Outcomes of Early Surgical Intervention in Geriatric Proximal Femur Fractures Among Patients Receiving Direct Oral Anticoagulation

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Objective: To evaluate the prehospital use of direct oral anticoagulant (DOAC) agents on the outcomes of early surgical fixation of a geriatric hip fracture.

Design: Case control study.

Setting: Two academic Level 1 trauma centers.

Intervention: Early (<48 h) surgical fixation of a geriatric proximal femur fracture.

Patients: Nineteen patients receiving Pradaxa (dabigatran), Eliquis (apixaban), or Xarelto (rivaroxaban) who underwent surgery between 2010 and 2015 and 74 control patients.

Main Outcome Measurements: Time to surgery, transfusion rates, changes in hemoglobin levels, postoperative complications, readmission rates, and survival out to 1 year.

Results: There were no differences in transfusions, changes in hemoglobin levels, wound complications, or survival at any time point. Patients on DOAC had a longer delay to reach the operating room (28.9 h v 21.4 h $P = 0.03$) and were more likely to undergo readmission within 30 days (21% vs. 5.3% $P = 0.05$). No readmissions occurred for a complication of the surgical site, bleeding, or a venous thromboembolic event.

Conclusions: Geriatric patients with hip fractures receiving DOAC before admission did not demonstrate worse outcomes with early surgical intervention. The increased readmission rate in this population seems attributable to the underlying cardiac conditions for which the patients were receiving anticoagulation. These results suggest that the delay recommended for patients using a DOAC before elective procedures may be unwarranted in the surgically urgent setting of a hip fracture. Additional studies will be necessary for appropriate meta-analysis.

Key Words: hip fracture, geriatric, direct oral anticoagulation, apixaban, Eliquis, rivaroxaban, Xarelto, dabigatran, Pradaxa

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

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BACKGROUND

Pradaxa (dabigatran)[1] was introduced into Europe in 2008 and approved for use in the United States in 2010, with multiple additional direct oral anticoagulants (DOAC) approved since, including Eliquis (apixaban),[2] Xarelto (rivaroxaban),[3] and Savaysa (edoxaban).[4] Xarelto, Eliquis, and Savaysa are direct inhibitors of factor Xa, whereas Pradaxa directly targets thrombin (factor IIa).[5] These medications are attractive to providers and patients alike, given their wide range of safety, rapid onset, and limited drug interactions—allowing for administration at fixed doses without routine monitoring.[6] Because the use of DOAC agents is increasing for a myriad of medical indications and the population of geriatric hip fracture patients is increasing at an exponential rate, the number of patients presenting while on these medications will likely increase dramatically over the next few years.

Unlike warfarin, pharmacologic methods of assessing DOAC activity are not reliable, and reversal cannot occur with administration of fresh frozen plasma, vitamin K, or platelets.[7] A reversal agent has been developed for Pradaxa,[8] but cost is prohibitive; there are no known reversal agents for any of the oral Xa inhibitors (Table 1). These medications have discontinuation guidelines before elective surgery with major bleeding risks,[1–4] but there are no guidelines for discontinuation before urgent surgical intervention, and there are no definitive time recommendations for delay to surgery. Previous studies have examined the outcomes of patients undergoing surgical intervention for a hip fracture while receiving aspirin, clopidogrel, and warfarin[10–15]; clopidogrel in particular also has no reversal agent and previously had recommendations to wait 5 days before urgent surgery.[16,17]

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TABLE 1. DOAC Properties[1–4]

	Half-Life	Target	Elimination	Recommended Drug Holiday Before Elective Surgical Procedures With High Bleeding Risk
Pradaxa (dabigatran)	12–14 h	Thrombin (factor IIa)	80% Renal 20% Hepatobiliary	1–2 d (CR_{CL} >50 mL/min) 3–5 d (CR_{CL} <30 mL/min)
Xarelto (rivaroxaban)	5–13 h	Factor Xa	66% Renal 28% Hepatobilliary	≥24 h
Savaysa (edoxaban)	6–11 h	Factor Xa	35% Renal 65% Hepatobilliary	≥24 h
Eliquis (apixaban)	8–15 h	Factor Xa	25% Renal 75% Hepatobiliary	≥48 h

Because large series of hip fracture patients have demonstrated decreased mortality associated with early surgical intervention at less than 48 hours, we sought to determine whether a difference in mortality and complications occurred when early surgery (<48 Hours) was performed in patients on a DOAC. It was theorized that there would be no difference in perioperative complications, bleeding risk, or mortality when comparing patients with early surgery, with or without a DOAC.

PATIENTS AND METHODS

After institutional review board approval, surgical, and billing records were searched from 2010–2015 to identify all patients between the ages 60 and 89 years who underwent surgical fixation of a geriatric hip fracture (OTA 31A or 31B)[9] within 48 hours of admission at 1 of 2 academic level 1 trauma centers. Admission records were queried to identify those patients whose medications included Xarelto, Pradaxa, Eliquis, or Savaysa before their admission. For each patient of interest, 4 additional control patients were identified. To allow for best evaluation of bleeding risk of early surgery through DOAC agents, patients were not included in the control group if their home medications were found to include Plavix, Coumadin, or greater than 81 mg of daily aspirin. Controls were matched to sex and construct: hemiarthroplasty, cephalomedullary nail (CMN), or sliding hip screw. Within these constraints, controls were age matched as closely as possible, with 92% (70/76) controls within 3 years of their intended match. The largest discrepancies (8 years) were accepted to accommodate a sliding hip screw, this construct being rare in an elderly patient population. Similarly, short CMNs were rarely used on patients not using Coumadin, Plavix, or a DOAC agent. To accommodate this, sex- and age-matched long CMN controls were identified, and estimated blood loss (EBL) and surgical time were adjusted based on reported differences.[18]

Medical records and radiographs were reviewed for injury patterns, demographics, home medications and compliance, admission and serial inpatient laboratory values, hospital and surgical courses, re-operation and readmission rates to 30 days, and survival out to 1 year. After reviewing medication compliance, patients who had discontinued DOAC agents >48 h before admission were excluded from analysis of perioperative bleeding factors (EBL, transfusion rate, and changes in hemoglobin levels). These patients were included in postoperative complication, readmission, reoperation, and survivorship analysis. Patients without a record of care before this hospitalization who were released to *pro re nata* at follow-up at an outpatient visit were excluded from analysis of survival at subsequent time points. All outcome analyses were repeated on construct-matched subgroups.

Analysis was performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Continuous variables were compared with independent samples *t* testing, and categorical variables were analyzed with χ^2 testing. The Fisher exact test was used when expected counts were less than 5. Statistical significance was defined as $P < 0.05$.

RESULTS

Nineteen patients were identified to be prescribed a DOAC before admission; 6 were taking Xarelto, 5 Eliquis,

TABLE 2. Sex, MOI, OTA Classifications, and Construct

	DOAC		Control	
Sex	8 F	11 M	32 F	44 M
MOI				
GLF	17	89.5%	69	90.8%
Fall >1 m	1	5.3%	6	7.9%
Other	1	5.3%	1	1.3%
OTA Class				
31 A1	4	21.1%	13	17.1%
31 A2	7	36.8%	23	30.3%
31 A3	2	10.5%	15	19.7%
31 B1	0	0.0%	1	1.3%
31 B2	4	21.1%	10	13.2%
31 B3	2	10.5%	11	14.5%
32 A1	0	0.0%	2	2.6%
31 C1	0	0.0%	1	1.3%
Hemiarthroplasty	5	26.3%	20	26.3%
Long CMN	9	47.4%	47	61.8%
Short CMN	4	21.1%	5	6.6%
SHS	1	5.3%	4	5.3%

MOI, mechanism of injury.

and 8 Pradaxa. No patients were identified to be taking Savaysa. Demographics are summarized in Table 2. One 81-year-old woman in the DOAC group sustained a spontaneous OTA 31-B2 fracture without inciting mechanism or identified underlying pathology. One 77-year-old male control patient was hit by a golf cart at low speed and sustained an OTA 31-A1–type fracture. Otherwise all patients sustained ground-level falls or falls from height <6 m such as a stepladder or a staircase.

Age-adjusted Charleston comorbidity scores were not significantly different, nor were admission laboratory values, including hemoglobin, creatinine, INR, partial thromboplastin times, or prothrombin times (Table 3). The DOAC group had significantly higher American Society of Anesthesiologist's physical status classification scores ($P = 0.02$). Three patients had discontinued their DOAC agent >48 h before admission, and these were excluded from analysis of perioperative bleeding factors as well as time-to-surgery and intraoperative time. One patient had been planning for a dental procedure, and 2 others admitted to noncompliance. The remainder of patients had received a DOAC agent between 7 and 41 hours before admission. Four patients had reported and documented ingestion within 48 hours before admission, and the remainder had neither documentation of the most recent dose nor any suggestion of noncompliance with their prescribed regimen. The average estimated time between the most recent ingestion and surgery was 39.5 h (SD 14.7). The shortest documented time from DOAC ingestion to surgery was 18 hours with Eliquis.

One DOAC patient and 3 control patients received spinal anesthesia as an adjunct to general endotracheal anesthesia. The DOAC patient received this at 29 hours from his most recent dose of Xarelto. One control patient received spinal anesthesia with MAC sedation. Otherwise all patients underwent general endotracheal anesthesia without adjuncts. With respect to perioperative bleeding, there were no significant differences identified between groups in EBL, transfusion rates, or the volume of blood transfused to patients requiring transfusion (Table 4, Fig. 1). This remained true when adjusting for known differences in EBL between short and long CMNs and on construct-based subgroup analysis (see **Appendix**, **Supplemental Digital Content 1**, http://links.lww.com/JOT/A319). There were no significant differences identified in the change in hemoglobin levels between admission and postoperative day 1 (ΔHb to POD1) or between admission and discharge (ΔHb to DC). No patients in the DOAC group required either fresh frozen plasma or platelets.

Patients receiving DOAC within 48 hours of admission had a significantly longer time to surgery compared with the control group (28.9 h vs. 21.4 h, $P = 0.03$). There were no significant differences in surgical time, length of stay, or rates of perioperative complications, including hematoma formation, persistent serous drainage, thromboembolic events, or need for reoperation (Table 4). Patients in the DOAC group were readmitted at a significantly higher rate compared with the control group (21% vs. 5.3% $P = 0.05$). There were no significant differences in documented survival between groups at 30 days,

TABLE 4. Perioperative Metrics and Postoperative Outcomes

	DOAC		Control		
	Mean	**SD**	**Mean**	**SD**	***P***
Perioperative Metrics					
EBL (mL)	218.8	125.0	199.0	163.4	0.66
EBL (mL, adj)	218.8	125.0	191.4	167.0	0.54
ΔHb to POD1 (g/dL)	−2.7	0.9	−2.7	1.8	0.98
ΔHb to DC (g/dL)	−3.2	1.4	−3.0	2.0	0.70
Transfusion rate	6/16	37.5%	25/64	39.1%	1.00
Transfusion rate (adj)	6/16	37.5%	24/64	37.5%	1.00
Units RBC/patient	0.63	0.90	0.87	1.40	0.48
mL/transfusion	546	168	754	481	0.31
Units RBC transfused	1.9	1.2	2.3	1.4	0.56
Surgery time (min)	82.7	37.9	93.5	44.2	0.37
Surgery time (min, adj)	82.3	35.7	88.2	42.5	0.61
Time to surgery (h)	28.9	11.8	21.4	12.4	0.03
Postoperative outcomes					
LOS	8.5	4.7046	6.719	3.1596	0.07
Hematoma	0/19	0%	3/76	3.9%	0.51
Persistent serous	2/19	10.5%	4/76	5.3%	0.56
DVT	0/19	0%	1/76	1.3%	0.80
In-patient mortality	0/19	0%	1/76	1.3%	0.80
Readmission	4/19	21.1%	4/75	5.3%	0.05
Reoperation	0/19	0%	1/76	1.3%	0.80
30-d survival	18/19	94.7%	64/76	84.0%	0.21
90-d survival	15/18	83.3%	53/71	77.9%	0.33
1-y survival	12/17	70.6%	39/66	59.1%	0.28

Fields identified with (adj) have adjusted EBL and surgical times to account for a mismatch between short CMN DOAC patients age-sex–matched long CMN controls. Perioperative metrics do not include the 3 patients identified to have been noncompliant with their DOAC before admission or their matched controls. mL/transfusion represents total volume transfused only among patients who received transfusions. Postoperative outcomes data represent all 19 DOAC using patients and matched controls. Patients released to PRN follow-up were excluded from analysis of subsequent survival time points.

TABLE 3. Age, Presenting Laboratory Values, and Comorbidity Scales: ASA and AACCI

	Mean	**SD**	**Mean**	**SD**	***P***
	DOAC		Control		
Age	78.2	7.9	77.8	7.6	0.85
PT (s)	14.2	3.6	13.5	2.0	0.44
PTT (s)	30.7	7.4	27.8	4.5	0.14
INR	1.2	0.3	1.1	0.1	0.11
Hb (g/dL)	12.6	1.5	12.1	1.9	0.28

	Median	**IQR**	**Range**	**Median**	**IQR**	**Range**	***P***
ASA	3	3–3	2–4	3	2–3	1–4	0.02
AACCI	5	4–7	3–9	5	4–6	2–11	0.30

ASA, American Society of Anesthesiologist Physical Status Classification; AACCI, age-adjusted Charlson comorbidity index; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; Hb, hemoglobin.

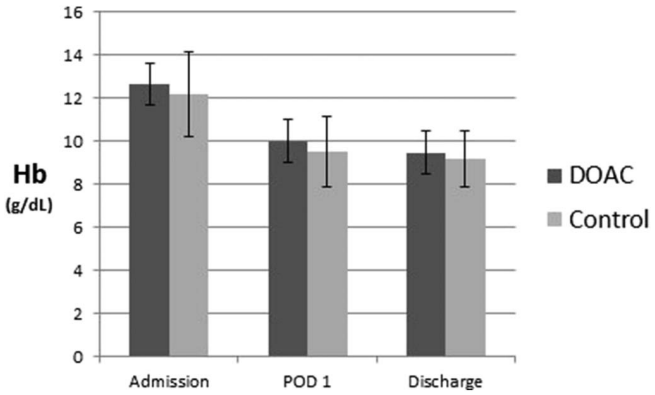

FIGURE 1. Hemoglobin levels over time.

90 days, or at 1 year. Documented survival at 1 year was 70.6% in the DOAC group and 59.1% among controls. Additional patients may have transitioned care to a local provider.

DISCUSSION

The results of this study suggest that early surgery (<48 hours) may be safe and effective in geriatric hip fracture patients presenting on a DOAC. No differences were found between groups with regard to bleeding risk, wound complications, in-hospital mortality, or survival to 1 year postinjury. Given the rapid metabolism and excretion of these agents requiring daily or twice daily dosing for maintenance of anticoagulation, it is unsurprising that intraoperative blood loss would be similar to patients without preoperative anticoagulation and that postoperative complications would not be increased relative to a control population on a postoperative DVT chemoprophylaxis regimen. Many studies have shown safety of DOAC agents as a regimen for postoperative DVT prophylaxis in major joint surgery.

Patients receiving DOAC within 48 hours before admission had longer time to surgery than those not on anticoagulation (28.9 h vs. 21.4 h, $P = 0.03$), which likely reflects the increased need for coordination and discussion between internists, anesthesiologists, and orthopaedic surgeons regarding medical clearance in the setting of a DOAC. Tran et al[15] reported a case-control study in 2015 on anticoagulated hip fracture patients, including a subgroup of 27 patients receiving DOAC before admission. In their report, these patients experienced the longest time to surgery at 67 hours compared with the control population at 26 hours. Tran attributed the longer delays to uncertainty in managing DOAC agents in these patients. At our institutions, these patients undergo surgical fixation as soon as medically cleared to avoid the complications associated with delays to surgery in geriatric hip fracture patients.

Previous reports by Moran et al and Zuckerman et al have established that delays to hip fracture surgery of more than 48 hours are associated with increased patient mortality.[19,20] Because our results demonstrate no difference with regard to perioperative complications, bleeding risk, or mortality between groups, the FDA recommendation to delay surgery by even 1 or 2 days in the presence of DOACs does not seem to be substantiated in urgent hip fracture surgery. A significant difference in readmission between the 2 groups was identified, but all of DOAC readmissions were unrelated to the hip fracture surgical site and likely reflect the additional cardiac, pulmonary, and cerebrovascular medical comorbidities present in the DOAC population. Specifically, the DOAC patients were readmitted for the diagnoses of a transient ischemic attack, a peridiverticular abscess, chest pain with a negative acute coronary syndrome work-up, and symptomatic atrial fibrillation with a rapid ventricular rate.

A major limitation to this study is its sample size. The 19 patients identified represent 2.4% of all the patients reviewed who underwent surgery within 48 hours in the reviewed time period. At the current power, this study can detect large differences between groups, but is unable to assert the significance of small differences between groups or reliably report on the frequencies of rare occurrences such as in-hospital mortality or venous thromboembolism. There exists an overt institutional preference at both centers toward long CMNs for intertrochanteric femur fractures, potentially limiting the external validity of the data of these conclusions. Another limitation is the retrospective nature of this study. Future prospective studies and meta-analyses involving a larger number of patients are necessary to corroborate the results of this initial report. Strengths to this study include its multicenter patient population, which allows for increased external validity, as well as a high rate of follow-up of patients in the DOAC group. To our knowledge, this is the first study to examine the outcomes of early intervention in this group.

In conclusion, geriatric patients with hip fractures receiving DOACs before admission did not experience increases in bleeding, need for transfusion, perioperative complications, or mortality. Given the known increases in mortality from delays to surgery beyond 48 hours, it seems reasonable to consider early intervention in this population rather than strict adherence to guidelines established for elective procedures. Further studies are necessary to confirm the results of this initial report.

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