudin is the agent most dependent on renal elimination and requires significant dosing reductions as renal function declines. In the setting of hemodialysis, doses as low as 0.0025 mg/kg/h have been observed. Bivalirudin is primarily eliminated independent of renal function, with 80% removed enzymatically. It has also been observed to be removed through ultrafiltration.[34] Although not indicated in HIT, bivalirudin has been used secondary to the short elimination half-life, and rapid off set of activity. It is also commonly used in the setting of ACSs, and may require dosing reductions when used during interventional procedures and concurrent renal failure.[35] For patients with renal dysfunction and HIT, dose reductions have been suggested.[36] The extent depends on degree of renal insufficiency and form of renal replacement therapy. Because bivalirudin has the potential for enzymatic degradation through thrombin, it may not be an ideal agent to flush lines. Citrate, saline, or lepirudin may be used to maintain catheters.[34] The target aPTT for both lepirudin and bivalirudin is 1.5 to 2.5 times baseline, and argatroban is 1.5 to 3 times baseline, which may be different from the range specified for UFH.

In the setting of CKD, dosing adjustments during dialysis that lasts 3 to 4 hours are probably not necessary as any small reduction in DTI activity most likely will not create a sudden systemic thromboembolic event. In the setting of isolated HIT, where no thrombosis is present, the lower end of the aPTT range (1.5-2 times baseline aPTT) may be targeted to minimize bleeding risks. If there are problems with the dialysis circuit thrombosis during this time, the rate and potentially the target range may need to be increased. Otherwise, no dosing adjustments or aPTT measurements before dialysis are necessary.

Pipeline Anticoagulants

Several new anticoagulant agents could reach the market in the near future. The closest agents include the oral direct anti-Xa inhibitor rivaroxaban and the DTIs desirudin (which is administered subcutaneously) and oral dabigatran. All 3 agents are completely or partially eliminated through the kidneys and will require dosing modifications in renal insufficiency. The dose of these agents may additionally depend on the indication for anticoagulation and any modifications for CKD. All 3 agents have the potential to elevate the INR and aPTT, which may determine the presence of pharmacologic activity; however, their use to modify dosing, especially in CKD, is at present unknown.

Measuring Anti-Xa Activity

Monitoring the LMWH anti-Xa activity has been proposed for patients with CKD. The target therapeutic ranges may vary, depending on drug, indication, dosing strategies, and assay techniques. In general, the peak anti-Xa activity (4 hours after subcutaneous LMWH dose) should be approximately 0.5 to 1.1 IU/mL for treatment doses and 0.2 to 0.4 IU/mL for prophylactic dosing.[37] If there is a decision to measure anti-Xa activity to determine any potential drug accumulation, it should be noted that analysis with initial dose may not provide

accurate prediction of future results. In one assessment, the estimated half-life of enoxaparin on day 1 was 7.3 hours compared with 15.9 hours on day 4.[38] This does not appear to be the case with dalteparin.[39] In the hemodialysis (HD)-dependent patient, elimination of dalteparin appears to be faster than enoxaparin.[40] Only minimal difference in anti-Xa activity between the first and subsequent dalteparin doses was observed with dalteparin in CKD.[40-42]

The anti-Xa activity assay has been suggested as a means to adjust the indirect parenteral anticoagulants. Fondaparinux levels of 0.5 to 1.5 μg/mL for treatment and 0.2 to 0.4 μg/mL for prophylactic dosing have been demonstrated in clinical studies using anti-Xa activity assay, but the target therapeutic ranges are still to be determined.[37] Outcome data with the use of anti-Xa activity monitoring, especially in the CKD population, have not been reported. When interpreting results, it is important to know the method used, specifically if the addition of AT occurs in the test, which may influence results (higher anti-Xa activity values if AT is added as part of the test in patients with low AT levels).[43]

In patients with CKD receiving UFH, current information does not demonstrate improved patient outcomes when using the anti-Xa assay over the aPTT. When monitoring LMWHs, the anti-Xa assay has been suggested in the setting of renal failure to identify potential drug accumulation; however, benefits of this approach remain unknown. Although a linear relationship occurs for fondaparinux with anti-Xa, it is still unclear whether anti-Xa is an effective predictor of efficacy and safety. The other potential drawback of using anti-Xa analysis in the setting of renal failure is the omission of other factors affecting hemostasis that may become more dominant in CKD, such a plasminogen activator inhibitor, and clinician response to unexpectedly low or high values, especially given previous observations of large variability and limited correlation in renal insufficiency.[44,45]

Reversal of Anticoagulation

Patients with elevated INR values or concurrent bleeding when receiving an anticoagulant require assessment to determine what, if any, pharmacological reversal is indicated. If a single "very high" INR or aPTT is observed in the absence of any bleeding, a repeat value, preferably by phlebotomy, should be considered. Recent observations have suggested no benefit to reverse warfarin with INR values up to 10 in the absence of bleeding.[46,47] The results are unclear on equating their observations to the renal failure population where bleeding risks are higher. When there is bleeding, or an interventional procedure is planned, holding the anticoagulant would be the preferred choice. Warfarin can be reversed by vitamin K, but this can take a considerable amount of time.[46,48] Administration of low dose (0.25-2 mg) of vitamin K by slow i.v. infusion over 30 minutes will work a little faster than a slightly higher oral dose to reverse a supratherapeutic INR back into the target range.[48] The intramuscular (IM) or SC routes are not recommended and work slower as compared with the oral route.[49] Higher doses may be considered in the presence of a life-threatening bleed or the need to reverse INR values below 2. If more emergent hemostasis is necessary, additional agents including fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), or activated recombinant factor VII (rFVIIa) may also be considered.[50,51] Use of FFP can be a challenge in CKD secondary to the fluid load because doses of 15 mL/kg or more may be necessary. PCC and rFVIIa even in very small volumes potentially have a higher risk of precipitating thromboembolic events.[52,53] The half-life of these coagulation factors is shorter than warfarin, so administration of vitamin K in addition to coagulation factors in patients with hemorrhagic complications is warranted to prevent a rebound increase in the INR 12 to 24 hours after coagulation factor administration.[54]

UFH activity can be reversed by administering protamine (1 mg per 100 units of UFH). For patients receiving a continuous infusion, the dose of protamine should consider the UFH dose over at least the previous 2 hours. The benefit of using protamine to reverse LMWH is controversial, but administering 1 mg of protamine per 100 anti-Xa units of LMWH partially reverses their effects. Fondaparinux and DTIs lack a specific antidote; however, FFP,

PCCs, or rFVIIa may be considered for emergent hemostasis in life-threatening situations.

Conclusion

UFH remains the parenteral anticoagulant of choice for patients with CKD because of its short half-life, reliable monitoring, reversibility, and independence of renal elimination. Warfarin provides a safe oral alternative to UFH and does not require any significant dosing alteration because of CKD alone. LMWHs, fondaparinux, and DTIs may offer alternatives to UFH in patients with CKD; however, more studies are needed to determine safe and efficacious dosing and appropriate monitoring strategies before these agents can be routinely recommended. Newer anticoagulants may soon become available, but their role in patients with CKD will have to be determined through postmarketing studies.

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