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Editorial Comment

EDITORIAL COMMENT

Transplant candidacy and unscheduled emergent surgery—a neglected aspect in prescribing direct oral anticoagulants in patients receiving dialysis

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To the Editor,

We read with interest recent studies and reviews arguing for the use of direct oral anticoagulants (DOACs) in patients with end-stage kidney disease (ESKD) [1–3]. However, we see the need to point out the repeated omission of the special circumstances concerning transplant candidacy and management in case of unscheduled emergent surgery.

The use of DOACs has been extended to patients with ESKD and dialysis following the Food and Drug Administration's (FDA) approval of apixaban for this patient group with a neutral to favorable risk–benefit profile compared to vitamin K antagonists (VKA) [4]. If the European Medicines Agency (EMA) adopts this decision, a further increase in DOAC use is likely.

Problematically, ESKD patients are at increased risk for complications requiring emergency intervention and when waitlisted may be called in for kidney transplantation (KT) at any time. Current perioperative guidelines for DOAC use recommend a preoperative pause of at least 48 hours [5], which is not compatible with the unpredictable timing of KT, except in scheduled surgery for a living kidney donation. The elimination half-lives of factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) range between 9 and 14 hours in patients with a creatinine clearance above 30 ml/min, making a 48-hour pause typically sufficient to achieve clinically negligible concentrations of DOACs [5]. However, because patients with ESKD were not included in these studies, this recommendation cannot be reliably extrapolated to this population.

Although specific reversal agents have become available, their cost and unacceptable risk–benefit profile in patients without life-threatening conditions or major bleeding precludes their use in this setting. Moreover, bleeding with subsequent blood transfusions pose the risk of human leukocyte antigen (HLA) sensitization. Thus, consideration of a DOAC should include the effect on potentially necessary surgical interventions, especially KT, and their possibility to receive an organ. This issue has been insufficiently elucidated in recent articles [1–3].

In our experience, the current perspective on using DOACs in waitlisted patients is heavily based on center-specific opinions due to lack of standardization:

Opinion one: Not using DOACs in dialysis patients at all

Given the lack of a convincingly demonstrated benefit for antithrombotic therapy, the outlined additional risks in ESKD patients may preclude the use of DOACs in this patient population [6], especially when eligible for KT. This seems pragmatic at first, but is prescribing a VKA truly worth the additional risk of adverse events such as a procalcific effect with

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predisposition to calciphylaxis and unfavorable risk–benefit ratio? The number of positional statements and positive safety signals for the use of DOACs in ESKD and dialysis are increasing [1–4]; however, it should be noted that the EMA currently discommends the use of DOACs with estimated glomerular filtration rate (eGFR) < 15 ml/min. Alternatively, low-molecular weight heparin (LMWH) in between intermittent hemodialysis is a frequent practice pattern, yet has an even weaker foundation in evidence [7]. The necessity of anti-Xa-monitoring in ESKD is hampered by availability in the outpatient care and may increase the risk of over-anticoagulation. Nevertheless, LMWH may seem reasonable for patients requiring anticoagulation with a predicted waiting time of less than one year.

Opinion two: Using DOACs but eliminate them before surgery

Observational, pharmacokinetic data on DOACs suggest a low dialyzability in conventional hemodialysis (HD) with a high chance that drug levels remain in the therapeutic range even 12 hours after HD as demonstrated by Bosch et al. using a single dose of 2.5 and 5 mg apixaban [8]. The use of hemoadsorption techniques, such as the CytoSorb filter, in some transplant centers to eliminate DOACs before surgery is supported primarily by a retrospective case-control study including emergent cardiac surgeries, reporting a decrease in postoperative blood transfusions [9]. However, this approach is constrained by low availability, low cost-effectiveness, and lack of outcome data, and may not be applicable in the setting of true emergency surgery. Additionally, the management of elevated DOAC levels prior to KT is unclear, as the acute reversal of DOAC (that is, with andexanet alpha) is short-lasting, costly, and potentially increases the incidence of perioperative venous thromboembolism [10].

Opinion three: Using DOACs and operate after checking anti-Xa

DOAC-specific anti-Xa tests are calibrated and validated for each specific DOAC, but essays are not internationally standardized, and results can vary significantly between individuals [11]. A threshold <30 ng/ml for apixaban and rivaroxaban is considered reasonable for surgery. Heparin anti-Xa assays might be used as a screening test, cutoffs with 0.2 IU/ml for apixaban and 0.3 IU/ml for rivaroxaban have been discussed [12]. However, due to a lack of recommendations on perioperative management, relying on anti-Xa levels could lead to cancelled surgeries, prolonged cold ischemia time, rescue allocations, and in the worst-case loss of the offered organ. Given apixaban's shorter half-life with a twice-daily dosing regime, apixaban might be preferable in the perioperative setting. However, in hemodialysis patients, apixaban's half-life significantly increases at higher doses, ranging from 7.5 hours with 2.5 mg twice-daily to 17.4 hours with 5 mg twice-daily standard dosing [13]. For patients on the waitlist, the potential risks from standard dosing clearly outweigh any benefits and a reduced dosing regimen should be employed. A Bayesian tool to guide apixaban discontinuation prior to high-risk surgery has recently been developed [14]. However, this tool has not been validated in ESKD patients and its application would be challenging in the time-sensitive context of KT or other emergent surgeries.

Nevertheless, the use of DOACs may be preferable for patients with long expected waiting times and scheduled living-donor KT.

The above-mentioned considerations should not be limited to transplant candidacy and may be extended to ESKD patients at high risk for emergent surgical interventions. In life-threatening situations that necessitate urgent surgery, the prophylactic use of specific reversal agents and hemoadsorption may be warranted. However, it remains an open question whether alternative anticoagulation strategies might serve as a more effective and proactive choice in such cases.

Given this variety of center-specific opinions, the lack of uniformity in practice has become a significant concern—particularly as the use of DOACs is anticipated to rise in case of potential label extensions. Currently, anticoagulant use in patients awaiting KT is not grounded on robust research due to a paucity of data and lack of a perioperative monitoring strategy, warranting informed consent and thorough discussion with the patient. Thus, standardized management guidelines for anticoagulant use in patients with ESKD on the waiting list are urgently needed.

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CONFLICT OF INTEREST STATEMENT

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