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Review of perioperative outcomes and management of hip fracture patients on direct oral anticoagulants

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- Anticoagulation use is common in elderly patients presenting with hip fractures and has been shown to delay time to surgery (TTS). Delays in operative treatment have been associated with worse outcomes in hip fracture patients. Direct oral anticoagulants (DOACs) comprise a steadily increasing proportion of all oral anticoagulation. Currently, no clear guidelines exist for perioperative management of hip fracture patients taking DOACs.
- DOAC use is associated with increased TTS, with delays frequently greater than 48 h from hospital presentation. Increased mortality has not been widely demonstrated in DOAC patients, despite increased TTS. Timing of surgery was not found to be associated with increased risk of transfusion or bleeding.
- Early surgery appears to be safe in patients taking DOACs presenting with a hip fracture, but is not currently widely accepted due to factors such as site-specific anesthesiologic protocols that periodically delay surgery. Direct oral anticoagulant use should not routinely delay surgical treatment in hip fracture patients.
- Surgical strategies to limit blood loss should be considered and include efficient surgical fixation, topical application of hemostatic agents, and the use of intra-operative cell salvage.
- Anesthesiologic strategies have utility in minimizing risk and a collaborative effort to minimize blood loss should be undertaken by the surgeon and anesthesiologist. Anesthesia team interventions include considerations regarding positioning, regional anesthesia, permissive hypotension, avoidance of hypothermia, judicious administration of blood products, and the use of systemic hemostatic agents.

Keywords

- hip fracture
- direct oral anticoagulant (DOAC)
- anticoagulation
- trauma
- geriatric
- surgical timing
- bleeding

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Introduction

Hip fractures are common and morbid injuries affecting the elderly population, largely due to high rates of osteoporosis and other factors that contribute to decreased bone mineral density (1). The incidence of hip fractures has been shown to range widely based on country, with an annual incidence in the United States of 957/100 000 for women and 414/100 000 for men (2, 3). While age-standardized rates were declining from 1995 to 2005, rates appear to have leveled off in the last decade (3, 4). With an aging population, the rate of hip fractures in patients over age 50 in the United States is expected to increase from 300 000 in 1990 to 512 000 annually by 2040 (5). Worldwide, by 2050, 6.26 million hip fractures are expected each year (6).

Hip fractures are associated with significant morbidity, mortality, and cost. These critical injuries are associated with increased short- and long-term all-cause mortality, reducing life expectancy by 1.8 years or 25% compared with age and sex-matched controls (7, 8). Approximately one-third of patients will expire within 12 months of injury (3, 9). Additionally, the financial burden of hip fractures is significant, with a lifetime attributable cost of $81 300, 44% of which is incurred from expenses related to nursing care (8). The total annual cost of hip fractures in the United States is expected to increase from $7.3 billion in 1983 to $16 billion by the year 2040 (5).

Importance of timing in surgical treatment

Surgical intervention of hip fractures is often indicated, except in certain cases such as non-ambulatory or high-risk patients with multiple severe comorbidities. Non-operative management is associated with four-fold higher mortality at 1 year and three-fold higher mortality at 2 years compared to surgical treatment (10). Prompt operative intervention (within 48 h of injury) is

associated with significantly improved outcomes (11, 12, 13). Further decreased time to surgery (within 24 h of hospital arrival) is associated with decreased pain and length of hospital stay (14). Meanwhile, delaying surgery for >48 h has been found to significantly increase the risk of short- and long-term mortality, minor and major medical complications, and the development of pressure sores (11, 12, 13, 14, 15).

Anticoagulation in hip fracture patients

Chronic anticoagulant use is frequently seen in elderly hip fracture patients due to underlying cardiovascular disease (16). This poses a significant challenge to timely operative intervention, with anticoagulated patients experiencing delays to surgical repair and longer hospital stays compared with non-anticoagulated patients (17). A survey study showed that 73.6% of surgeons felt that adequate clinical guidelines for patients with hip fractures receiving anticoagulation did not exist (18). Approximately 3–4% of all trauma patients are using oral anticoagulation prior to hospital arrival and in 2006, 12.8% of trauma patients aged 65 or older were utilizing Warfarin. As such, the proportion of hip fracture patients on anticoagulation is likely significant (19, 20).

Direct oral anticoagulants

Direct oral anticoagulants (DOACs) have emerged as a popular alternative to vitamin K antagonists (VKAs) for stroke prophylaxis in non-valvular atrial fibrillation, venous thromboembolism (VTE), and secondary prevention of adverse outcomes following acute coronary syndromes. DOACs include direct factor Xa inhibitors (apixaban, rivaroxaban, edoxaban, and betrixaban) and direct thrombin (factor IIa) inhibitors (dabigatran is the only current oral formulation), all of which affect the coagulation cascade (Fig. 1). The half-lives of DOACs range from 5 h to 27 h, largely relying on renal clearance, which may dramatically increase effective half-lives in the elderly (Table 1) (20, 21, 22, 23).

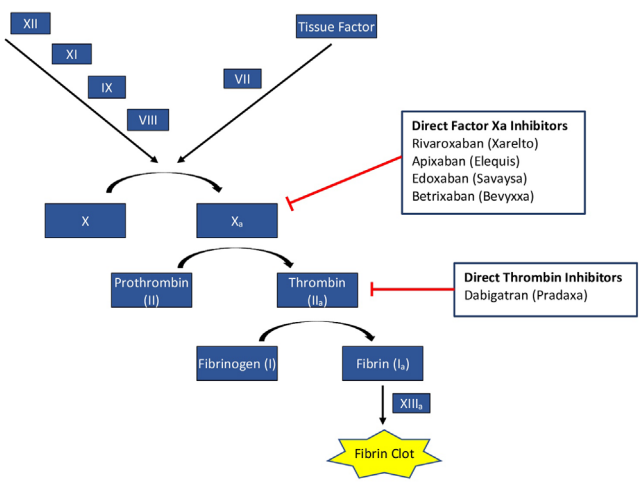

Figure 1
Coagulation cascade with direct oral anticoagulant sites of action.

With a favorable safety profile, decreased risk of major bleeding, and no need for routine drug monitoring or dietary regulation, DOAC use has increased dramatically at the expense of VKAs since their introduction to clinical practice in 2010 (24, 25). DOACs have also shown comparable outcomes to low-molecular-weight heparin (LMWH) in the setting of hip fractures (26). In 2015, DOACs accounted for 56.5% of all oral anticoagulant prescriptions and are now the anticoagulant of choice for many patients with atrial fibrillation or a history of stroke/transient ischemic attack (TIA) (27).

DOAC use in hip fracture patients

Recent literature shows that DOAC use in hip fracture patients ranges from less than 1% to nearly 20% (Table 2). It should be noted that the proportion of anticoagulated patients on DOACs is rising, and a recent study showed that overall DOAC use percentages may not fully capture the most current rates (28). These trends in DOAC use have led to a need for further investigation of how DOACs affect hip fracture management (Fig. 2). The present paper summarizes existing literature and sheds light on optimal perioperative management of hip fracture patients on this form of anticoagulation.

Time to surgery

A significantly increased time to surgery (TTS) in hip fracture patients on DOACs compared with non-anticoagulated patients has been described in several studies (Table 3). A recent systematic review and meta-analysis of 39 446 patients found DOAC patients faced an average surgical delay of 15.46 h (95% CI: 9.20–21.72 h) compared with non-anticoagulated controls (29). The amount of surgical delay DOAC patients faced compared with non-anticoagulated patients varies significantly between studies, ranging from no significant difference to 41 h longer (30, 31). However, these studies were limited by low sample size, as well as a retrospective design in the study by Leer-Salvesen *et al.*, thereby making it difficult to draw definitive conclusions. The proportion of patients on DOACs who underwent surgery after 48 h was also greater than in non-anticoagulated patients in most studies (Table 3), but significant variation has been reported with proportions ranging from 9% to 49% (32, 33). You *et al.* found that anticoagulated patients had three-fold higher odds of receiving surgery >48 h from admission compared with non-anticoagulated controls,

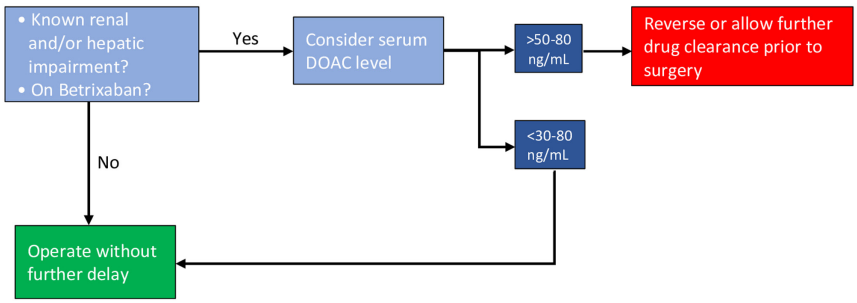

Figure 2
Proposed workup of otherwise medically cleared patients on DOAC prior to surgical repair of hip fracture.

although they did not distinguish between DOAC and VKA users for this analysis (29). The shortest mean or median TTS for DOAC patients was 27.6 h and the longest was 66.9 h (Table 3) (16, 32).

While surgical delay in DOAC users compared with non-anticoagulated patients was near universal, no clear methodological reasons between studies explain the significant variation in the amount of surgical delay and absolute TTS that DOAC patients experienced. More likely, increasing familiarity with DOAC medications and variable access to DOAC reversal agents over time account for the TTS differences seen between studies. Tran *et al.*, collecting data from 2010 to 2014, suspected the significant surgical delay they found in DOAC users was due to uncertainty surrounding perioperative management of DOACs (mean DOAC TTS of 66.9 h vs 26.2 h for non-anticoagulated patients) (16). A 2018 case–control study of 796 hip fractures found waiting for a decrease in DOAC drug activity was responsible for surgical delay in 70% of DOAC users (no DOAC patients were reversed), while only 32% of patients on VKA (who were routinely reversed with vitamin K) experienced a surgical delay due to INR levels (33). Bruckbauer *et al.* cite a lack of specific tests for rapid quantification of Xa and thrombin inhibitors, and no specific reversal agents for FXa inhibitors at the time, for the increased TTS and higher proportion of patients receiving surgery after 48 h observed in DOAC users compared with non-anticoagulated patients (35). Additionally, hospital and region-specific procedural differences, due to a lack of established guidelines, are likely to have played a role in the TTS variability seen between studies (30). These findings highlight the delay in definitive surgical treatment that frequently occurs in patients on DOACs and underscore the need for a better understanding of the anticoagulants, and comprehensive clinical guidelines for their management, in hip fractures.

Mortality consequences of delayed time to surgery in patients taking direct oral anticoagulants

Interestingly, the increased surgical delay seen in hip fracture patients on DOACs was not widely associated with increased mortality (Table 4). A retrospective cohort of 320 hip fracture patients ≥65 years old found no significant difference in mortality rates between DOAC, VKA, and non-anticoagulated patients (35). This was observed despite three times as many DOAC patients were operated on after 48 h as non-anticoagulated patients (13% DOAC vs 4.3% non-anticoagulated; mean TTS: 29.5 h for DOAC vs 12 h for non-anticoagulated) (35). Another study, which showed the largest discrepancy between the proportion of DOAC patients operated on after 48 hcompared with non-anticoagulated patients (48.9% DOAC vs 8% nonanticoagulated), also showed no difference in in-hospital or 1-ear mortality between groups (33). Multiple other studies, including a systematic review of 39 446 patients, have shown similar findings of no increased mortality risk associated with delayed surgery in DOAC users (28, 29, 32, 34, 36, 37, 38).

One recent retrospective cohort of 3418 patients ≥65 years old who underwent operative repair for hip fracture found DOAC users to have a decreased risk

Table 1 Pharmacokinetics and pharmacodynamics of direct oral anticoagulants (22, 54, 55, 56).

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target	Thrombin (IIa)	Factor Xa	Factor Xa	Factor Xa	Factor Xa
$T_{1/2}$ (h)	12–17	Young, healthy: 5–9; Elderly: 11–13	8-15	10–14	19–27
T_{max} (h)	2	2–4	1–3	1–2	3–4
Bioavailability (%)	7	66	50	62	34
Renal excretion (%)	80	66	25	35	17.8
Fecal excretion (%)	82–88	26.4	46.7–56	62.2	85
CYP450 metabolism	No	Yes	Yes	No	No
Specific reversal agents	Idarucizumab	Andexanet alfa	Andexanet alfa	–	–
Time alloted prior to spinal anesthesia (h)	24	24	24	24	72

h, hours; $T_{1/2}$, drug half-life; T_{max}, time to reach peak concentration in plasma after oral dose.

Table 2 Epidemiology of DOAC, VKA use in hip fracture patients.

Study	Study type	Inclusion criteria	*n*	Hip fracture patients	
				DOAC	VKA
Tran et al. (16)	CCS*	Operative, isolated hip fracture	2258	1.2%	10.3%
Lott et al. (43)	RCS	Isolated hip fracture, ≥60 years	479	0.8%	7.7%
Sabo et al. (31)	PCS	Low-energy, operative hip fracture	55	9.1%	14.5%
Taranu et al. (17)	PCS	Hip fracture, >60 years	1965	4.5%	7.1%
Bruckbauer et al. (35)	RCS	Isolated hip fracture, ≥65 years	320	16.9%	18.4%
Cafaro *et al.* (42)	RCS	Acute operative hip fracture, ≥18 years	472	6.6%	5.9%
Daugaard *et al.* (36)	RCS	First time hip fracture, ≥65 years	74791	1.4%	5.6%
Hourston *et al.* (32)	RCS	Surgically treated femoral neck fracture	844	3.8%	9.8%
Schermann *et al.* (40)	RCS	Operative (CRIF or HA only) intertrochanteric and femoral neck fracture, ≥65 years	1714	5.2%	9.3%
Schuetze *et al.* (47)	RCS	Operative, isolated per- or subtrochanteric fracture	327	15.9%	7.6%
Viktil *et al.* (23)	PCS	Operative acute hip fracture, ≥65 years	167	6.6%	8.4%
Creeper *et al.* (56)	RCS	Acute hip fracture	1240	6.6%	5.4%
Hoerlyck et al. (61)	RCS	Hip fracture, ≥50 years	2307	1.4%	8.7%
Meinig *et al.* (51)	RCS	Isolated operative fragility hip fracture, ≥65 years	459	19.8%	39.0%
Saliba *et al.* (39)	RCS	Operative hip fracture, ≥65 years	3418	7.2%	4.8%
Tarrant *et al.* (28)	RCS	Hip fracture, ≥65 years	3264	3.4%†	

*Overall percentage, however, rates increased annually and were 9% in 2018; †Percentages for DOAC and VKA patients calculated from a cohort of all hip fracture patients.
CCS, case–control study; CRIF, closed reduction internal fixation; DOAC, direct oral anticoagulation; HA, hemiarthroplasty; PCS, prospective cohort study; RCS, retrospective cohort study.

of 30-day and 90-day mortality compared with non-anticoagulated patients, despite experiencing longer TTS and hospital length of stay (39). The authors attributed this to the antithrombotic and protective effects during the perioperative period despite the discontinuation of DOACs, early postoperative therapeutic dose anticoagulant administration, and healthy user effect-related biases. Additionally, they reported that the time delay was insignificant and likely utilized for anticoagulant reversal rather than acute medical optimization. The relative surgical delay for DOAC patients compared with non-anticoagulated patients in this study was small, however, with median TTS of 31.8 h in DOAC patients and 24.6 h in non-anticoagulated patients. Longer-term mortality was not assessed. To our knowledge, only one other study has replicated a decreased mortality rate in DOAC users despite increased surgical delay (36). This study showed a decreased 30-day mortality in DOAC users but only in the cohort undergoing surgery >36 h after admission. Interpretation of these data is complicated by the fact that DOAC users were compared with non-DOAC users (including patients on antiplatelet medication, VKAs, and no anticoagulation) rather than only non-anticoagulated patients, therefore adding methodological bias to this study.

Contrary to the majority of other studies, two publications found increased mortality among DOAC users (37, 40). The first study reported on a retrospective cohort of 1714 proximal hip fractures in patients ≥65 years old, looking only at patients surgically managed with closed reduction internal fixation (CRIF) or hemiarthroplasty (HA) (40). The authors found 1-year mortality was significantly higher in DOAC patients who underwent CRIF (but not HA), for which delayed TTS was an independent risk factor; however, other contributing risk factors for increased 1-year mortality existed in this subgroup including older age and higher comorbidity burden. TTS, 1-month mortality and 1-year mortality rates were not significantly different in DOAC and non-anticoagulated patients who underwent HA. The second, a case–control study of 84 hip fracture patients undergoing surgery <48 h vs>48 h from admission, found DOAC patients with >48 h surgical delay had a significantly higher 90-day mortality compared to those receiving early surgery (37). However, this DOAC patient group had a higher American Society of Anesthesiologists (ASA) physical status classification, increased preoperative medical complications, and lower preadmission mobility which may have acted as confounders for both TTS and 90-day mortality (13, 14).

The generally observed lack of increased mortality rates despite an increased TTS (often beyond the recommended 48 h) in DOAC users may be explained by the age and comorbidities of these patients. A systematic review and meta-analysis of 257 367 hip fracture patients found that older patients and those at higher baseline risk experience a lesser 1-year mortality benefit from early surgery than younger, lower risk patients (14). The majority of studies presently reviewed included only geriatric hip fractures; studies often excluded patients <65 years old, and average patients' age was consistently in the 80s. Additionally, while most studies reported increased TTS in DOAC patients, the absolute delay relative to non-anticoagulated patients was often minimal and thus may not have been of clinical significance. For example, five studies (30, 32, 34, 40, 41) showed an absolute increase

Table 3 Time to surgery in hip fracture patients on DOAC vs VKA and no oral anticoagulation. Data are presented as mean±S.D., median or as median (IQR).

Study	Study Design	*n*	No OAC TTS	DOAC TTS	VKA TTS	Major Findings	LOE
Tran et al. (16)	CCS	520	26.2h (17.3-40.6)	66.9h (38.1-78.9)	39.4h (26.6-46.4)	TTS: DOAC > VKA > No OAC	III
Franklin et al. (41)	CCS	93	21.4h ± 12.4	28.9h ± 11.8		TTS: DOAC > No OAC	III
Frenkel Rutenberg *et al.* (33)	CCS	796	28.7h ± 25.7; 92% <48h	55.3h ± 38.8; 51% <48h	59.2h ± 45; 59% <48h	TTS >48h: DOAC > No OAC	III
Sabo *et al.* (31)	PCS	55	25h ± 19h	66h ± 16h	38h ± 21h	TTS: DOAC > VKA > No OAC	II
Taranu *et al.* (17)	PCS	1965	22.57h	Rivaroxaban: 35.04 h; Dabigatran: 48.28 h; Apixaban: 36.7h	28.34h (median)	TTS: Anticoagulated > No OAC.	II
Bruckbauer *et al.* (35)	RCS	320	12h 85% <24h; 4.3% >48h	29.5h; 37% <24h; 13% >48h	50.8% <24h; 8.4% >48h	TTS: DOAC > No OAC. Greater proportion DOAC operated on >48h after hospitalization	III
Cafaro *et al.* (42)	RCS	472	44h (28-63)	61 h (42-77)	64h (50-84)	TTS: DOAC and VKA > No OAC, DOAC = VKA	III
Daugaard *et al.* (36)	RCS	74 791		44.1% <24h; 17.5% 24-36h; 38.4% >36h	37.7% <24 h; 21.3% 24–36 h; 40.7% >36 h	TTS > 36 h in twice as many DOAC, VKA patients vs No OAC	III
Hourston *et al.* (32)	RCS	844	22 h 85% <36 h; 94% <48 h	29h; 59% <36 h; 91% <48 h	27h; 77% <36 h; 95% <48 h	DOAC use independently associated with increased TTS >36 h but not >48 h. TTS VKA = No OAC	III
Schermann *et al.* (40)	RCS	1714	CRIF: 31.2h ± 22.2; 82% <48 h n.s.; HA: 36.6 h ± 25.8 n.s.; 77.5% <48 h n.s.	CRIF: 40.2± 26.9; 74% <48h n.s.; HA: 42.3 h ± 27.3 h n.s.; 74% <48 h n.s.		TTS: DOAC > No OAC in CRIF only. DOAC = No OAC in HA	III
Viktil *et al.* (23)	PCS	167		44 h	25 h	TTS: DOAC > VKA	III
Brown et al. (34)	CCS	144	19.8 h± 10.5 h	27.6 h ± 16.3; 50% <24h; 92% <48 h		TTS: DOAC > No OAC. No statistical comparison done for proportion of DOAC vs. *No-OAC receiving surgery <24 h, <4 8h	III
Gosch *et al.* (62)	CCS	102	30 h ± 18.7	42.7 h ± 14.2	40.5 h ± 15.1	TTS: OAC (DOAC + VKA) > No OAC	III
King *et al.* (37)	RCS	84	25.98 h ±11.4	32.21 h ± 7.83		TTS: DOAC > No OAC	III
Leer-Salvesen *et al.* (30)	RCS	314	26.1 h ± 19.0 h	28.9 h ± 12.9 n.s.		TTS: DOAC = No OAC	III
Saliba *et al.* (39)	RCS	3418	24.6 h (17.3–30.7); 90.0% <48 h	31.8 h (24.9–52.8); 71.7% <48 h	31.4 h (22.5–55.3); 67.2% <48 h	TTS: DOAC, VKA > No OAC. Lower proportion of DOAC, VKA patients operated on <48h after hospitalization	III
Tarrant *et al.* (28)	RCS	112	1.2d† ± 0.7	1.8d† ± 1.3		TTS: DOAC > No OAC	III
Rostagno *et al.* (38)	RCS	280	2.15 days ± 1.07	3.6 days ± 2.7		TTS: DOAC > No OAC	III
You *et al.* (29)	SRMA	39 446				Mean difference for DOAC TTS vs no-OAC: +15.46 h (95% CI: 9.20–21.72 h). TTS: DOAC = VKA	III

†TTS was calculated from time of last DOAC dose, not from time of hospital arrival; *No statistical comparison specifically for patients on DOAC vs No OAC. 95% CI, 95% confidence interval; CCS, case-control study; CRIF, closed reduction internal fixation; d, days; DOAC, direct oral anticoagulant; h, hours; HA, hemiarthroplasty; IQR, interquartile range; LOE, level of evidence; n.s., not significantly different from comparison group(s); No OAC, no oral anticoagulation; PCS, prospective cohort study; SD, standard deviation; SRMA, systematic review/meta-analyses; TTS, time to surgery; RCS, retrospective cohort study; VKA, vitamin K antagonists.

in mean or median DOAC TTS of less than 10 h relative to non-anticoagulated patients and eight studies (17, 30, 31, 34, 35, 40, 41, 42) showed an absolute increase in DOAC TTS of less than 24 h compared with non-anticoagulated patients.

Safety of early surgery

Early surgical treatment of hip fractures appears safe in DOAC users. A recent study compared hip fracture patients on DOACs who were surgically repaired <48 h vs>48 h after hospital admission, including a control group of non-anticoagulated patients who underwent surgery <48 h after admission (40). The authors found no significant difference in perioperative hemoglobin change, transfusion rates, or hematoma formation between early (<48 h) and late (>48 h) operated DOAC patients or between early operated DOAC and non-anticoagulated patients. These results are also consistent with another recent study that found no increased risk of transfusion, surgical blood loss, operative time, or inpatient mortality in DOAC patients who were operated on <48 h compared to those operated on >48 h from admission (43).

DOAC users also do not appear to fare worse than non-anticoagulated controls when operated on <48 h from admission. A case–control study compared 19 patients on

Table 4 Bleeding and transfusion rates, mortality and other complications associated with DOAC use in hip fracture.

Study	Study type	*n*	Major findings	LOE
Franklin *et al.* (41)	RCCS	93 (19 DOAC, 74 No OAC control)	Patients on DOAC operated on within 48 h showed no differences in transfusions, changes in Hgb levels, wound complications, or survival at any time point. DOAC patients had longer TTS and were more likely to undergo readmission within 30 d than controls (no readmissions for complications of the surgical site, bleeding, or VTE).	III
Frenkel Rutenberg *et al.* (33)	RCS	796	No increased morbidity, in-hospital, or 1-y mortality in DOAC users vs controls, despite significantly larger proportion of patients on DOACs experiencing delayed TTS (>48 h). DOAC users did not have adverse outcomes compared with VKA users.	III
Mullins *et al.* (44)	RCCS	125 (63 DOAC, 62 control)	No relationship found between TTS and perioperative change in Hgb or probability of transfusion in patients on DOACs.	III
Bruckbauer *et al.* (35)	RCS	320	Patients on DOACs and VKAs were transfused at significantly higher rates than non-anticoagulated patients (53.7% of DOAC, 54.2% of VKA, vs 38% No OAC). DOAC use was associated with longer TTS. No difference in in-hospital mortality was observed between groups.	III
Daugaard *et al.* (36)	RCS	74 791	DOAC users had slightly increased risk of transfusion compared with non-DOAC users when operated on <24 h. DOAC users delayed >36 h had lower 30-d mortality risk than non-users. TTS of >36 h was twice as common for DOAC users vs non-DOAC users.	III
Hourston *et al.* (32)	RCS	844	DOAC use had no effect on 30 dy, 6 m, or 1 yr survival, whereas VKA use was associated with decreased 30-d survival. DOAC use, but not VKA use, was independently associated with increased TTS >36 h but not >48 h. Anticoagulation did not increase hospital LOS.	III
Lott *et al.* (43)	RCS	78	Patients receiving antiplatelet or DOAC therapy who underwent surgery <48 h from admission were at no higher risk for transfusion, increased surgical blood loss, longer operative time, or inpatient mortality.	III
Schermann *et al.* (40)	RCS	1714	Patients on DOACs who underwent CRIF had increased TTS and risk of 1-y mortality than non-AC patients. For both CRIF- and HA-treated patients, DOAC users had similar perioperative Hgb change, transfusion rates, and perioperative mortality compared to non-AC controls.	III
Schuetze *et al.* (47)	RCR	327	DOAC patients presented with lower Hgb concentrations and had 3.4-fold increased risk for intraoperative blood transfusions compared with controls. Anticoagulation showed no significant effect on complication rates and mortality in patients operated within 24 h.	III
Aziz *et al.* (45)	Mixed R/PCS	120	DOAC use associated with increased blood loss, transfusion rates, and TTS; however, DOAC patients presented to hospital with lower Hgb and subsequent blood loss was minimal.	III
Brown *et al.* (34)	RCCS	144 (36 DOAC, 108 No OAC controls	Patients on DOACs had no difference in EBL, change in Hgb, or rates of transfusion, reoperation, readmission, DVT, or 30-day mortality compared with non-AC controls. DOAC users had longer TTS, but 92% were operated on within 48 h.	III
Gosch *et al.* (62)	RCCS	102 (6 DOAC, 15 VKA, 61 control)	DOAC and VKA users had longer TTS and LOS than non-AC controls. DOAC and VKA use was associated with increased minor but not major bleeding; Hgb decrease was similar in all groups. Combined endpoint (in-hospital mortality, mortality, 3+ pRBCs, revision surgery, major bleeding, Hgb loss ≥ 6 g/dL, MI, stroke, thromboembolic events) was significantly higher for DOAC users than non-AC patients. No difference in mortality between groups.	III
King *et al.* (37)	RCS	84	No significant difference in perioperative Hgb levels, transfusion rates, or hematoma between DOAC users operated on <48 h, >48 h, and non-DOAC user controls operated on <48 h. DOAC users operated on >48 h had significantly more deaths than DOAC users operated on <48 h. DOAC users who received surgery <48 h still had significantly increased TTS compared to non-DOAC controls.	III
Leer-Salvesen *et al.* (30)	RCR	314	Perioperative blood loss, transfusion rates, and risk of bleeding complications and mortality were similar between DOAC users and non-AC patients. Five times more wound oozing in DOAC patients than non-OAC patients. No difference in TTS or hospital LOS was seen between groups.	III
Saliba *et al.* (39)	RCS	3418	DOAC use associated with reduced risk of 30-d and 90-d mortality among elderly patients with hip fracture. Only patients on VKA required significantly higher number of blood transfusions. DOAC and VKA use was associated with >TTS and >LOS than non-AC patients.	III
Tarrant *et al.* (28)	RCS	3264	Timing of surgery in DOAC users did not affect 30-d mortality, serious AEs, transfusions rates, or postoperative day 1 Hgb levels. DOAC patients had significantly longer TTS than age and sex-matched non-AC controls.	III
Xu *et al.* (46)	SRMA	21,417	Neither perioperative RBC transfusion nor EBL were significantly different between DOAC and non-AC patients.	III
Rostagno *et al.* (38)	RCS	280	Neither anticipation nor delay in surgery did result in increased mortality, length of stay or complication rates with the exception of larger perioperative blood loss (Hb levels < 8 g/dL) in DOAC patients.	
You *et al.* (29)	SRMA	39,446	DOAC users had longer TTS than no-OAC controls, but no difference in in-hospital or 30-d mortality, or hospital LOS.	III

AC, anticoagulated; AEs, adverse events; CCS, case–control study; CRIF, closed reduction internal fixation; d, days; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; EBL, estimated blood loss; h, hours; Hgb, hemoglobin; HA, hemiarthroplasty; LOE, level of evidence; LOS, length of stay; MI, myocardial infarction; OAC, oral anticoagulant; pRBC, packed red blood cells; PCS, prospective cohort study; RCCS, retrospective CCS; RCS, retrospective cohort study; RCR, retrospective chart review; SRMA, systematic review/meta-analyses; TTS, time to surgery; VKA, vitamin K antagonist; VTE, venous thromboembolism; y, years.

DOACs aged 60–89 to 74 non-anticoagulated controls, all of whom underwent surgery within 48 h of admission (41). Non-anticoagulated controls were matched based on sex, construct (hemiarthroplasty, cephalomedullary nail [CMN], or sliding hip screw), and age as closely as possible. The authors found no significant differences between groups in estimated blood loss (EBL), transfusion rates, or the volume of blood transfused in patients who required transfusion. These findings persisted after adjusting for known differences in EBL between short and long CMN

and on construct-based subgroup analysis. There were also no significant differences in surgical time, length of stay, or rates of perioperative complications, including hematoma formation, persistent serous drainage, or need for reoperation between groups. Furthermore, 30-day, 90-day, and 1-year survival were not significantly different between DOAC and non-anticoagulated patients in this cohort of patients undergoing surgery <48 h from admission.

Surgical timing, blood loss, and transfusion rates

Delaying surgery does not appear to reduce perioperative blood loss or transfusion rates in DOAC users. In a cohort of 63 first-time proximal femur fracture patients on DOACs, one study found no relationship between TTS from admission and probability of transfusion or perioperative hemoglobin change (44). Similarly, another study found no relationship between TTS from the last DOAC dose and transfusion rates or postoperative day 1 hemoglobin in a cohort of 112 patients age 65 and older admitted for proximal femur fracture (28). A third one found prolonged waiting for surgery in DOAC patients had no effect on blood loss (45).

Indeed, many studies have shown no increased risk of blood loss or transfusion rate in DOAC patients undergoing hip fracture surgery at all (Table 4). A systematic review and meta-analysis of hemostatic complications in 21 417 hip fracture patients found that neither perioperative red blood cell transfusion rates nor EBL wassignificantly different in DOAC and non-anticoagulated patients (transfusion OR 0.93–2.00; EBL +2.8 mL in DOAC, $P = 0.83$) (46). Similar rates of transfusion and blood loss between DOAC users and non-anticoagulated patients were seen even with similar TTS (<8-h difference) between groups (30, 34, 39, 41).

However, one study showed a 53.7% transfusion rate in DOAC vs 38% transfusion rate in non-anticoagulated patients, despite non-significantly different admission hemoglobin levels (34). Another retrospective cohort study also showed a slightly increased transfusion rate in DOAC patients (RR 1.14 [1.02–1.27]) compared with non-users but only in those patients operated on <24 h after admission (35). Hemoglobin on admission and hemoglobin drop were not reported. These latter data might suggest an increased risk of transfusion in DOAC patients operated on within 24 h of admission; however, interpretation of these findings is complicated by the fact that, unlike many similar studies, DOAC users were compared with non-users rather than non-anticoagulated patients. That is to say, the comparison group included all patients on VKA, antiplatelet therapy, and non-anticoagulated patients combined, thereby precluding the ability to draw strong conclusions when comparing the two cohorts in this study.

Other studies have also reported an increased rate of transfusion or hemoglobin loss in DOAC users, although these findings were associated with decreased hemoglobin levels on arrival. One study found that between 23% and 40% of DOAC users required transfusion, compared with 0% of non-anticoagulated controls (45). This difference was primarily due to DOAC users having a significantly lower arrival hemoglobin than non-anticoagulated patients (mean DOAC arrival Hgb: 86.7–89.3 g/L vs 122.1 g/L for controls). Similarly, another paper found that when DOAC users were operated on within 24 h, they were at 3.4 times increased risk of intraoperative transfusion compared with non-anticoagulated patients; again, this was predominantly driven by a significantly lower hemoglobin at admission compared with controls (47). These findings support the idea that most blood loss in DOAC patients occurs prior to hospital arrival rather than from intraoperative bleeding. If further substantiated, this would argue the futility of delaying surgery for purposes of mitigating surgery-associated blood loss.

Preoperative DOAC reversal

While increased perioperative blood loss in DOAC patients has not been consistently shown, DOAC reversal is an appealing option to mitigate concern for surgical bleeding. The FDA has approved two specific reversal agents for DOACs. Idarucizumab can be used to reverse dabigatran and andexanet alfa can be used to reverse apixaban and rivaroxaban (Table 1). However, cost, availability, preparation, and risk of thrombosis may complicate their use. Further, these reversal agents are not approved for all DOACs (48). Prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (APCC) have also been used off-label for DOAC reversal, although there is little clinical evidence to support their use (49). Activated charcoal may be administered to decrease DOAC blood levels but only if DOAC ingestion occurred within the last 2 h (49). Tranexamic acid (TXA) constitutes another potential option for treating DOAC-related bleeding. TXA is an antifibrinolytic that works by inhibiting plasminogen so that the fibrin matrix cannot be stabilized (50). While no clinical studies have yet been conducted examining the effect of TXA on DOAC-associated bleeding, consensus recommendations suggest TXA can be considered as an adjuvant in the acute setting as there are likely few negative effects (49).

To our knowledge, only two studies have directly compared the effects of anticoagulation reversal vs non-reversal in hip fractures (51, 52). Both studies found that reversing anticoagulation was not associated with decreased bleeding, transfusion rates, or mortality and reversed patients had increased TTS and hospital length of stay. Unfortunately, the application of these

findings to DOACs specifically is limited. The first study contained only 51 patients on DOAC in a cohort of 459 anticoagulated patients (51). Reversal for DOAC patients was achieved via non-specific reversal agents or a 'watch and wait' strategy allowing for DOAC serum levels to decrease by 94–97%. No DOAC patients received idarucizumab, and andexanet alfa was not yet approved during study enrollment. The second study included 41 patients on DOACs of 1984 total anticoagulated patients with hip fractures of which only four were reversed (52). Further, the reversed patients in this latter study were significantly different from non-reversed patients, being significantly more likely to be white and male, having more comorbid conditions, and having a higher INR at admission. Neither study analyzed DOAC patients separately from VKA patients.

Other studies have incidentally compared reversal in DOAC and VKA patients with hip fractures. One found similar transfusion rates among DOAC and VKA patients (54% vs 53.8%, respectively), despite significantly reduced rates of reversal among the DOAC cohort (35). Another case–control study also showed no difference in outcomes between DOAC and VKA patients, despite no DOAC and all VKA patients receiving reversal (33). These findings suggest DOAC reversal may not be necessary, but the interpretation is greatly limited by the observational nature of the studies and the fact that no comparison was made between patients on DOACs who were reversed vs not reversed prior to surgery. Thus, additional research is urgently needed to determine the costs and benefits of using targeted reversal strategies for hip fracture patients on DOACs.

Preoperative DOAC clearance and serum level measurement

Early guidelines for patients on DOACs suggested a benefit to delaying emergency surgery 12–24 h from the last DOAC dose to allow for drug clearance (53). However, newer studies have suggested DOAC drug clearance is unpredictable and recommend anti-factor Xa levels to enable safe early surgery (55, 56). One study found approximately 40% of hip fracture patients had serum DOAC levels >80 ng/mL at 24 h, with 1 out of 36 patients having a level >80 ng/mL at 48 h, while another study found 52% of patients had drug levels <50 ng/mL within 12 h of presentation (55, 56). One caveat to consider with serum level testing is that no clear DOAC serum cutoff level has been established for safe surgery, with suggested levels ranging from 30–80 ng/mL (53, 55). Additionally, one study found that monitoring DOAC levels in hip fracture patients and waiting to operate until levels reached <50 ng/mL was actually associated with increased rates of transfusion and longer TTS than simply waiting 24 or 48 hh after the last DOAC dose (45). Of note, this particular cut-off level was per hospital protocol and not applicable to all DOACs due to various half-lives and therapeutic ranges. This finding occurred despite no differences in arrival hemoglobin between groups. The authors suggest the increased transfusion rate seen in later-operated DOAC patients (surgery once serum concentration reached <50 ng/mL) was secondary to additional complete blood counts and uncertainty that took place during the extra time before the operation.

While the majority of patients are likely to have acceptable serum DOAC levels at the time of surgery without additional delay for drug clearance or reversal, there may be a minority who have therapeutic concentrations that cause excessive bleeding. Renal impairment is one condition that is well known to predispose patients to higher circulating doses of DOACs, for longer periods of time. Indeed, one study showed a significant trend toward greater transfusion rates in DOAC patients with increasing chronic kidney disease (CKD) stages on admission for hip fracture (44).

Preoperative strategies to facilitate early and safe surgery

Current guidelines recommend early surgery for hip fractures within 48 h of injury, but more recent studies have suggested that early surgery within 24 h may further improve outcomes, highlighting the importance of optimizing preoperative management (57, 58). A recent study by Shah *et al.* proposed a systematic, evidence-based guideline for the perioperative management of hip fracture patients taking DOACs (59). The authors provided an algorithm accounting for renal impairment, liver profile, blood count, and coagulation screens, as well as DOAC-specific Anti-Xa assay to ensure a level of less than 50 ng/L, that could be used to better guide preoperative management and allow for earlier surgery. They also recommended a multidisciplinary approach to care that involves the patient, hematology, anesthesia, and orthopedic surgery teams (59).

Collaboration between the surgical and anesthesia teams to optimize the patient for surgery in the setting of DOAC use is tantamount to achieving a more safe and more efficient surgical setting. Anesthetic strategies described in another study by Shah *et al.* to minimize blood loss included tranexamic acid, permissive hypotension, central neuraxial anesthesia, correct patient positioning, and avoidance of hypothermia (60). The authors also reported promising hemostatic strategies that included the use of pharmacological agents such as desmopressin, prothrombic complex concentrate, fibrinogen concentrate, and the use of viscoelastic hemostatic assays. However, the optimal use for these agents is unclear at this time and represents important areas of ongoing research. Incorporating these strategies in the perioperative period with patients taking DOACs may facilitate and improve care.

Conclusions

Given the current evidence, we propose reserving DOAC levels and DOAC reversal for patients deemed at higher risk of bleeding complications, in particular, patients with decreased renal and/or hepatic function, and those on longer-acting DOAC medications such as betrixaban. For the majority of remaining DOAC patients, surgery should proceed as soon as the patient is medically cleared. Furthermore, close collaboration between surgery and anesthesia teams, as well as utilizing anesthetic strategies and pharmacologic agents to mitigate blood loss, is fundamental in optimizing patient care and outcomes. A comprehensive guideline to properly address and manage hip fracture patients taking DOACs is needed.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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