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General

Perioperative Management of Traditional and Direct Oral Anticoagulants in Hip Fracture Patients

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Hip fractures are an increasingly common injury in the senior population and almost always require surgical fixation or prosthetic replacement. These surgeries, according to the American Academy of Orthopaedic Surgeons, are considered high-risk for bleeding, especially in a population fraught with comorbidities and often presenting on anticoagulation medications. Direct oral anticoagulants represent a class of drugs that have been becoming more popular in use in this population, with many benefits over the historically used Warfarin. There are recommendations for preoperative discontinuation and postoperative resumption of these medications, which can be more readily managed for elective surgeries. However, there is a paucity of literature detailing best practice guidelines for the perioperative management of direct oral anticoagulants when a patient presents with a hip fracture. This review article summary of the periprocedural management of DOACs for hip surgery was developed by examining the American College of Chest Physicians evidence-based clinical practice guidelines, Perioperative Guidelines on Antiplatelet and Anticoagulant Agents written by anesthesiologists, various retrospective studies, and drug labels for pharmacokinetic data. These recommendations should be used as a guideline, along with the collaboration of multidisciplinary hospital teams during inpatient admission, to manage these complex patients.

INTRODUCTION

The incidence of hip fractures in patients over the age of 65 produces an estimated 300,000 admissions in the United States annually.[1] Hip fractures are expected to increase 11.9% from 2010 (258,000) to 2030 (289,000) by conservative estimates.[2] In addition, hip fractures 1-year mortality rates are around 30%, demonstrating the importance of proper management for these patients.[3] A major risk factor for mortality is delayed surgical intervention, with a delay of more than 48 hours from admission associated with increased 30-day and 1-year mortality.[4,5] A contributing factor to delayed surgical intervention is the optimization of patient comorbidities, including anticoagulation medication management.[5] Historically, warfarin (Coumadin) has been used for anticoagulation, which requires waiting for an international normalized ratio (INR) of < 1.5 prior to surgery.[6] Furthermore, warfarin reversal using prothrombin complex concentrate (Kcentra) is costly. The advent of direct oral anticoagulants (DOACs) circumvents this problem, as blood draws and frequent monitoring are no longer necessary and half-lives are more predictable.[7] Therefore, orthopedic surgeons are now encountering a greater number of patients with hip fractures who are taking DOACs in lieu of the more traditional warfarin.[8]

Given that orthopedic surgeons rarely manage anticoagulants, it is important for them to gain an understanding of their patients' anticoagulation requirements for perioperative management of anticoagulation before and after hip fracture surgery. Many geriatric patients at risk of hip fractures use anticoagulants for prevention and treatment of venous thromboembolism, atrial fibrillation, and valvular heart disease.[9] These conditions require a multidisciplinary approach and perioperative optimization prior to schedul-

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ing surgery for a hip fracture. Patients who are anticoagulated at the time of fracture are at risk for surgical comorbidities if not properly optimized, including but not limited to excessive blood loss and need for blood transfusion.[10] In addition, postoperative hematoma presents another complication that can lead to wound dehiscence and infection.[11] Therefore, reversal of anticoagulants has been a topic of interest, including establishing the timing of discontinuation of anticoagulants before and after surgery.

The relatively recent introduction and predominance of DOACs in this population calls into question the unique perioperative management in comparison to warfarin, aspirin, and heparin. Lastly, there has been debate regarding the complication risk of DOACs and safety of usage prior to major procedures. Therefore, this review article consolidates the available evidence for the management of several classes of anticoagulation and antithrombotic prophylactic medications during the perioperative period for hip fractures. These recommendations should be used as a guideline, along with the collaboration of multidisciplinary hospital teams to manage these complex patients.

METHODS

This review article of the periprocedural management of DOACs for hip surgery was developed by examining the American College of Chest Physicians evidence-based clinical practice guidelines, Perioperative Guidelines on Antiplatelet and Anticoagulant Agents written by anesthesiologists, various prospective and retrospective studies, and drug labels for pharmacokinetic data.[12,13]

BACKGROUND: MECHANISM OF ACTION, PHARMACOKINETICS & PHARMACODYNAMICS

Maximum concentration (C_{max}) refers to the maximum concentration a drug achieves after 1 dose. The half-life ($t_{1/2}$) refers to the time it takes for the plasma value of the drug to reach one-half its initial concentration. Table 1 provides an overview of commonly used medications.

TRADITIONAL ANTICOAGULANT AGENTS

Warfarin (Coumadin). Warfarin is a vitamin-K epoxide reductase inhibitor in the liver, inhibiting the production of vitamin-K dependent clotting factors.[14] Warfarin reaches a C_{max} in 2-6 hours.[15] The $t_{1/2}$ of warfarin ranges from 20-60 hours depending on drug interactions, body mass index, diet, and genetics.[12,16] Moster and Bolliger determined that optimal timing of warfarin withdrawal prior to surgery is 3-5 days for procedures with both minor and major bleeding risk.[12] Warfarin should be resumed 24 hours postoperatively after minor surgery and 48-72 hours after major surgery.[5] Therapeutic warfarin levels vary among individuals and are based on a variety of factors; therefore, the prothrombin time and INR must be monitored preoperatively following warfarin withdrawal.[15] Various studies show an INR below 1.5-1.8 is needed before hip surgery.[17,18]

To reverse the effects of warfarin, many agents can be used. Non-specific products such as fresh frozen plasma (FFP), recombinant factor VIIa, activated prothrombin complex concentrate (PCC) and four-factor prothrombin complex concentrate (4F-PCC) have all shown ability to reverse warfarin as well as DOACs.[43] However, reversal if often quite costly as the cost of 4F-PCC can cost between $2748 to $5495 dollars for 25 to 50 units per kilogram.[44]

Unfractionated heparin. Heparin binds to antithrombin-3, activating an enzyme inhibitor that inactivates thrombin and factor Xa. In addition, unfractionated heparin binds and inhibits factor IIa. Unfractionated heparin is administered intravenously and requires monitoring of activated partial thromboplastin time (aPTT). An aPTT 1.5-2.5 times above control is accepted as therapeutic.[45,46] The $t_{1/2}$ is approximately 60 minutes and clearance of unfractionated heparin occurs faster than low-molecular weight heparin (LMWH).[46]

Patients who cannot tolerate LMWH due to renal failure, often use unfractionated heparin as an alternative.[47] Additionally, unfractionated heparin can be reversed rapidly via protamine, a cationic protein that binds rapidly to the anionic heparin.[18,48]

Low-molecular weight heparin (LMWH). LMWH is usually preferred in comparison to unfractionated heparin for patients with risk for deep venous thrombosis and venous thromboembolism.[49] Enoxaparin (Lovenox) is a LMWH that is usually used closer to perioperative procedures due to the short $t_{1/2}$ (4 hours), higher bioavailability, and its ability to be injected subcutaneously for those undergoing orthopedic procedures.[50] It is recommended that LMWH be started greater than 12 hours after surgery. However, unlike unfractionated heparin, LMWH is contraindicated in patients with renal insufficiency due to renal clearance.[47] For those with hip fractures, it is recommended an anti-factor Xa assay be used if monitoring is necessary, rather than aPTT.[46] The consensus recommendation for hip fracture patients presenting to the emergency department is to avoid surgical delays, even among patients who report taking a therapeutic dose of vitamin K and non-vitamin K anticoagulants within 24 hours before surgery, in order to reduce mortality rates associated with delays greater than 48 hours.[51]

In patients requiring anticoagulation or on warfarin at home, bridging therapy with LMWH is known to be administered based on risk stratification when immediate surgery is required and the INR is above target levels.[52] However, new studies have demonstrated that bridging therapy is not effective in reducing thromboembolic events while increasing risk of perioperative bleeding, especially in high-risk procedures.[12,53] Yassa et al., believe that bridging therapy in hip fracture patients should only be used in severe cases of high VTE risk.[52]

DIRECT ORAL ANTICOAGULANTS (DOACS)

DOACs are a newer generation of anticoagulants that have been increasing in use. Some of the commonly prescribed DOACs include the factor Xa inhibitors (rivoraxaban, apixaban, edoxaban, betrixaban) and the factor II (thrombin) inhibitor dabigatran. Aigner et al. conducted a retrospec-

Table 1. Pharmacokinetics of Commonly used Medications

Drug	Mechanism	Time to Peak	Half-Life	Renal Clearance	Monitoring	Reversal Agent
Warfarin[13-19]	Vitamink K antagonist	2-6 hours	20-60 hours	No, hepatic	INR	Vitamin K PCC FFP Factor VII
Dabigatran[19-22]	Direct thrombin inhibitor	1-2 hours	12-17 hours	Renal (80%)	aPTT	Idarucizumab
Apixaban[19,23-26]	Direct Xa inhibitor	3-4 hours	12 hours	Renal (27%)	PT aPTT	Adnexanet alfa 4F-PCC/PCC
Rivaroxaban[19,23-25, 27]	Direct Xa inhibitor	2-4 hours	5-9 hours	Renal (35%)	PT aPTT	Adnexanet alfa 4F-PCC/PCC
Edoxaban[24,28-32]	Direct Xa inhibitor	1.5 hours	10-14 hours	Renal (50%)	PT aPTT	None
Aspirin[14,33-35]	COX inhibitor	1-2 hours	3.5-4.5 for its active metabolite salicylate	Variable, both renal and hepatic	Blood salicylate	Alkinization
Clopidogrel[14,36,37]	P2Y12 receptor inhibitor	1-2 hours	6 hours	No, hepatic	Platelet monitoring	None
Prasugurel[14,38-40]	P2Y12 receptor inhibitor	1-2 hours	7 hours	No, hepatic	Platelet monitoring	None
Ticagrelor[14,41,42]	P2Y12 receptor inhibitor	2-8 hours	9 hours for active metabolite	No, hepatic	Platelet monitoring	None

4F-PCC/PCC, four-factor prothrombin complex concentrate; aPTT, activated partial thromboplastin time, ; COX, cyclooxygenase; FFP, ; INR, international normalized ratio; PCC, prothrombin complex concentrate; PT, prothrombin time.

tive database study of over 15,000 hip fracture patients, in which they reported that more patients were taking DOACs than vitamin K antagonists in 2018.[23]

Rivaroxaban/Apixaban. Rivaroxaban (Xarelto) has a $t_{1/2}$ of 5-9 hours in healthy adults with a longer $t_{1/2}$ up to 13 hours in the elderly.[24,54] Rivaroxaban bioavailability is 80%-100% at 10 mg irrespective of caloric intake.[25] Apixaban (Eliquis) is 50% bioavailable for doses up to 10 mg and has a higher plasma concentration in the elderly.[27] It is prescribed twice daily and can be given with or without food.[26,27] The $t_{1/2}$ of rivaroxaban is 5-9 hours for healthy individuals of age 20-45 years with a C_{max} of 2-4 hours.[24,25] Apixaban has a $t_{1/2}$ of 12 hours with a C_{max} of 3-4 hours.[54, 55] Rivaroxaban has one-third of its dose eliminated as unchanged drug renally with the remaining two-thirds metabolized by the liver.[24,25] The major routes of elimination for apixaban are biliary, intestinal, and renal (27%).[24,25] It is suggested that rivaroxaban and apixaban be discontinued 24 hours before a minor procedure and 48 hours before major procedures.[12]

The currently approved reversal agent for both rivaroxaban and apixaban is andexanet alfa, determined by the Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) study.[56] This single group cohort study evaluated the ability to reverse factor Xa inhibitors in patients with major bleeding, which was achieved within minutes. At 4, 8, and 12 hours after andexanet infusion, the median value for anti-factor Xa activity was reduced from baseline by 42%, 48%, and 62%, respectively, for rivaroxaban[56] and by 32%, 34%, and 38%, respectively, for apixaban.[56] According to the FDA, administration of a dose of 400 mg via intravenous bolus at a target rate of 30 mg/min followed by continuous infusion at 4 mg/min for up to 120 minutes is recommended for rivaroxaban users with a dose ⩽ 10 mg and apixaban users with a dose of ⩽ 5 mg. An initial dose of 800 mg intravenous bolus at a target rate of 30 mg/min followed by continuous infusion at 8 mg/min for up to 120 minutes is recommended for rivaroxaban users with a dose of ⩾ 10 mg or apixaban users with a dose of ⩾ 5 mg.[19,57] If no andexanet alfa is available then four-factor prothrombin complex concentrate (Kcentra) of 2000 units is recommended for urgent invasive procedures. Another study showed that both 37.5 IU/kg and 25 IU/kg of 4F-PCC restored rivaroxaban-induced prothrombin time prolongation after 15 minutes ($P < 0.001$).[58] Levels of rivaroxaban and apixaban can be measured accurately with prothrombin time and activated prothrombin time.[28] Frontera et al. report that the median cost of andexanet is $22120 per patient compared to $5670 per patient for 4F-PCC.[29] In addition, the cost of adexanet exceeds the hospital reimubursement by a median of $7604, decreasing the feasibility for practical use.[29]

Edoxaban (Savaysa). Edoxaban has a $t_{1/2}$ of 10-14 hours and a C_{max} of 1.5 hours.[30,54] Elimination occurs through the fecal (60%) and renal (30%) routes.[31,54] However, edoxaban is not recommended for hepatic patients over more traditional anticoagulants, such as warfarin.[32] The advantage of edoxaban compared to its DOAC counterparts is the lack of interaction with cytochrome p-450 enzymes as well as its once daily dosing.[20,59] Oral bioavailability of edoxaban is 62%.[21] Bridging therapy is not recommended for those on edoxaban due to its fast onset of action. Edoxaban should be discontinued 24 hours prior to minor procedures and 48 hours prior to major procedures.[12,31] Levels of edoxaban can be measured with PTT and aPTT.[28]

Dabigatran (Pradaxa). Dabigatran has a $t_{1/2}$ of 12-17 hours and a C_{max} of 1-2 hours.[22] Its mean bioavailability is 6.5% (3-7% range) but can be increased if the tablet is cut prior to ingestion.[54,59] Dabigatran has the highest renal clearance (80%) of all the DOACs.[22,59] Thus, it is important to check creatinine levels prior to ingestion. For those with a creatine clearance ⩽ 30 ml/min, it is recommended that unfractionated heparin be used in lieu of LMWH.[60] Heparin should not be used as bridging therapy for dabigatran resumption due to increased bleeding risk. It is recommended that surgery be delayed 1-2 days for those with a creatine clearance of ⩽ 50 ml/min.[22,54] Dabigatran levels can be measured with aPTT.[22]

Dabigatran has a specific reversal agent, idarucizumab (Praxbind), that was approved following the prospective single cohort study "The Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD)."[61,62] The study looked at two groups, one with uncontrolled bleeding and one undergoing an emergency procedure. Results showed that administration of 5 mg of idarucizumab via intravenous infusion rapidly reversed dabigatran levels by 88%-98% of patients within minutes based on dilute thrombin time or ecarin clotting time.[61,62] Pollack et al. used 20 ng/ml as the cutoff for patients classified as abnormally high levels of dabigatran. For emergency situations in which immediate hip fracture surgery is indicated, idarucizumab use seems to provide the best solution due to the rapid reversal.[61,62] When idarucizumab is not available, Schulman et al. recommend using 50 units/kg intravenous 4F-PCC for urgent invasive procedures.[33,57] Dabigatran should be discontinued 24 hours before minor procedures and 48 hours before major procedures.[12]

ANTIPLATELET AGENTS

Aspirin. Aspirin works by irreversibly inhibiting cyclooxygenase 1 and 2 enzyme, thereby preventing thromboxane synthesis and clot formation. The $t_{1/2}$ is approximately 20 minutes for aspirin; however, its metabolite salicylate has a $t_{1/2}$ of 3.5-4.5 hours.[34] The rate of aspirin elimination is heavily influenced by pH and is excreted renally. It takes around 48 hours for aspirin to be fully eliminated.[35] The AAOS recommend conducting surgery within 24-48 hours of hip fracture despite patients being on aspirin.[63] The American College of Chest Physicians and the AAOS jointly suggested the use of low-dose aspirin following surgery for thromboembolism prophylaxis up to 35 days.[13,36]

Clopidogrel (Plavix). Clopidogrel is an oral thienopyridine that is metabolized by CYP450 enzymes to produce its active metabolite that participates in antiplatelet activity.[37] Its active metabolite binds irreversibly to platelet $P2Y_{12}$ receptor, thereby preventing binding of ADP to its platelet receptor, and thus platelet activation and aggregation. Clopidogrel has a C_{max} of 1-2 hours and a $t_{1/2}$ of approximately

6 hours, with elimination occurring both via urine and feces.[37] Soo et al. conducted a meta-analysis reporting that operating early on patients with clopidogrel is safe and does not pose a significant risk of hemorrhage.[38] However, the studies included were observational studies that were nonrandomized and unblinded.[38]

Prasugrel (Effient). Prasugrel is an oral thienopyridine that similar to clopidogrel that is metabolized by CYP450 enzymes.[39] It irreversibly binds to the ADP $P2Y_{12}$ receptor, preventing platelet activation and aggregation. The C_{max} is 1-2 hours, and the active metabolite has a $t_{1/2}$ of 7 hours.[39] Most of the elimination occurs in urine with the rest via feces. The American Academy of Cardiology recommends prasugrel over clopidogrel for patients with acute coronary syndrome after percutaneous coronary intervention.[40] Yang et al. conducted a systematic review citing that it is unnecessary to delay hip fracture surgery for those on antiplatelets; however, no study has specifically evaluated prasugrel as the studies use clopidogrel as the standard antiplatelet therapy.[41]

Ticagrelor (Brilinta). Ticagrelor is a thienopyridine, like prasugrel and clopidogrel, that is metabolized by CYP450 enzymes. Unlike clopidogrel and prasugrel, ticagrelor is a reversible inhibitor of the ADP $P2Y_{12}$ receptor, thus also preventing platelet activation and aggregation.[42] The C_{max} is 2-8 hours, and the $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for its active metabolite. The primary route of elimination is biliary secretion.[42] The use of ticagrelor in hip fracture remains largely unknown.[52] Ticagrelor is recommended over clopidogrel for patients with acute coronary syndrome to reduce major adverse coronary events; however, this increases bleeding risk.[64]

PERIOPERATIVE MANAGEMENT

DISCONTINUATION PREOPERATIVELY

Until recently, there were no set guidelines for DOAC perioperative management. The first large study to provide a frame was the COncentration of RIvaroxaban, Dabigatran and Apixaban (CORIDA) study, a multicenter prospective observational study with the purpose to determine the optimal duration of DOAC discontinuation that achieves minimal anticoagulant effect at the time of an elective procedure.[65] The study used the International Society on Thrombosis and Haemostasias' published safety thresholds for concentration cut-off.[65,66] The authors determined that a DOAC mean discontinuation of 49-72 hours before a high bleeding risk procedure achieved perioperative DOAC concentrations of ⩽ 30 ng/ml, which was acceptable within the published thresholds for high bleeding risk surgery.[66]

The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study evaluated DOAC patients being treated for atrial fibrillation that needed anticoagulant interruption for an elective procedure.[67] Interruption protocols of 1 or 2 days prior to elective surgery were used for low and high bleeding risk procedures, respectively. DOACs were resumed 1 day after low bleeding risk procedures and 2 to 3 days after high bleeding risk procedures. This protocol resulted in low rates of bleeding and arterial thromboembolism for planned, elective procedures; however, applicability of these results are merely extrapolated to hip fracture surgery but were not studied directly.[67]

Several recent studies evaluated DOACs in the setting of hip fracture, the majority of which demonstrate significant delays in time to surgery (TTS) in patients taking DOACs compared to those not on anticoagulation (Table 2).[18,23,68-80] Aigner and colleagues conducted a retrospective analysis of more than 15,000 hip fracture surgery patients, corroborating the significantly increased TTS compared to control (patients waiting for surgery > 24 hours, DOAC 54%, vitamin K antagonists 50%, and Control 25 %) $p < 0.0001$.[23] Despite the large sample size, Aigner et al. speculate the significant difference in TTS could be due to a lack of standardized tests to measure the anticoagulant effect of the drug.[23] Creeper et al. suggest that while there was significant delay in TTS for DOAC vs warfarin users, the delay may be unnecessary due to significant proportion of patients with early DOAC levels below ⩽ 50 ng/mL.[76] The mean time to a DOAC level of ⩽ 50 ng/mL was approximately 24.3 hours. Therefore, a more standardized guideline and laboratory studies for measuring DOAC levels prior to surgery may be warranted to determine if DOAC delay for TTS is needed.

Aziz et al. conducted a study to evaluate if waiting 24 or 48 hours since the last DOAC dose, or until the DOAC concentration ⩽ 50 ng/mL, was better for hip fracture surgery outcomes.[71] The authors concluded that monitoring the DOAC dose resulted in the greatest TTS (53.3 hours) compared to waiting 24 hours (TTS = 17.5 hours) or 48 hours (TTS = 22.5 hours), $p < 0.0001$.[71] Among the 120 patients, there were no significant differences in mortality, blood transfusion, and hemoglobin drop among the 3 groups, indicating that monitoring DOAC concentration is likely unnecessary.[71] The findings corroborate the PAUSE trial and the CORIDA trial, suggesting that an interruption protocol of 24 hours for low bleeding risk procedures and 48 hours for high bleeding risk procedures may be more effective.[18,23,65,67] Of note, prior studies relied on pharmacokinetics in relation to atrial fibrillation. Patients with alternative diagnoses may still have therapeutic levels of DOAC at time of surgery due to reduced elimination rates.[18]

The use of DOACs was also reviewed when comparing different treatments for hip fracture. Schermann et al. evaluated both closed reduction internal fixation and hip arthroplasty in DOAC users compared to control, finding a significant delay in TTS (40.2 ± 26.9 vs 31.2 ± 22.2 hours) as well as length of surgery (122.0 ± 58.0 vs 110.7 ± 48.9 minutes) in the closed reduction internal fixation group compared to control.[80] However, there was no difference in both closed reduction internal fixation and hip arthroplasty when looking at DOAC compared to control in percentage of surgeries undergoing hip surgery under 48 hours.

RE-INITIATION POSTOPERATIVELY

Careful, patient-specific, consideration must be given for DOAC resumption postoperatively as the physician must weigh the risk of clotting due to delays to the risk of he-

Table 2. Evidence for Perioperative Management Strategies

Medications	Discontinuation before Surgery		Time to Resume After Surgery		Special Considerations
	Minor Surgery	Major Surgery	Minor Surgery	Major Surgery	
Warfarin[14,51]	3-5 days		24 hours after minor procedures	48-72 hours after major procedures	INR <1.5-1.8 before starting surgery Bridging therapy with heparin if INR above target levels but should be avoided in high-risk bleeding procedures
Dabigatran[14,19,24]	24 hours before minor surgery	48 hours before major surgery	24 hours for minor procedures	24-48 hours for major procedures	An additional 1-2 day waiting period prior to surgery if creatine clearance <50 ml/min
Apixaban[14,31,338]	24 hours before minor surgery	48 hours before major surgery	24 hours for minor procedures	24-48 hours after major procedures	Additional laboratory tests to determine withholding period if creatinine <50 ml/min
Edoxaban[14,19,24]	24 hours before minor surgery	48 hours before major surgery	24 hours for minor procedures	24-48 hours after major procedures	Additional laboratory tests to determine withholding period if creatinine <50 ml/min
Rivaroxaban[14,19,24]	24 hours before minor surgery	48 hours before major surgery	24 hours for minor procedures	24-48 hours after major procedures	Additional laboratory tests to determine withholding period if creatinine <50 ml/min
Aspirin[14,19,24]	Patient specific		Within 24 hours		For patients with severe cardiovascular risk, continue therapy preoperatively due to aspirin withdrawal syndrome.
Clopidogrel[14,24]	5 days; however, no consensus as some studies indicate cessation not needed		Within 24 hours		
Prasugurel[14,24]	5 days; however, no consensus as some studies indicate cessation not needed		Within 24 hours		Recommended over clopidogrel with patients with acute coronary syndrome after percutaneous coronary intervention
Ticagrelor[14,24]	5 days; however, no consensus as some studies indicate cessation not needed		Within 24 hours		Recommended over clopidogrel with patients with acute coronary syndrome to decrease major adverse cardiac effects but can have higher risk of bleeding

INR, international normalized ratio.
References: Moster et al,[14] Shaw et al[24] Yassa et al,[51] and Cuker et al[19]

morrhage. In the PAUSE trial, it was shown that for low risk bleeding procedures and high risk bleeding procedures, DOACs can be resumed 24 hours and 48-72 hours, respectively.[67] Other studies have indicated similar results with resumption of DOACs for high risk bleeding procedures beginning as soon as 24 hours.[12] Looking specifically at hip fractures, Giannoudi and Giannoudis reinforce previously mentioned studies stating that anti-factor Xa DOACs can be reinstated 24-36 hours after proximal femur hip surgery and after 24 hours for antithrombin DOACs.[59]

In addition, Goh et al. conducted a single-center, retrospective, population-based cohort study among hip fracture patients. Goh et al. indicate that the British National Formulary have stated that DOACs can be reinstated sooner than previously thought: 1) apixaban can be administered 2.5 mg x 2 daily at 12-24 hours after surgery; 2) rivaroxaban can be administered 10 mg x 1 daily at 6-10 hours after surgery; and 3) dabigatran can be administered at 75 mg 1-4 hours after surgery followed by 150 mg x 1 daily for 10 days.[81] For the newer DOAC edoxaban, Fuji et al. administered edoxaban 6-24 hours after surgery on Japanese patients. Results show that edoxaban at 30 mg once daily had similar efficacy to enoxaparin for prevention of thromboembolic events.[82] Other studies show doses of up to 60 mg of edoxaban is well tolerated; however, edoxaban should not be taken more than once a day due to significant increase in bleeding in patients that took edoxaban 30 or 60 mg twice a day.[83] Zhou et al. conducted a retrospective cohort study demonstrating that edoxaban has significantly lower rates of new onset hip fractures, medically attended falls and all-cause mortality compared to warfarin users.[84]

SAFETY AND EFFICACY

The major outcomes that have been studied in the hip fracture literature with respect to DOACs are outlined in Table 3 and include, blood transfusion, mortality, hemoglobin drop, and hospital length of stay.[18,23,68-80] Several studies demonstrate that patients taking DOAC have a risk of increased transfusion rate.[77,85] Schuetze et al. demonstrated that patients taking DOACs have a 3.4-fold increased transfusion rate.[77] Furthermore, if operated in the first 6 hours after admission, the risk of transfusion was significantly lowered; however, an operating time > 90 minutes lead to 5.5 significant increase in risk of transfusion.[77] Schuetze et al speculate that delaying surgery beyond 6 hours may mitigate the effects of oral anticoagulants; however, patients could be more susceptible to pulmonary embolisms, urinary infections, ulcers and myocardial ischemia that can contribute to a longer hospital length of stay.[29,77]

Additionally, the association between increased mortality rate and TTS has been demonstrated, with a delay by more than 48 hours portending a higher mortality rate in patients with hip fractures.[4,5,68,77] Most studies have found no significant relationship between DOAC compared to control in regards to hemoglobin drop or DOAC.[68-70,72,75,78-80]

With regards to hospital length of stay, a majority of studies have found no significant difference between those on DOACs compared to those not on anticoagulants prior to admission.[69,70,73-75,79] Aigner et al. found a slight significance of in-hospital mortality with warfarin and DOAC compared to control groups (DOAC 17.0 days [interquartile range 11.1-23.0], vitamin K antagonists 17.1 days [interquartile range 12.1-24.0], and Control 15.1 days [interquartile range 10.0-21.1]).[23]

SUMMARY

There is a growing body of evidence that hip fracture surgeries are delayed in patients taking DOACs compared to those not on anticoagulants. More research is needed in focusing on if these delays are preventable, as some studies suggest that most patients have ⩽ 50 ng/ml DOAC levels at time of surgery, even when under 24 hours from presentation. In addition, a standardized protocol should be developed based on the highest level of evidence, considering that recent literature has questioned whether the best approach to determine surgical timing should be based on last DOAC dose versus DOAC concentrations ⩽ 50 ng/ml. This would empower orthopedic surgeons and the multidisciplinary teams taking care of these patients to safely avoid unnecessary delays to the operating room. At this time, it appears that patients taking DOACs may safely proceed to surgery for acute presentation of hip fracture, with a recommendation for surgery within 48 hours. A multidisciplinary approach should be utilized, and consideration of renal clearance, comorbidities, risk of high bleeding events with surgery, or management of concurrent thromboembolic disease should be managed appropriately. The resumption of DOACs postoperatively may require a bridging agent, but generally may be safely resumed 1-2 days postoperatively with close monitoring for hematoma or increased blood loss.

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Table 3. Summarizes the main outcomes of major new studies regarding hip fracture

Hip Fracture Study	Groups	Median TTS/Delay to Surgery	Red Blood Cell Transfusion	Mortality	Hb Drop	HLOS
Aigner et al. (2022)[53]	1) DOAC 2) VKA 3) No anticoagulant (control)	TTS significant difference compared to control (patients waiting for surgery > 24 hours, DOAC 54%, VKA 50%, and control 25%) p<0.0001		Significant difference compared to control for mortality during in-patient stay: DOAC 8% VKA 6.5 % Control 4.6 %		Slight significant difference compared to non-coagulated Significant difference in VKA compared to DOAC DOAC: 17.0 days (IQR 11.1-23.0) VKA: 17.1 days (IQR 12.1-24.0) Control: 15.1 days (IQR 10.0-21.1)
Aziz et al. (2019)[70]	Group 1: Wait 24 hours since last DOAC dose until surgery Group 2: Proceed to surgery once DOAC <50 ng/ml Group 3: Wait 48 hours since last DOAC dose until surgery Control group	TTS between the 3 protocol groups was significantly different at 17.5 (Group 1), 53.3 (Group 2) and 22.5 hours (Group 3), (p<0.0001). DOAC significant delay in TTS vs control	No statistically significant difference	No change in mortality	Median Hb on arrival to hospital was higher in the control group (124 g/L) compared with the 3 protocol groups (87 g/L) (t-test p<0.0001)	
Bruckbauer et al. (2019)[69]	1) Warfarin 2) DOAC 3) No antithrombotic	DOAC and Warfarin patients had the longest time to surgical hip fracture fixation (29.5 and 24 hours). This period was significantly longer compared with patients in the no-antithrombotic group (12 hours) 50.8% of Warfarin and 37.0% of DOACs had their	38% in the no-antithrombotic groups received any transfusion compared with 54.2% in patients on Warfarin and	No statistically significant difference	Not significant between DOAC vs Warfarin	No statistically significant difference

Hip Fracture Study	Groups	Median TTS/Delay to Surgery	Red Blood Cell Transfusion	Mortality	Hb Drop	HLOS
		surgical hip fracture stabilization within the first 24 hours	53.7% in the DOAC group (p<0.0001)			
Cafaro et al. (2019)[72]	1) DOAC 2) VKA 3) No OAC	Median TTS was longer in the VKA group (64 hours; IQR: 50–84) and in the DOAC group (61 hours; IQR: 42 to 77) versus the No OAC group (44 hours; 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).	Higher rate of packed red blood cell transfusion in DOAC vs VKA and No OAC groups (58%, 29%, and 31%. respectively p<0.01)		Higher rate of preoperative bleeding in DOAC vs VKC and No OAC groups (24%, 14%, and 10%, respectively, p<0.02)	No statistically significant difference
Cavaillez et al. (2021)[71]	1) DOAC <30 ng/ml morning of surgery 2)DOAC 30-50 ng/ml morning of surgery	Median delay between last DOAC concentration dosage and surgery was 7.2 (IQR 4.8-12.9) hours in the group with a DOAC concentration between 30-50 ng/mL and 13.3 (IQR 7.0-33.6) hours in the group with DOAC concentration <30 ng/mL (p=0.02).	No statistically significant difference	No statistically significant difference	No statistically significant difference	
Creeper et al. (2022)[75]	1) DOAC 2) Warfarin 3) No anticoagulants (control)	TTS longer for those anticoagulated vs non-anticoagulated with those on DOAC significantly longer than those on warfarin (median difference of 16 hours) 52% of those that had a level within 12 hours had <50 ng/ml within 12 hours Mean time to level <50 ng/ml was 24.3 hours	No statistically significant difference	No significant difference when comparing <30 ng/ml vs <50 ng/ml in DOAC group No significant difference in DOAC vs warfarin	Dual group (antiplatelet + anticoagulant) significant Hb drop compared to control	
Franklin et al., (2018)[78]	1) DOAC 2) No anticoagulant (control)	Patients receiving DOAC within 48 hours of admission had a significantly longer TTS compared to control (28.9 vs. 21.4 hours, p=0.03)	No statistically significant difference	No statistically significant difference	No statistically significant difference	No statistically significant difference
Hoerlyck et al. (2020)[68]	1) Anticoagulated (DOAC + Warfarin) 2) Non-anticoagulated	Anticoagulated 27 hours (IQR=12-42) Non-anticoagulated 25 hours (IQR=7-43)	No statistically significant difference	No statistically significant difference	No statistically significant difference	No statistically significant difference once cofounding variables controlled
Krespi et al. (2021)[67]	DOAC patients Grouped on TTS 1) <24 hours 2) 24-48 hours 3) > 48 hours	N/A	No statistically significant difference Early surgery no effect on transfusion	Trend toward increased 30-day mortality in the ≥48 hour group compared to the 24-48 hour and ≤24 hour groups (13.0%, 4.3% and 3.1%, respectively; p=0.099) Not statistically significant but limited by sample size	No statistically significant difference Early surgery no effect on blood loss	

Hip Fracture Study	Groups	Median TTS/Delay to Surgery	Red Blood Cell Transfusion	Mortality	Hb Drop	HLOS
Mahmood et al. (2021)[77]	1) Warfarin 2) Antiplatelet 3) DOAC 4) Control	Mean TTS (hours) Control 23.5 Antiplatelet 24.4 Warfarin 29.6 DOAC 28.1 No significant difference	Significant difference in antiplatelet group compared to the other groups: 32.3% antiplatelet 21.6% control 21.7% warfarin 23.2% DOAC	Mortality rates at 30 days were 4.8% for the control group, 12.6% for the antiplatelet group, 7.0% for the warfarin group, 9.5% for DOAC group, p=0.004 Mortality rates at 1 year were 22.4% for the control group, 32.3% for the antiplatelet group, 29.3% for the warfarin group and 29.0% for the DOAC group (p=0.007) All significant differences went away when matched for ASA, age, and sex	No statistically significance in postoperative Hb loss	
Matheron et al. (2022)[74]	1) DOAC 2) No anticoagulant (control)	The mean TTS was 49.5 hours in the DOAC group versus 31.3 hours in the control group (p=0.0002)	No statistically significant difference	No statistically significant difference	No statistically significant difference	No statistically significant difference
Rostango et al. (2021)[73]	1) DOAC 2) No anticoagulants (control)	TTS was significantly longer in patients treated with DOACs vs control (3.6 vs 2.1 days). Significant difference in percentage treated under <48 hours for DOAC (47%) vs control (80%)	No statistically significant difference	No statistically significant difference	DOAC (37%) vs control (12%) in Hb <8.0 g/dl	No statistically significant difference
Schermann et al. (2019)[79]	1) DOAC 2) Control 2 types of procedures: CRIF Hemi-arthroplasty	CRIF group had significant difference in duration of surgery (110.7 ± 48.9 control vs 122.0 ± 58.0 minutes DOAC) CRIF group had significant difference in TTS (31.2 ± 22.2 control vs 40.2 ± 26.9 hours DOAC) Hemi-arthroplasty group only had significant difference in duration of surgery (126.2 ± 39.8 control vs 143.7 ± 38.5 minutes DOAC) No difference in surgeries < 48 hours	No statistically significant difference	CRIF group had a significant difference in 1 year mortality (16.1% control vs 26.7% DOAC) partly due to increased waiting TTS as well as age and higher comorbidity burden	No statistically significant difference	
Schuetze et al. (2019)[76]	1) Aspirin 2) Platelet aggregation inhibitor 3)DOAC 4) VKA 5) Control	No statistically significant difference between anticoagulant groups	Patients taking DOAC resulted in a 3.4-fold increased. If operated in the first 6 hours after admission, risk was significantly lowered by factor II. Operating time >90 minutes led to 5.5 significant increase in risk	Not significant when anticoagulation group operated <24 hours Only ASA classification and age significant on 1-year mortality	If operating time >90 minutes, Hb significantly higher VKA significantly lower postoperative Hb DOAC significantly lower Hb at admission	

Hip Fracture Study	Groups	Median TTS/Delay to Surgery	Red Blood Cell Transfusion	Mortality	Hb Drop	HLOS
Vitkil et al. (2019)[17]	1) Warfarin 2) DOAC 3) Platelet inhibitors	DOAC (44 hours) Warfarin (25 hours)	N/A	N/A	N/A	N/A

ASA, American Society of Anesthesiologists ; CRIF, closed reduction internal fixation; DOAC, direct oral anticoagulant; Hb, hemoglobin; HLOS, hospital length of stay; IQR, interquartile range; N/A, ; OAC, ; TTS, time to surgery: VKA, vitamin K antagonists.

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