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Delayed time to emergency hip surgery in patients taking oral anticoagulants

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ABSTRACT

Introduction: Surgical intervention within 48 h of admission in patients with acute hip fractures has been associated to lower morbidity and mortality. Patients anticoagulated with vitamin K antagonists (VKAs) have longer time to corrective surgery than those not anticoagulated. Sparse data exists on time to surgery (TTS) in patients taking direct oral anticoagulants (DOACs). The aim of this study is to establish TTS among non-anticoagulated and anticoagulated patients taking either VKA or DOAC.

Materials and methods: We conducted a retrospective cohort study of consecutive patients admitted with acute hip fracture between July 1, 2016 and December 31, 2017. Patient-, anticoagulant- and surgery-related characteristics were collected. The primary outcome was TTS calculated from time of admission. Median TTS with interquartile range (IQR) was compared among 3 groups of patients: DOAC, VKA and No OAC.

Results: A total of 472 patients were included: 12.5% (59/472) were anticoagulated (28/472 on VKAs and 31/472 on DOACs). Median TTS was longer in the VKA group [64 h (IQR: 50–84)] and in the DOAC group [(61 h; IQR: 42 to 77)] versus the No OAC group [44 h (IQR: 28–63), $p = 0.0006$ and $p = 0.003$ respectively]. There was no significant difference in median TTS in the VKA group versus the DOAC group ($p = 0.6396$).

Conclusion: Patients taking either VKA or DOAC have significant delays to emergency hip fracture surgery compared to those not anticoagulated. Future studies aimed at examining this relationship more closely are warranted. In the meantime, an action plan aimed at early identification and appropriate management of anticoagulation in this vulnerable group of patients is necessary.

1. Introduction

Hip fractures are a significant public health issue [1]. Data from Osteoporosis Canada estimated that the total number of hip fractures in Canada in 2018 was 30,000 with associated costs exceeding $2.3 billion; these numbers are projected to steadily increase over time [2,3]. Early surgical intervention, within 48 h of admission, is associated with lower morbidity and mortality and is considered best practice [1,3]. In Canada, only 66% of all patients with acute hip fracture proceed to surgery within this timeframe [4], indicating the existence of certain barriers to achieving this ideal benchmark. Additional barriers to timely surgery are expected in patients treated with anticoagulants, as an appropriate washout period is required to mitigate perioperative bleeding risks. Despite the availability of an effective reversal agent, recent observational studies have shown that patients taking vitamin K antagonists (VKAs) have longer time to surgery than those not anticoagulated [5–8]. Direct oral anticoagulants (DOACs) largely have no readily available antidote in the preoperative setting and thus, we hypothesize that they may be associated with further increased surgical delays.

Between 2008 and 2014, the total number of oral anticoagulant (OAC) prescriptions in Canada rose from approximately 4.8 to 7 million, while the proportion of VKA prescriptions decreased from 99 to 67%, suggesting a rapid increase in DOAC use [9]. There is currently sparse data on the relationship between DOACs and time to emergency surgery (TTS) among patients who present with hip fractures [10–12].

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In these studies, albeit very few in numbers, patients on DOACs experienced delays to surgery ranging from 29 to 67 h compared to 12 to 25 h in those who were not anticoagulated.

The aim of this study is to determine TTS among non-anticoagulated patients and anticoagulated patients presenting to the Emergency Department (ED) with a hip fracture, further discerned by class of oral anticoagulant.

2. Material and methods

We conducted a retrospective cohort study of consecutive patients with an admission diagnosis of hip fracture requiring surgical repair presenting to the ED of the Jewish General Hospital (JGH) between July 1, 2016 and December 31, 2017. The JGH is a 637 bed tertiary care hospital center in Montreal, Canada that admits approximately 550 patients with hip fracture annually. Patients were included if they were 18 years of age or older, diagnosed with acute hip fracture, and admitted for surgical repair. Patients were excluded if they did not undergo surgical hip fracture repair during the index hospitalization, if they were transferred from or to another hospital, if they already had a hip surgery during study period or if they required additional surgical interventions. No patients were included more than once into the study cohort.

Data were collected from the electronic medical record (EMRs) starting from ED presentation until hospital discharge. Baseline patient characteristics included age, patient sex, creatinine clearance (calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation), hemoglobin and platelet count on ED presentation, indication for anticoagulation for the anticoagulated groups, antiplatelet use, and American Society of Anesthesia (ASA) classification. Information concerning preoperative DOAC and VKA use was collected (molecule, dose, frequency of administration for DOAC and International Normalized Ratio (INR) for VKA), as well as perioperative use of reversal and/or hemostatic agents (Prothrombin Complex Concentrate (PCC), vitamin K, Idarucizumab and/or plasma). Exact timing of last anticoagulant dose was not consistently available in patients' EMRs and therefore not included in results. Surgery-related characteristics included date of ED presentation, date and time (either daytime, evening, or overnight, defined as 08:00–16:00, 16:00–24:00, and 00:00–08:00, respectively) of hospital admission, date and time of surgery, type of surgery, pre- and postoperative medical consultations (either Internal Medicine or Thrombosis/Hematology), and hospital discharge date.

The primary outcome of TTS was defined as time from hospital admission to time of surgery and reported in hours. Secondary outcomes included length of hospital stay, defined as time from admission to discharge and reported in days; acute venous thromboembolism (VTE) including distal and proximal lower limb deep vein thrombosis (DVT) on venous duplex study and/or pulmonary embolism (PE) on computed tomographic (CT) pulmonary angiography and/or ventilation-perfusion scan; stroke, documented as a clinical diagnosis by a neurologist and/or compatible radiological findings on CT head; any major bleeding, as defined by the International Society on Thrombosis and Hemostasis (ISTH) [13], encompassing the period from ED presentation to hospital discharge including surgical bleeding; preoperative major bleeding, as defined by ISTH, encompassing the period from ED presentation to the time of surgery not including surgical bleeding; packed red blood cell (pRBC) transfusions from ED presentation to discharge; and death, which was ascertained by the presence of a death certificate. All components of the primary and secondary outcomes data were adjudicated.

Data was analyzed using SAS/STAT® software. Simple descriptive statistics (means with standard deviation (SD) and/or proportions, and medians with minimum and maximum values) were used to summarize patient, anticoagulant and surgical characteristics of the cohort separated into three groups depending on anticoagulation type and status: VKA group, DOAC group, and No OAC group. TTS was reported as a continuous variable (hours). Median TTS with interquartile range (IQR) was established for each group. Median TTS was compared among the DOAC, VKA and No OAC groups using Mann Whitney to detect significant differences with p-value ≤ 0.05. Kaplan-Meier analyses were performed to further define delays to surgery according to anticoagulant group. Statistically significant differences in secondary outcomes were detected between groups using one-way ANOVA with p-

Table 1
Baseline characteristics.

Anticoagulation group	VKA	DOAC	No OAC
	$n = 28$	$n = 31$	$n = 413$
Patients characteristics			
Median age, years (range)	90 (69–96)	86 (60–95)	84 (29–98)
Female sex	15 (53.6)	24 (77.4)	298 (72.2)
ASA class, median (range)	3 (2–4)	3 (2–4)	3 (1–4)
Creatinine clearance[a]:			
> 50 mL/min	16 (57.1)	19 (61.3)	311 (75.3)
31–50 mL/min	6 (21.4)	10 (32.3)	67 (16.2)
< 30 mL/min	3 (10.7)	2 (6.5)	25 (6.1)
On dialysis	3 (10.7)	0 (0.0)	9 (2.2)
Hemoglobin, mean ± SD (g/L)	119.1 ± 17.1	117.3 ± 16.8	123.6 ± 18.3
Platelet count, mean ± SD ($\times 10^9$/μL)	184.2 ± 51.2	244.1 ± 94.6	230.8 ± 77.7
Antiplatelet use[b]	2 (7.1)	4 (12.9)	129 (31.2)
Anticoagulant characteristics			
Indication for anticoagulation:			
Atrial fibrillation	26 (92.9)	27 (87.1)	NA
Venous thromboembolism	2 (7.1)	4 (12.9)	NA
Mechanical valve	0 (0.0)	0 (0.0)	NA
CHADS2 score, mean (range)	3 (1–5)	3.1 (1–6)	NA
Vitamin K use	13 (46.4)	12 (42.9)	NA
Plasma use	0 (0.0)	0 (0.0)	NA
PCC use	7 (25.0)	4 (12.9)	NA
Surgical characteristics			
Time of admission[c]:			
Daytime	15 (53.6)	15 (48.4)	213 (51.6)
Evening	7 (25.0)	12 (38.7)	141 (34.1)
Overnight	6 (21.4)	4 (12.9)	59 (14.3)
Season of admission:			
Fall	7 (25.0)	9 (29.0)	112 (27.0)
Winter	9 (32.1)	7 (22.6)	121 (29.3)
Spring	8 (29.0)	7 (22.6)	87 (21.0)
Summer	4 (14.9)	8 (25.8)	93 (22.5)
Type of surgery:			
Total hip arthroplasty	7 (25.0)	10 (32.2)	133 (32.2)
Open reduction internal fixation	18 (64.3)	21 (67.7)	198 (47.9)
Cephalomedullary percutaneous pinning	3 (10.7)	0 (0.0)	52 (12.6)
Other	0 (0.0)	0 (0.0)	30 (7.3)
Preoperative consultation:			
Internal medicine	26 (92.9)	31 (100.0)	370 (89.6)
Thrombosis/hematology	2 (7.1)	1 (3.2)	2 (0.5)

A total 472 patients were included, of whom 13% (59/472) were taking OAC medications at the time of admission; 28 were on VKA, whereas 31 were on a DOAC. Unless otherwise specified, data is presented as total number (n), followed by percentage (%) in brackets. ASA: American Society of Anesthesiologists; CHADS2: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus; prior stroke or transient ischemic attack; DOAC: direct oral anticoagulant; FFP: fresh frozen plasma; NA: not applicable; OAC: oral anticoagulant; OR: operating room; VKA: vitamin K antagonist; VTE: venous thromboembolism.

[a] Creatinine clearance was calculated using the CKD-EPI formula.

[b] Antiplatelet use preoperatively, including acetylsalicylic acid, clopidogrel, ASA-dipyridamole, ticagrelor, and prasugrel.

[c] Daytime hours considered as 08:00–16:00, evening as 16:00–24:00, and overnight as 00:00–08:00.

value ≤ 0.05. Multilinear regression analyses assessing patient- and surgery-related variables were undertaken.

3. Results

Between July 1, 2016 and December 31, 2017, 569 patients presented with a hip fracture. Of these, 94 were excluded as they did not receive surgical treatment or were transferred from another hospital center. The final study population consisted of 472 patients, among whom 12.5% (59/472) were prescribed an OAC. In all, 28 were on VKA (47.5% of anticoagulated patients) and 31 were on a DOAC (52.5% of anticoagulated patients).

Table 1 shows baseline patient-specific and surgical characteristics among VKA, DOAC and No OAC groups. The study population consisted primarily of women (71.4%), notably in the DOAC group (77.4%) and the No OAC group (72.2%). The median age of the study population was 84 years [range 29–98] and ASA class was 3 [range 1–4], representing an elderly and comorbid population. Additionally, a greater proportion of patients in the No OAC group were on antiplatelets on arrival.

The most common indication for anticoagulation was atrial fibrillation. The most frequent surgery was open reduction with internal fixation. A small proportion of patients on VKA (7.1%) and DOAC (3.2%) were seen by a Thrombosis/Hematology consultant pre-operatively, though almost all, 92.9% and 100% respectively, were seen by an Internal Medicine consultant.

Prior to surgery, 96.4% of patients in the VKA group had an INR above 1.5, of whom 25% received both vitamin K and PCC and 21.4% received vitamin K alone. The majority of DOAC patients (71%) were prescribed the reduced DOAC dose (Table 2).

Median TTS (Fig. 1) was longer in VKA patients [64 h (IQR 50–84)] compared to No OAC patients [44 h (IQR 28–63), $p = 0.0006$]. Similarly, the DOAC group had a longer TTS [(61 h; IQR: 42 to 77)] when compared to No OAC patients [(44 h; IQR: 28 to 63; $p = 0.003$)]. There was no significant difference in median TTS when comparing patients on VKA to those on DOACs ($p = 0.6396$). In our cohort, none of the VKA patients proceeded to surgery before 48 h, whereas 12/31 (39%) and 248/413 (60%) of the DOAC and No OAC patients, respectively, had surgery within 48 h. The probability of proceeding to surgery by 48 h was calculated as 24% in VKA patients, 41% in DOAC patients and 61% in No OAC patients (Fig. 2).

Differences in pre-specified secondary outcomes until discharge from hospital were observed as well (Table 3). Rates of preoperative major bleeding and pRBC transfusions were higher ($p = 0.02$ and $p = 0.01$, respectively) in the DOAC group [6/25 (24%) and 18/31 (58%)] when compared to the VKA [3/21 (14.2%) and 8/28 (29%)] and the No OAC group [28/351 (10%) and 127/413 (31%)].

We undertook multilinear regression analyses to better elucidate the influence of patient- and surgery- related characteristics on TTS. Anticoagulation was independently correlated to longer TTS (14.80 h, $p = 0.0014$) when compared to non-anticoagulation; as was ASA class 4 compared ASA class 1 (34.34 h, $p = 0.0002$)Table 4.

Table 2
DOAC type.

	High dose	Low dose
Dabigatran – N (%)	1 (3.2)	5 (16.1)
Apixaban – N (%)	7 (22.6)	14 (45.2)
Rivaroxaban – N (%)	1 (3.2)	3 (9.7)

High dose DOAC: Dabigatran 150 mg twice daily, Apixaban 5 mg twice daily, Rivaroxaban 20 mg once daily. The majority of patients were prescribed a low dose DOAC: Dabigatran 110 mg twice daily, Apixaban 2.5 mg twice daily, and Rivaroxaban 15 mg once daily.

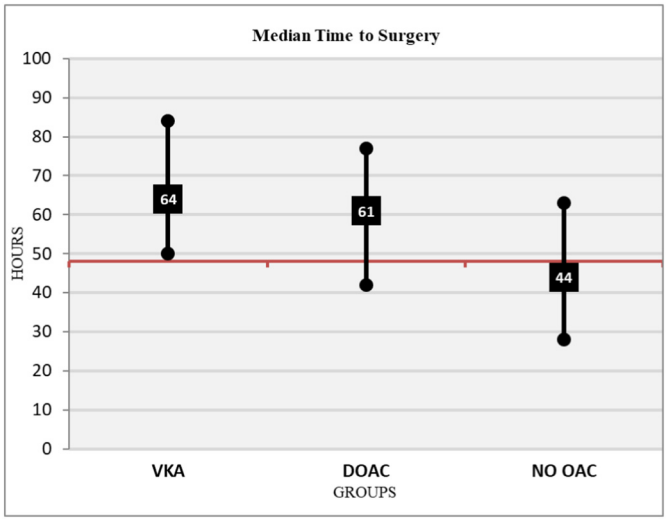

Fig. 1. Median time to surgery.
Median TTS was longer in anticoagulated patients [64 h (interquartile range, IQR 49–84 $p = 0.0006$) in the VKA group and 61 h (IQR 42–77, $p = 0.003$) in the DOAC group] compared the No OAC group [44 h (IQR 28–63)]. Red horizontal line representing benchmark TTS of 48 h. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

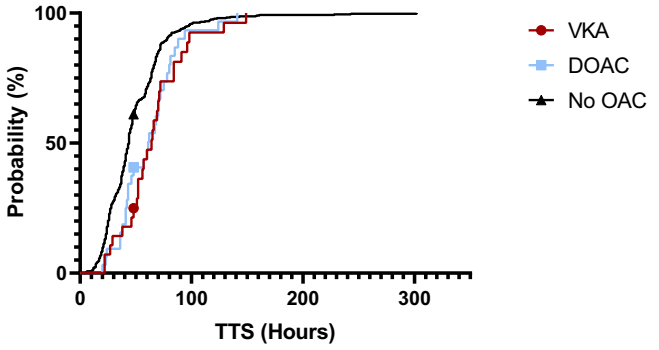

Fig. 2. Probability of proceeding to surgery.
Curves for No-OAC group, DOAC group, and VKA group demonstrating each individual group's probability of proceeding to surgery within a specific time frame. The 48-hour mark is represented by symbols ● (VKA), ■ (DOAC), ▲ (No OAC) noting the smallest probability in the VKA group and the largest in the No OAC group.

4. Discussion

Our results show that patients presenting with hip fracture taking oral anticoagulant medications, whether VKA or DOAC, have longer delays to urgent surgery compared to those who are not anticoagulated. This finding is consistent with previously published reports [5,6,8,10–12], though none have assessed the influence of individual classes of anticoagulants on surgical delays, a unique feature of our study. In our cohort, no VKA patients and only 39% of DOAC patients had surgery within 48 h, compared to 60% of the No OAC group. Our No OAC group's proportion was similar to the reported national average benchmark of 66% [4] highlighting that anticoagulation confers an additional disadvantage, on top of other contributing patient-related and/or systems-related factors, to proceeding to surgery within 48 h.

Although the exact causes of surgical delays associated with anticoagulation remain to be established, we postulate that delays seen in the DOAC group may have been due to lack of specific laboratory testing of drug activity, lack of easily accessible and effective hemostatic/reversal agents, conflicting perioperative management guidelines

Table 3
Secondary outcomes.

Outcome	VKA n = 28	DOAC n = 31	No OAC n = 413	*p*-Value
Mean LOS (days) (SD)	15.6 (7.5)	16.1 (10.8)	16.7 (18.8)	0.90
Venous thromboembolism (VTE) - N (%)	0 (0.0)	1 (3.2)	9 (2.2)	0.21
Deep vein thrombosis - N (%)	0 (0.0)	1 (3.2)	5 (1.2)	–
Pulmonary embolism - N (%)	0 (0.0)	0 (0.0)	4 (0.9)	–
Any major bleeding – N (%)	21 (75.0)	25 (80.0)	351 (84.9)	0.33
Preoperative major bleeding - N (%)	3 (14.2)	6 (24.0)	28 (10.0)	0.02
pRBC transfusion - N (%)	8 (28.6)	18 (58.0)	127 (30.8)	0.01
Stroke - N (%)	0 (0.0)	0 (0.0)	3 (0.7)	0.28
Death - N (%)	2 (7.1)	2 (6.5)	14 (3.4)	0.25

LOS was measured in days starting from the day of admission and ending on the day of discharge. Any major bleeding, as defined by ISTH bleeding definition, was any major bleeding from presentation to discharge. Preoperative major bleeding was any major bleeding limited to the preoperative period and was higher in the DOAC group [6/25 (24%)]. Transfusion of pRBC were higher in DOAC group [18/31 (58%)]. Statistical significance set to p-value ≤ 0.05.

Table 4
Multivariate linear regression results.

Variable	Point estimate of the regression coefficient	Standard error of the regression coefficient	*p* value
OAC vs No OAC	14.80	4.60	0.0014
Age	0.17	0.15	0.2539
Gender:			
Female vs male	−1.49	3.31	0.6531
ASA class			
2 vs 1	5.75	7.42	0.4391
3 vs 1	7.60	7.31	0.2990
4 vs 1	34.34	9.12	0.0002
Surgery type:			
Open reduction internal fixation (ORIF) vs hemiarthroplasty	−3.10	3.38	0.3589
Percutaneous pinning vs hemiarthroplasty	2.30	5.15	0.6547
Other vs hemiarthroplasty	−2.07	6.67	0.7565
Weekday of admission:			
Tuesday vs Monday	4.85	5.46	0.3752
Wednesday vs Monday	4.14	5.71	0.4694
Thursday vs Monday	2.01	5.43	0.7113
Friday vs Monday	7.13	5.50	0.1955
Saturday vs Monday	6.39	5.54	0.2499
Sunday vs Monday	−3.51	5.74	0.5416
Season:			
Winter vs Fall	3.03	4.04	0.4533
Spring vs Fall	0.85	4.35	0.8400
Summer vs Fall	2.48	4.21	0.5561

The anticoagulated cohort (OAC) including both DOAC and VKA groups vs the No OAC group had 14.8 h longer TTS when adjusted with statistical significance (p 0.0014). ASA class 4 compared to ASA class 1, 4 indicating a higher comorbidity status, had longer TTS (p 0.0002). No other findings were statistically significant.

between expert groups [14–16] and lack of a standardized pre-operative management protocol at our institution. Conversely, VKA activity is easily measured, antidotes to safely reverse their effect (using PCCs and vitamin K) [17] are readily available, and reversal protocols in many centers, including our own, are accessible to frontline clinicians. For these reasons we hypothesized increased delays in the DOAC group, yet we observed similar delays in both groups raising the possibility that factors other than anticoagulant management itself led to the delays. However, we noted that only a quarter of the patients on VKA received PCC and vitamin K and half received vitamin K alone, despite well-established reversal strategies [17], highlighting a serious care gap for this group. In fact, the VKA group was the least likely group to proceed to surgery within 48 h with only a 24% chance compared to 41% and 61% in the DOAC and No OAC groups, respectively. We believe the low proportion of use of a reversal agent contributed to the demonstrated delays to surgery in this group and indicates the necessity of identifying these patients promptly at their presentation to apply the recommended reversal procedure as standard routine practice.

Moreover, we noted a considerable number of major bleeding events across all our groups. Our cohort's significantly higher proportion of major bleeding compared to that reported in other studies [16] is likely accounted for by the inclusion of surgical and non-surgical bleeding in our assessment of events. Though we did not distinguish intraoperative major bleeding from postoperative major bleeding, we did ascertain preoperative major bleeding. Compared to the VKA and No OAC groups, we found that patients in the DOAC group had more preoperative major bleeding and required more pRBC transfusions, despite a larger proportion of low-dose regimen users, similarly to findings of two recent studies [10,18]. This increased preoperative bleeding may have contributed to delays detected in the DOAC group. It is also possible that these findings relate to the lack of anti-Xa DOAC antidotes in Canada for reversal of DOAC-induced bleeding and/or an inadequate interruption time of the medication. We were unable to confirm this for our cohort due to the unavailability of the timing of the last DOAC dose in the EMRs we reviewed. A recent study establishing a safe and effective interruption schedule for patients using DOACs in the setting of invasive procedures [16] did not separately ascertain outcomes in the setting of hip fractures, and thus, it is plausible that the recommended schedule may not be adequate for this exact setting. To our knowledge, no study examining this specific question is available yet. The large proportion of bleeding events noted in our study calls for a closer look into targeted interruption regimens and the potential role for hemostatic agents and monitoring of levels in patients with acute hip fractures.

Strengths of our study include the overall large sample size, the advanced age of our population and their high comorbidity index (ASA class) making it generalizable to real-world patients with acute hip fractures. Our stratification of anticoagulation into status and class is an additional strength. However, it is important to note that there are also several limitations to our study. First, it is a single center cohort with relatively low numbers of patients in the anticoagulated groups. It is retrospective in nature and data were collected from electronic medical charts, allowing for potential confounders to influence the detected effects. Multilinear regression analyses demonstrated that anticoagulation status was an independent predictor of longer TTS, however this result must be interpreted with caution given our relatively small anticoagulated cohort, and therefore, there remains the possibility that differences in these patients baseline characteristics may have led to the observed delays. For example, the VKA group was the only group where men and women were more evenly distributed; the others had a larger proportion of females. We questioned whether this relatively larger proportion of males in the VKA group led to the increased TTS, as it has previously been reported that males with hip fracture tend to have more significant morbidity [19]. However, comparable male to female proportions have been observed in previously published studies describing similar delays to surgery in anticoagulated patients [5,7,10,12]. Furthermore, comorbidity indices, such as ASA class and CHADS2 score, as well as baseline hemoglobin, were similar between groups suggesting that anticoagulation status itself could have led to the observed delays though true causality could not be established and thus, future studies further examining this relationship are warranted.

Ultimately, these delays to surgery in patients taking VKAs or DOACs with acute hip fractures represent a call to action to identify anticoagulated patients rapidly upon arrival to ensure adequate interruption of anticoagulation and, when required, reverse its effect to prevent additional delays to the necessary surgical intervention. Expert

panels have developed guidelines to assist clinicians with perioperative management of anticoagulants that are based on OAC-, patient-, and surgery-specific characteristics [14–16]. Our data substantiates the need to ensure that these expert guidelines and existing best practice protocols are appropriately implemented and adhered to.

5. Conclusion

To our knowledge, this is the first study to establish the relationship between surgical delays in patients with acute hip fractures and their anticoagulant status, stratified into presence or absence of anticoagulation as well as class of oral anticoagulant, i.e. DOAC vs. VKA. Our results demonstrate that patients taking either class of oral anticoagulant have prolonged delays to emergency hip fracture surgery compared to those not on anticoagulants. An action plan aimed at early identification and cessation of anticoagulation is warranted in this vulnerable group of patients. Future research further examining this relationship as well as assessing the role of antidotes and serum drug activity monitoring will be of value.

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