RESEARCH LETTER

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TO THE EDITOR:

Perioperative management of apixaban in patients with advanced CKD undergoing a planned invasive procedure

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Oral anticoagulation therapy is used for both the prevention of stroke in atrial fibrillation (AF) and the treatment of venous thromboembolism (VTE). AF and VTE are both common among patients with chronic kidney disease (CKD).[1,2] Approximately 15% to 20% of patients on dialysis have AF.[3] CKD is consistently identified as a risk factor for bleeding, including anticoagulation-associated bleeding.[4] As a result, the prevention of AF/VTE-related morbidity in patients with CKD is difficult. There is growing interest in using apixaban in patients with kidney dysfunction due to its convenience and low dependence on renal elimination. Limited pharmacokinetic data have shown that patients with advanced CKD experience modest increases in apixaban area under the curve (AUC) plasma concentration-time values compared with patients with normal kidney function after a single dose.[5] Dialysis has little effect on apixaban levels.[6]

Up to 15% to 20% of patients on anticoagulation therapy require perioperative interruption of their therapy every year.[7] Interruption of apixaban in patients with advanced CKD can be challenging due to altered pharmacokinetics and delayed clearance.[8] There is no data to guide clinicians facing this situation. The perioperative management of direct oral anticoagulants (DOACs) in patients with advanced CKD was identified as an important area for future research by the American College of Chest Physicians.[7] We conducted a single-center, retrospective cohort study of consecutive apixaban-treated patients with advanced CKD who underwent a planned invasive procedure between June 2019 and March 2023, with the goal of describing the perioperative management of apixaban in this population and to determine the postoperative risks of major bleeding (MB), thromboembolism, and death. The study was approved by the Ottawa Health Science Network Research Ethics Board and was conducted according to the Declaration of Helsinki.

Patients were included if they were 1) anticoagulated with apixaban for any indication and at any dose, and 2) had advanced CKD (CrCl $\leq$ 30 mL/min based on the Cockcroft-Gault formula) or were undergoing dialysis for $\geq$3 months before the perioperative anticoagulation encounter. Patients with acute kidney injury were excluded.[9] A procedure was defined as "planned" when occurring $\geq$72 hours from the decision to proceed with an invasive intervention. Perioperative management of apixaban was at the discretion of the treating physician. Procedural bleed risk stratification was retrospectively assigned according to binary risk strata (low/moderate- vs high-bleed-risk), as recommended by the International Society on Thrombosis and Haemostasis (ISTH).[10] We recorded data on demographics, apixaban indication/dosing, renal function, procedure details, and perioperative management. Adjudicated clinical outcomes (G.H. and J.R.S.) included the 30-day postoperative risks of arterial thromboembolism (ATE), VTE, MB, clinically relevant non-major bleeding (CRNMB) and all-cause mortality. Surgical MB and CRNMB were defined using ISTH criteria[11-13]; thrombotic outcome definitions are outlined in supplemental Table 1. Continuous variables are summarized using median and interquartile

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Data are available upon reasonable request from the corresponding author, Joseph R. Shaw (josshaw@toh.ca).

The full-text version of this article contains a data supplement.

Table 1. Perioperative management, kidney function and dialysis status

Parameter			N = 60 (perioperative interruptions)
Perioperative management			
Procedure details	Setting, n (%)	Inpatient*	26 (43.3)
		Outpatient	34 (56.7)
	Bleeding risk†, n (%)	Low/moderate	22 (36.7)
		High	38 (63.3)
Perioperative consultation	Consultation setting, n (%)	In-person	40 (66.7)
		Virtual	20 (33.3)
	Thrombosis medicine consultation, n (%)		28 (46.7)
	Anesthesiology consultation, n (%)		46 (76.7)
	Specialist providing anticoagulation management advice, n (%)	Thrombosis	28 (46.7)
		Anesthesiology	32 (53.3)
Perioperative anticoagulation	Therapeutic bridging anticoagulation, n (%)		2 (3.3)
	Prophylactic LMWH, n (%)	Preoperative	1 (1.7)
		Postoperative	7 (11.7)
	Prophylactic UFH, n (%)	Preoperative	2 (3.3)
		Postoperative	4 (6.7)
	Prophylactic LMWH/UFH duration (d), median (IQR)	Preoperative	2 (1.3-3.5)
		Postoperative	3 (1.5-5)
	Alternative postoperative antithrombotic regimen implemented‡, n (%)		5 (8.3)
	Apixaban dose reduction recommended during perioperative consultation, n (%)		7 (11.7)
Kidney function and dialysis status			
Documented CKD or kidney failure§, n (%)			50 (83.3)
Creatinine‖ (umol/L), median (IQR)			197 (136-290)
Creatinine clearance‖,¶ (mL/min), median (IQR)			24 (19-27)
Dialysis anticipated within 6 months, n (%)			11 (18.3)
Dialysis#, n (%)			5 (8.3)

LMWH, low-molecular-weight-heparin; UFH, unfractionated heparin.

*A procedure was designated as occurring on an inpatient basis when a patient was admitted to hospital for at least an overnight stay.

†According to ISTH Perioperative and Critical Care Scientific and Standardization Committee Procedural/Surgical Bleed Risk stratification.

‡Two patients were maintained on long term prophylactic UFH, 1 was switched to warfarin, 1 was switched to edoxaban 30 mg once daily, and 1 patient had their apixaban discontinued and was replaced with aspirin 81 mg once daily.

§Documented diagnosis of CKD or kidney failure within 6 months preceding the perioperative encounter in question. Specific nephrology diagnoses included polycystic kidney disease (n = 5), ischemic nephropathy (n = 5), diabetic nephropathy (n = 4), focal segmental glomerulonephritis (n = 3), C3 glomerulonephritis (n = 2), IgA nephropathy (n = 1) and amyloidosis (n = 1).

‖ Excluding patients undergoing dialysis (n = 55). Creatinine conversion to mg/dL = μmol per liter/88.4.

¶Creatinine clearance estimated using Cockcroft-Gault formula.

#Three patients were receiving intermittent hemodialysis and 2 were receiving peritoneal dialysis.

range (IQR) and categorical variables as frequencies and proportions. The 30-day risks of clinical outcomes are reported as proportions (on a per-interruption basis) with corresponding 95% confidence intervals (CIs) using the method of Agresti-Coull (optimized coverage probability of the 95% CI) or the "rule of three" for null outcome values.[14,15] Anticoagulation interruption/resumption intervals were compared across bleed risk strata using the Mann-Whitney *U* test. Analyses were conducted using SAS Version 9.4 (Cary, NC).

We screened 5776 encounters and identified 60 perioperative interruptions meeting eligibility among 49 apixaban-treated patients with advanced CKD (supplemental Figure 1). The median age of patients was 80 years (IQR, 73-85), median weight was 70.4 kg (IQR, 55.7-82.5), and 51.0% (25/49) were male. The indication for anticoagulation was AF for most patients (41/49; 83.7%) and VTE for the remainder; median CHA_2DS_2-VASc score for AF patients was 5 (IQR, 4-5). Most patients were receiving reduced-dose apixaban (2.5 mg orally twice daily) at the time of the interruption (48/60; 80.0%). Only 69.0% of patients with AF receiving reduced-dose apixaban at the time of the interruption (29/42) met criteria for dose reduction.[16] Four patients were receiving concurrent antiplatelet therapy, and 15 were receiving moderate CYP3A4 inhibitors. Data related to perioperative management and kidney function are provided in Table 1. Most procedures (63.3%) were stratified as high-bleed-risk. Common procedure types included urologic (25.0%), vascular (21.7%), and interventional radiology (15.0%) procedures (supplemental Table 2); 11 interruptions involved neuraxial anesthesia. Median CrCl was 24 mL/min (IQR, 19-27) and over a quarter (26.7%) of patients were either undergoing dialysis at the time of the interruption (n = 5) or dialysis was anticipated within 6 months (n = 11). Apixaban interruption/resumption intervals are reported in Figure 1. The median apixaban interruption interval was 84 hours (IQR 60-84) for both low- and high-bleed-risk procedures. We identified 4 MB events (only 2 of which were directly attributable to surgery), corresponding to a 30-day risk of MB of 6.7% (95% CI, 2.2-16.4). Details surrounding MB events are presented in supplemental Table 3. We identified 2 CRNMB events, corresponding to a 30-day risk of 3.3% (95% CI, 0.3-12.0). None of the interruptions were associated with ATE or VTE (30-day risk of 0%; 95% CI, 0-5.0). Three patients experienced type 2 myocardial infarctions (supplemental Table 1) within 30 days, and 1 patient died on postoperative day 10 (toxic megacolon). Apixaban levels (STA-Apixaban; Diagnostica Stago, Asnières-sur-Seine, France) were measured to guide interruption in 3 cases and were within anticipated trough range based on dosing and interval since last intake.

We present novel data on apixaban-treated patients with advanced CKD who underwent a planned invasive procedure. Interruptions were over twice as long for patients undergoing a low-bleed-risk procedure as compared with a recent perioperative DOAC management study (84 hours vs ~39 hours, PAUSE study[17]), and longer than guideline-recommended intervals.[7] This could have been due to perceived delayed apixaban clearance in patients with kidney dysfunction. As expected, patients with CKD were at risk of bleeding complications on anticoagulation. On the other hand, we observed only 2 MB events felt to be directly related to surgery (3.3%), corresponding to a risk of MB similar to that observed among warfarin- or DOAC-treated patients when best practices are followed (~ 1%-3%).[17,18] We did not observe any postoperative ATE or VTE. The interruption intervals observed in this study equate to holding apixaban for 1 to 2 additional days before a procedure compared to guideline-recommended practice. Our

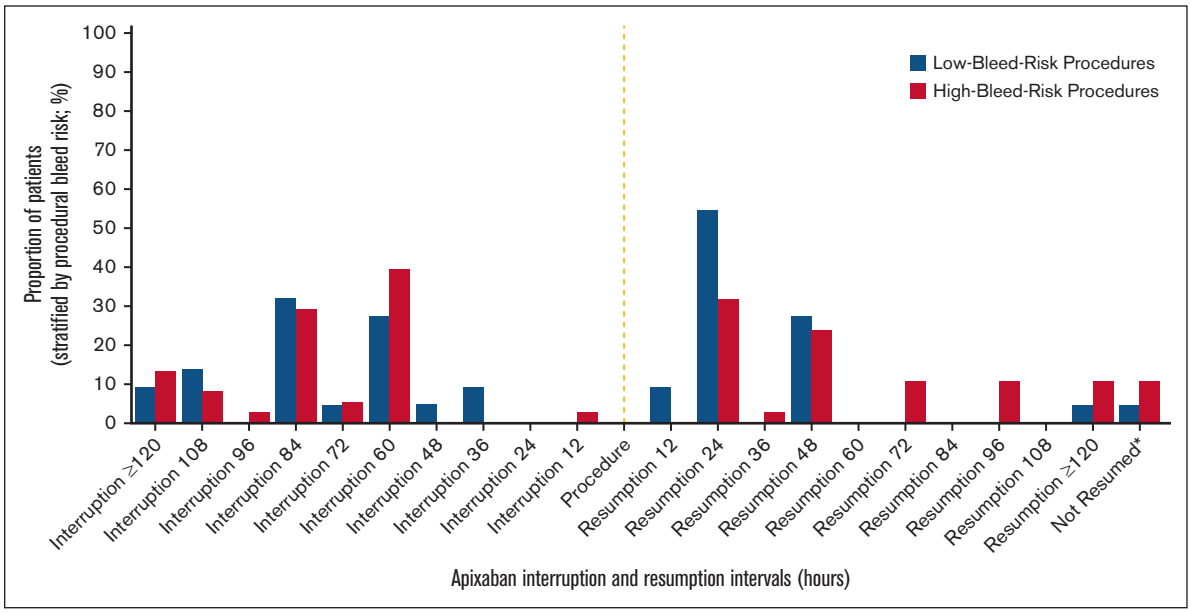

Figure 1. Perioperative apixaban management in patients with advanced chronic kidney disease. Apixaban interruption and resumption intervals in hours, stratified according to procedural bleed risk. Intervals represent the time between last dose of apixaban before the procedure and the procedure itself, approximated to the nearest 12 hours. Apixaban was not resumed after the procedure for 1 patient undergoing a low-bleed-risk procedure and 4 patients undergoing high-bleed-risk procedures. The median interruption and resumption intervals for patients undergoing low/moderate-bleed-risk procedures was 84 hours (IQR 60-84) and 24 hours (IQR 24-48), respectively. The median interruption and resumption intervals for high-bleed-risk procedures was 84 hours (IQR 60-84) and 48 hours (IQR 24-72), respectively. Interruption intervals were not significantly different according to procedural bleed risk ($P = 0.38$), but patients who had undergone a high-bleed-risk procedure had significantly longer resumption intervals ($P = 0.0037$).

results, although preliminary, are reassuring and seem to indicate that planned procedures can be undertaken in this patient population without undue risk of bleeding or thrombosis, provided anticoagulation is managed carefully.

Patients in this study had significant renal dysfunction, with CrCl values well below those described in the PAUSE study.[17] Most patients were receiving reduced-dose apixaban despite only two-thirds meeting criteria for dose reduction. Perioperative consultants often recommended apixaban dose reduction or rotation to a different anticoagulant. Preoperative interruption intervals in this study were similar for low- and high-bleed-risk procedures. Taken together, these findings suggest physicians were apprehensive about perioperative apixaban use in patients with advanced CKD and placed greater emphasis on kidney dysfunction than procedural bleed risk when deciding on an interruption interval.

Limitations of this study include its retrospective design with resulting potential for information bias, as well as a small sample size which leads to wide CIs and uncertainty surrounding risk estimates. Little information was available on residual apixaban levels, as few patients had a level drawn. Nonetheless, our findings provide preliminary but important data on apixaban-treated patients with advanced CKD undergoing invasive procedures.

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Contribution: J.R.S. conceptualized the study; K.D., M.C., and J.R.S. developed the methodology; G.H., K.D., and J.R.S. conducted the investigation; J.R.S. provided supervision; G.H. and J.R.S. wrote the original draft of the manuscript; and G.H., K.D., D.I.M., M.M.S., E.C., J.D., M.C., and J.R.S. reviewed and edited the manuscript.

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