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Proximal femur fractures in patients taking anticoagulants

Ioannis V. Papachristos[1]
Peter V. Giannoudis[1,2]

- Thirty per cent of patients presenting with proximal femoral fractures are receiving anticoagulant treatment for various other medical reasons. This pharmacological effect may necessitate reversal prior to surgical intervention to avoid interference with anaesthesia or excessive peri/post-operative bleeding. Consequently, delay to surgery usually occurs.
- Platelet inhibitors (aspirin, clopidogrel) either alone or combined do not need to be discontinued to allow acute hip surgery. Platelet transfusions can be useful but are rarely needed.
- Vitamin K antagonists (VKA, e.g. warfarin) should be reversed in a timely fashion and according to established readily accessible departmental protocols. Intravenous vitamin K on admission facilitates reliable reversal, and platelet complex concentrate (PCC) should be reserved for extreme scenarios.
- Direct oral anticoagulants (DOAC) must be discontinued prior to hip fracture surgery but the length of time depends on renal function ranging traditionally from two to four days.
- Recent evidence suggests that early surgery (within 48 hours) can be safe. No bridging therapy is generally recommended.
- There is an urgent need for development of new commonly available antidotes for every DOAC as well as high-level evidence exploring DOAC effects in the acute hip fracture surgical setting.

Keywords: anticoagulants; hip fracture; proximal femoral

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Introduction

Each year over 300,000 people over 65 years old sustain a hip fracture in the USA.[1] In 2017, 67,000 people older than 60 years old presented with neck of femur fracture (NOF) in the United Kingdom.[2] The expected incidence in 2050 of proximal femoral fractures is 7 million. This increase comes as a result of an aging population, with associated frailty and osteoporosis. Another aspect of aging is that these patients suffer from multiple co-morbidities, hence they are usually being treated with anticoagulants for cardiovascular or cerebrovascular diseases. As a matter of fact one-third of patients presenting with proximal femoral fractures are being anticoagulated at the same time.[3] This can have serious implications for the time to surgery as the anticoagulant effect of these drugs may have to be reversed to allow neuraxial anaesthesia or to prevent excessive peri-operative bleeding. Time to surgery is well known to correlate directly with hip fracture patient morbidity and mortality.[4] Delay of more than 48 hrs to surgery has been found to be related to systemic problems (chest infections, decubitus ulcers, pulmonary oedema, impaired mobility-functional results) leading to prolonged length of stay, morbidity and mortality.[5] Recently it was shown that delay to surgery of more than 24 hrs is a risk factor for wound infection.[6] Therefore, in England, National Health Service (NHS) Trusts are incentivized by a 'best practice' tariff (extra financial benefit of £1335 per patient introduced in 2010) for hip fracture surgery (HFS) in the first 36 hrs from admission. Despite this, time to surgery varies greatly between countries and in hospitals in the UK and, in 2017, only 70% of NOFs were operated on in the first 36 hrs. Taking into consideration that in 2020 this cut-off will be 24 hrs rather than 36 hrs it is more than evident that the number of outliers will dramatically increase. Delay to surgery cannot always be attributed solely to anticoagulants, as other causes (theatre space availability, optimizing of other co-morbidities) can be responsible, but it is established that earlier surgery promises better patient functionality and survival. Patients with proximal femoral fractures commonly take oral platelet inhibitors (aspirin, clopidogrel, ticagrelor, prasugrel) or oral vitamin K antagonists (warfarin, acenocoumarol, phenprocoumon) or newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban). In this instructional lecture we will try to outline the key points of each

drug and their impact on time to surgery. We will also explore current practice, highlight best up-to-date recommendations and elucidate future directions.

Platelet inhibitors

Aspirin is traditionally used for prevention of cardiovascular events. It irreversibly inhibits cycloxygenase-1 (COX-1) resulting in reduced production of thromboxane A2 (TXA2) thus preventing platelet aggregation and clot formation. Dipyridamole and cilostazol are phosphodiesterase inhibitors which prevent adenosine platelet re-uptake, blocking platelet aggregation. Recent evidence showed that patients receiving aspirin, dipyridamole, or both, who have hip fractures may safely undergo urgent surgery without delay.[7] In cases with unexpected or serious bleeding, the antiplatelet effect can be reversed with transfusion of two units of platelets 2 hrs after the last dose of aspirin. Neuraxial anaesthesia during aspirin treatment has been proven safe.[8]

Clopidogrel has a more potent antiplatelet profile. It is a thienopyridine which irreversibly binds to the platelet receptor P2Y12 inhibiting Adenosine diphosphate (ADP)-dependent signalling pathways involved in platelet congregation. Due to this mechanism traditionally a washout period of 5–7 days had been advised in order to regain platelet function.[9] This recommendation applies especially in elective surgery.[10] Zhang et al supported the view that continuing clopidogrel during HFS resulted in more intra-operative transfusions, increased intensive care unit (ICU) admissions, higher length of stay and lower one-year survival rate.[11] This finding was negated by a recent review and systematic analysis which demonstrated that stopping clopidogrel induces cardiovascular or cerebrovascular complications without avoiding bleeding.[12] A systematic review demonstrated that early surgery in patients under clopidogrel is safe with marginal increase in transfusions.[13] In another study, length of stay or ICU admissions were not any different from operated hip fracture patients not on clopidogrel, hence no need for clopidogrel cessation was postulated.[14] This increasing amount of evidence is supported by another study which, apart from showing the safety of peri-operative continuation of clopidogrel, revealed that patients undergoing dual antiplatelet treatment (DAT) – clopidogrel plus aspirin – need higher amounts of transfusions.[15] Patients on a dual antiplatelet regimen usually have severe cardiovascular disease with stents and therefore the American College of Chest Physicians (ACCP) and the American College of Cardiology (ACC) suggest that if one drug needs to be stopped this should be clopidogrel and in the extreme cases when this is medically risky, a short bridging therapy with parenteral glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) can be applied.[16] Despite these recommendations there is evidence that continuation of dual antiplatelet treatment is safe, taking into account a greater peri-operative blood loss.[17] Noteworthy, for neuraxial anaesthesia, in the case of clopidogrel or newer antiplatelet drugs prasugrel and ticagrelor, five to seven days of drug cessation are needed prior to HFS in order to avoid spinal hematomata.[18] Prasugrel and ticagrelor share the same mechanism of action with clopidogrel. However, both have stronger antiplatelet activity than clopidogrel. Ticagrelor is a reversible platelet ADP inhibitor which acts faster than clopidogrel. Platelet infusions are ineffective with both of these drugs. Interestingly, there are no studies investigating these drugs in relation to acute hip fracture surgery.

Vitamin K antagonists (VKA)

Warfarin is the main vitamin K antagonist (VKA), acting by inhibiting the liver carboxylation of glutamic acid residues in the N-terminal regions of the vitamin K dependent clotting factors (II, VII, IX, and X). The inhibition of these factors prevents the formation or propagation of clots. Apart from warfarin, acenocoumarol and phenprocoumon are also used (mainly in Germany). They are most commonly prescribed for atrial fibrillation (83%), thrombosis (DVT/PE, 18%), mechanical heart valve (5%) as well as by 7% of cases for multiple indications.[19] The prevalence of warfarin medication in hip fracture patients is estimated to be between 5–10.3%.[20,21]

VKA anticoagulant action is monitored by prothrombin-INR (international normalized ratio) measurements. An INR equal to or less than 1.5 is a pre-requisite for surgery especially for regional anesthesia.[22] Therefore, reversal of anticoagulant effects of VKAs is obviated prior to hip fracture surgery. This can lead to substantial delays in the operating theatres. It was estimated that warfarinized patients are only 20% likely to be operated on within the first 48 hrs.[21] This delay, apart from implications for morbidity/mortality rate, also carries negative financial consequences for hospitals: in one study, it was estimated that £80,000 of financial loss occurred from failing to achieve the 'best practice' tariff (BPT) due to warfarin.[23]

Approaches for VKA reversal as reflected by INR correction are: discontinuation of the coagulant with or without oral/intravenous vitamin K administration, adding prothrombin complex concentrate (PCC) or giving fresh frozen plasma (FPP).[24] Warfarin has a half-life of 35 hrs, whereas different clotting factors share different half-lives (the shortest is factor VII with 6 hrs and longest is factor II with 60hrs). Taking into consideration these variable half-lives and adding the variability of the presenting INR one can realize that solely discontinuing warfarin cannot give a predictable timeframe of INR target reversal. Therefore, simply stopping warfarin can take up to five days to

achieve an acceptable coagulation state.[25] This 'wait and see' approach is not considered acceptable nowadays with the proven benefits of early surgery.

The risk of thrombo-embolic recurrence after coagulation withdrawal is considered low (up to 0.3%). Supplementation of vitamin K (Phytonadione) replenishes the body's vitamin K storage and re-activates prothrombin factors leading to INR correction. Both oral and intravenous (IV) routes of vitamin K administration have been proved effective in warfarin reversal; however, the IV route seems to be more predictable and quicker due to increased bio-availability.[26] Testing INR in the first 6 hrs after vitamin K supplementation is based on the six-hour half-life of factor VII. However, other authors have suggested INR measurements every 12 hrs.[23] There is no consensus regarding the optimal dose, route and timeframe of vitamin K administration. Adverse reactions to vitamin K administration are estimated at around 2% and include allergic reactions, acute thrombosis or warfarin resistance. Intravenous administration of 1 mg vitamin K upon admission reduced the average time to surgery from 73 hrs to 38 hrs and increased the proportion of patients operated on within 48 hrs from 30% to 80%.[27] Other studies suggest higher doses (3 mg) of IV vitamin K for rapid and successful INR reversal.[28] These higher doses, though offering stronger INR correction potential, can theoretically increase warfarin resistance, making re-instatement of anticoagulant treatment more difficult post-operatively.[29]

Intravenous vitamin K has been found to result not only in decreased delay to surgery but also in a very low complication rate[30] and shorter length of stay.[31] When the oral route for vitamin K administration is sought, 5 mg initially can be a reasonable dose with an additional oral dose of 1–2 mg in 24 hrs if the perceived INR target is not achieved, as is a usual practice in many British hospitals. However, time to theatre can be widely variable and we do not consider it as effective as the intravenous route.[32] We must highlight that operated warfarinized hip fracture patients after INR correction in another study did not need more transfusions compared with non-anticoagulated patients, a finding which lends support to the idea that these patients can even be operated on with a higher INR than 1.5.[33]

The British Committee for Standards in Haematology (BCSH) advises that warfarin can be re-started on the first post-operative day provided adequate haemostasis has been achieved in theatre.[34] However, this can be deemed as subjective even for a highly experience surgeon, therefore, variations exist leading to warfarin re-initiation even 72 hrs post-operatively. As warfarin is a slow-acting drug, we believe that re-starting it between 24–36 hrs post-operatively will not prolong the length of stay and that is also safe. Bridging with low molecular weight heparin is a standard routine after warfarin discontinuation and takes place pre and post surgery. The British Society of Haematology advises risk stratification of patients regarding thrombosis risk and highlighting especially high-risk patients (metallic heart valves, DVT/PE, stroke, ischaemia) < 3 months.[35]

Prothrombin complex concentrates (PCC) can also be used when urgent (< 6 hrs) warfarin reversal is needed. They comprise high (x 25) concentrations of inactive clotting factors (II, VII, IX, X) as well as protein C and S. Two different commercial formulations exist named Beriplex and Octaplex. They reverse INR in 30 minutes and their action lasts up to 6 hrs. Both have been proved efficient in reversing the warfarin effect in significant bleeding.[36] A three-factor PCC (3-PCC) also exists; however, a recent study has showed that 4-PCC is more effective in restoring INR.[37] Co-administration of oral 5 mg vitamin K is advised because it prevents rebound INR increases after 6 hrs.[38] Moreover, administration of PCC with fresh-frozen plasma (FFP) has been correlated with increased 30-day mortality.[39] Beriplex costs 600 euros and in some studies is considered a cost-effective saving, producing £1250 per patient.[40] Currently, the sole clear indication is for young warfarinized patients with intracapsular hip fracture, where prompt (< 6 hr) fixation is indicated to avoid avascular necrosis.[41]

Fresh-frozen plasma (FFP) is the liquid blood component containing all the coagulation factors. It has traditionally been postulated as another VKA reversal; however, it is considered less effective compared with PCC in restoring normal INR with the added risk of volume overload and higher thrombo-embolic events.[42] The literature nowadays does not support its use in VKA reversal for proximal femoral surgery.

Direct oral anticoagulants (DOACs)

This new category includes dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis) and edoxaban (Lixiana) and was quite recently introduced in 2013 for prevention of thrombo-embolism after elective total hip or knee replacement. Their indications were extended to treatment of venous thrombo-embolism (VTE) and prevention of stroke in patients with non-valvular atrial fibrillation (AF). These drugs have been shown to be more effective than warfarin in reducing the incidence of stroke and systemic embolic events with the added benefit that no monitoring is needed, the dose is fixed with rapid onset and offset plus without dietary requirements or drug-to-drug interactions. Therefore, these non-vitamin K antagonist oral anticoagulants (NOACs) are now rapidly gaining popularity over warfarin for AF and for treatment/prophylaxis of VTE in orthopaedic surgery.[43] Moreover, they do not induce osteoporosis as is the case with long-term VKAs.[44] DOACs undergo renal clearance (80% for

dabigatran, 50% for edoxaban, 35% for rivaroxaban, and 27% for apixaban) and thus can accumulate in patients with declining renal function. The dose needs to be adjusted in renal impairment.

Dabigatran is a direct factor IIa (thrombin) inhibitor with a half-life of 12–17 hrs and 1–3 hrs needed for peak action. It is cleared mainly by the kidneys and is contra-indicated in patients whose creatinine clearance is less than 30 mL/min. Rivaroxaban, apixaban and edoxaban are all direct factor Xa inhibitors. Rivaroxaban has a half-life of 9–13 hrs and 1–3 hrs for peak action, apixaban a half-life of 8–10 hrs and peaks in 1–3 hrs, and edoxaban exhibits a half-life of 10–14 hrs with rapid absorption in 1–3 hrs. Routine monitoring of these drugs is not needed, and validated tests do not exist. Thrombin time is sensitive even with low blood levels of dabigatran but most importantly the existence of normal thrombin time excludes clinically significant levels of this anticoagulant. Direct thrombin time (dTT) and ecarin clotting time (ECT) are linearly correlated with dabigatran but are not widely available. Specialized anti-XA laboratory tests elaborate clinically relevant drug rivaroxaban or apixaban concentrations but are expensive, not widely available and there is a lack of adopted drug-specific standard curves.[45] Therefore, in a proximal femoral fracture case we cannot use any tests to evaluate the level of coagulation and therefore, the reversal plan can only be based on the name of the drug, timing of the last dose as well as renal function.

A recent study has shown that DOAC treatment is related to a significant delay to surgery (beyond 36 hrs).[46] This problem is exacerbated by the confusion caused by the lack of consensus on the appropriate drug-free interval until hip fracture surgery. The British Society of Haematology recommends a 48-hour DOAC-free period prior to elective orthopaedic surgery in patients with normal renal function.[35] This can be extended up to four days in cases of severe renal impairment. The International Society on Thrombosis and Haemostasis (ISTH) base their empirical suggestions on three half-lives and advise pre-operative suspension of three days before elective surgery. According to the Association of Anaesthetists of Great Britain and Ireland (AAGBI) neuraxial blockade should be avoided for 24–48 hrs after the last dose of apixaban and for 48 hrs for rivaroxaban. Otherwise general anaesthesia should be considered.[20] Rivaroxaban and apixaban share shorter half-lives than dabigatran and it has therefore been advised that only 24 hrs delay should be adequate.[47] All these recommendations were established for elective planned surgery and not in an acute fractured hip setting where early surgery is one of the top priorities.

In its general guideline for AF, NICE advises that bridging anticoagulation is not generally necessary for planned surgery due to the predictable decline in effect of drugs and their rapid onset of action upon restarting after surgery.[48] On the other hand, the British Society of Haematology (BSH) recommends standard thromboprophylaxis with Low Molecular Weight Heparin (LMWH) post-operatively up to 48 hrs when DOACs are re-introduced.[35] The American Society of Regional Anesthesia and Pain Medicine (ASRA) recommends recommencing these drugs no sooner than 6 hrs post a neuraxial procedure, but removal of an indwelling epidural catheter and interventional pain guidelines are suggested as reasons for waiting for 24 hrs.[49] Others recommend that the bridging decision should weigh the thrombo-embolic vs. bleeding risk and the withdrawal period of the drug and suggest post-operative LMWH if patients are unable to take oral drugs. Again the DOAC should restart as soon as possible within 12 hrs of the last dose of LMWH.[50] In a study of bridging dabigatran in elective procedures it was found that bridging increased significantly the risk of major bleeding compared to non-bridging, failing to reduce the occurrence of thrombo-embolic events.[51] Therefore we do not recommend bridging as standard practice in hip fracture surgery.

On the other hand, major bleeding has been reported in 25% of patients under dabigatran undergoing major orthopaedic surgery but it was safe to restart the drug in 0–2 days.[52] A recent study showed that patients undergoing early surgery for extracapsular hip fracture under DOAC had a 3.4-fold increased risk for intra-operative blood transfusion.[53] In this study all patients had been operated on within 24 hrs and quite interestingly the patients operated on in the first 6 hrs avoided intra-operative blood transfusion. There is growing evidence supporting early hip fracture surgery (within 48 hrs) for patients under DOACs,[54-56] although these studies conclude that bigger studies with robust evidence are needed to ensure that early surgery is indeed safe.

As uncertainty exists regarding the best policy and the timeframe for discontinuation or not of peri-operative DOACs, the quest for reversal agents is essential. Idarucizumab (Praxbind), a monoclonal antibody binding dabigatran with 350 times greater affinity than thrombin, is licensed as reversing agent for dabigatran.[57] A dose of 5 mg can bind Pradaxa in minutes, completely reversing the elevated dilute thrombin time and ecarin clotting time in 88–98% of patients, with the added benefit not being prothrombotic (unlike PCCs).[58] Andexanet alpha (Ondexxya) has been granted conditional approval by European Medicines Agency as a reversal agent for rivaroxaban, apixaban and edoxaban.[59]

Haemodialysis is an option for patients suffering from renal impairment under dabigatran as it can remove over 60% of this drug.[60] However, this is not very practical in everyday practice and also does not apply to rivaroxaban or apixaban due to their high protein binding. Activated charcoal can be useful in drug overdose but is limited to

administration within 2 hrs of last DOAC dose.[61] PER977 (ciraparantag) has been named as a universal antidote to all DOACs, heparin and fondaparinux, and is under development. It is a small synthetic molecule binding factor Xa, thrombin inhibitors and heparin through strong interactions. Tranexamic acid, an antifibrinolytic agent can also be used as it is safe, inexpensive and has shown efficacy in reducing blood loss. However, its application in DOACs has not been studied.

Discussion

Anticoagulation interfering with surgical treatment of proximal femoral fractures is emerging as a constantly growing healthcare problem. The ideal approach to deal with this matter is close collaboration of a multidisciplinary team of orthopaedic surgeons, physicians, anaesthetists and transfusion specialists. Currently, it has been established that early surgery, preferably in less than 48 hrs, should be encouraged. The presence and type of any anticoagulation has become a mandatory 'box to be evaluated' during admission of these patients.

Unfortunately, one should be made aware that there is a striking absence of generally adopted guidelines by international orthopaedic associations. In NICE hip fracture management guidance (updated in 2017), there is no reference to peri-operative handling of anticoagulants in patients presenting with proximal femoral fractures.[62] In their latest (2014) evidence-based clinical guidance, the American Academy of Orthopaedic Surgeons advice is limited to aspirin and clopidogrel, reporting that there is some evidence that peri-operative cessation of each or both is not needed.[63] The British Orthopaedic Association, despite having launched a 'living document' in 2014 regarding VTE prophylaxis in Orthopaedic surgery, has not yet provided practical orthopaedic advice regarding this complex problem.[64] Hence, all our guidance is taken from non-orthopaedic associations or general health state bodies. The European Heart Rhythm Association, in their 2018 practical guide on the use of NOACs in patients with atrial fibrillation undergoing urgent surgical intervention, recommend that hip fracture surgery should be deferred until ideally 24 hrs after the last dose.[65] They also advise that the coagulation state should be assessed in the waiting time with a full panel of coagulation assays (including Prothrombin time (PT), activated partial thromboplastin time (aPTT), anti-Factor Xa, or dTT/ecarin chromogenic assay (ECA)). Of note, the same body for elective procedures advises 48 hr pre-operative discontinuation of rivaroxaban/apixaban/edoxaban, whereas for dabigatran it is 48 hrs for Creatinine clearance (CrCl)> 50 mL/min and 72 hrs if CrCl < 30 mL/min. This means that they acknowledge the different priorities that urgent surgery may be associated with. Bridging therapy is not recommended, and regular drugs can be re-started 24 hrs post-operatively. In 2018, the Australian Clinical Excellence Commission[66] recommended reversal with an intravenous dose of 3 mg of vitamin K upon admission and, if immediate reversal is needed, Prothrombinex-VF along with vitamin K (dose of PCC depending on the initial and target INR) or if Prothrombinex-VF is not available, FFP at a dose of 10–15 mL/kg. In cases of DOACs they recommend Pradaxa cessation for two days (CrCl ≥ 80 mL/min), three days (CrCl = 50–80 mL/min) or four days (CrCl 30–49 mL/min). For CrCl < 30 mL/min Pradaxa is contra-indicated. For Xarelto and Eliquis a two-day (CrCl > 50 mL/min) or three-day (CrCl 30–50 mL/min) drug holiday is needed. Recommencement is advised two to three days post-operatively and they generally advise against epidural anaesthesia. Regarding antiplatelets, their advice is not clear whether it refers to elective or urgent procedure and we can only extract that they generally tend to maintain aspirin. The ASRA in conjunction with the European Society of Anaesthesiology (ESA) published their exhaustive guideline in 2018 regarding regional anaesthesia in patients receiving antithrombotic or thrombolytic therapy.[67] Neuraxial block can be performed in patients under rivaroxaban/apixaban/edoxaban after three days on average and for dabigatran this timeframe can extend to five days depending on renal function. The first dose should be given only 6 hrs after the neuraxial puncture or neuraxial catheter withdrawal. They advise warfarin cessation five days prior the neuraxial procedure because a normal INR does not guarantee full restoration of all clotting factors and hence there is an increased risk for spinal bleeding.

From all the above we can conclude that antiplatelets do not seem to be a problem as in most cases it is safe for them to be continued peri-operatively. Aspirin is no longer a problem and even co-administration with clopidogrel does not preclude early hip fracture surgery. Regarding VKAs, prompt reversal with vitamin K should be encouraged as soon as an initial INR value is quickly obtained on admission (this can be feasible with modern bed-side portable devices). The first dose should be guided by this result, but we think that an intravenous dose of 1 gr should be adequate. Rechecking INR in 6 hrs should guide further steps and if not less than 1.5 an additional dose of IV 1 gr can be given and surgery to be expected in the next 6 hrs. The oral route with 5 mg is another option but we believe that the intravenous route gives better bioavailability. Restarting VKA can take place in the first 24 hrs parallel to bridging LMWH.

In hip fracture patients taking new oral direct anticoagulants, timing of the last dose, name of the agent and, foremost, the renal function will guide the timing-to-surgery plan. The problem is that all recommendations cover mainly elective procedures where the patient can wait and where the risks associated with the physiological

Table 1. Summary of recommendations regarding peri-operative anticoagulants in proximal femoral fractures (enclosed in brackets is the relevant supporting reference)

	Anticoagulation effect monitoring	Duration of pre-operative drug cessation (hours)	Bridging	Re-instatement
Antiplatelets (aspirin, clopidogrel, ticagrelor, prasugrel) Level of evidence of referenced studies: Ref. No. 7: Level III Ref. No. 17: Level III Ref. No. 63: Level V	N/A[7,17]	N/A[63]	N/A[7,17,63]	N/A[7,17,63]
VKA Level of evidence of referenced studies: Ref. No. 22: Level V Ref. No. 27: Level III Ref. No. 33: Level III Ref. No. 34: Level V Ref. No. 35: Level III	INR < 1.5 (or slightly higher)[22,33]	Upon admission +IV 1 mg vit. K (re-check INR in 6 hours), then +1 mg[27]	Pre + post-op with LMWH (risk stratification)[35]	24–36 hours post-op[34]
Dabigatran Level of evidence of referenced studies: Ref. No. 45: Level III Ref. No. 50: Level III Ref. Nos. 53–56: Level III Ref. No. 63: Level V Ref. No. 65: Level V Ref. No. 68: Level II	DOAC plasma concentrations, dTT, ECT, negative TT[45,63,68]	24–48 hours (in moderate to severe renal impairment/expect transfusions)[53–56,65]	N/A[65]	24 hours post-op[50]
Rivaroxaban/Apixaban/Edoxaban Level of evidence of referenced studies: Ref. No. 45: Level III Ref. No. 47: Level V Ref. No. 50: Level III Ref. Nos. 54–56: Level III Ref. No. 63: Level V Ref. No. 65: Level V Ref. No. 68 Level II	DOAC plasma concentrations, anti-Xa assays[45,63,68]	24–48 hours (in moderate to severe renal impairment)[47,54–56,65]	N/A[65]	24 hours post-op[50]

Note. N/A, not applicable; VKA, vitamin K antagonist; INR, international normalized ratio; LMWH, Low Molecular Weight Heparin, ; DOAC, direct oral anticoagulants; dTT, direct thrombin time; ECT, ecarin clotting time; TT, Thrombin time .

state of a fracture do not necessitate prompt surgery. In this respect, it was generally agreed that three to five half-lives (depending on renal function) of DOAC cessation should eliminate their anticoagulation effect hence the general two-to-three-day recommended duration. A DOAC plasma concentration lower than 30 ng/mL precludes anticoagulation effect and is recommended in urgent surgery, however, it is not practically feasible and available.[68] Taking into account the recent studies showing that early hip fracture surgery under NOACs is feasible and safe, we can lower this timeframe from 48 hrs to 24 hrs, extending to 48 hrs in the presence of disturbed renal function and marginal higher transfusions to be expected in dabigatran. Anticoagulation can be restarted 24 hrs post-operatively without bridging, offering also an option for orthopaedic VTE prophylaxis. A summary of up-to-date recommendations can be found in Table 1.

Assessing the extensive literature, we can highlight that there are no studies investigating the various anticoagulants and correlating them with different types of proximal femoral fractures. Therefore, we do not know whether a type of fracture behaves better with a specific anticoagulant. The domain of proximal femoral fracture surgery and anticoagulants is huge and there are many questions to be answered. In fact, as we expect more and more patients to present with DOACs in the next years, it seems that this healthcare problem will increase. Therefore, large studies with high-quality evidence regarding all effects of these drugs in the acute fracture hip setting are urgently required. The development of accessible specific reversal agents which bind these drugs and do not risk a hyperthrombotic state should be seen as a public health necessity. This patient population is frail and pharmacologically vulnerable, hence modern solutions are needed. Consequently, we believe that this specific domain will be of great concern and interest to both clinicians and researchers in the years to come.

AUTHOR INFORMATION

[1]Academic Department of Trauma & Orthopaedics, School of Medicine, University of Leeds, UK.
[2]NIHR Leeds Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK.

Correspondence should be sent to: Peter V. Giannoudis, Academic Section of Trauma & Orthopaedic Surgery, Leeds General Infirmary, Clarendon Wing Level A, Great George Street, Leeds, LS1 3EX, UK.
Email: pgiannoudi@aol.com

ICMJE CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Centers for Disease Control and Prevention. Hip fractures among older adults. https://www.cdc.gov/homeandrecreationalsafety/falls/adulthipfx.html (date last accessed 25 September 2019).

2. Royal College of Physicians. *National Hip Fracture Database annual report 2018*. London: RCP, 2018. https://www.nhfd.co.uk/files/2018ReportFiles/NHFD-2018-Annual-Report-v101.pdf (date last accessed 25 September 2019).

3. Schuetze K, Eickhoff A, Dehner C, Gebhard F, Richter PH. Impact of oral anticoagulation on proximal femur fractures treated within 24h: a retrospective chart review. *Injury* 2019;50:2040–2044.

4. Moja L, Piatti A, Pecoraro V, et al. Timing matters in hip fracture surgery: patients operated within 48 hours have better outcomes. A meta-analysis and meta-regression of over 190,000 patients. *PLoS One* 2012;7:e46175.

5. Ryan DJ, Yoshihara H, Yoneoka D, Egol KA, Zuckerman JD. Delay in hip fracture surgery: an analysis of patient-specific and hospital-specific risk factors. *J Orthop Trauma* 2015;29:343–348.

6. Cordero J, Maldonado A, Iborra S. Surgical delay as a risk factor for wound infection after a hip fracture. *Injury* 2016;47:S56–S60.

7. Lin SY, Huang HT, Chou SH, et al. The safety of continuing antiplatelet medication among elderly patients undergoing urgent hip fracture surgery. *Orthopedics* 2019;42:268–274.

8. Vela Vásquez RS, Peláez Romero R. Aspirin and spinal haematoma after neuraxial anaesthesia: myth or reality? *Br J Anaesth* 2015;115:688–698.

9. Grujic D, Martin D. Perioperative clopidogrel is seven days enough? *Am Surg* 2009;75:909–913.

10. Breivik H, Bang U, Jalonen J, Vigfússon G, Alahuhta S, Lagerkranser M. Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. *Acta Anaesthesiol Scand* 2010;54:16–41.

11. Zhang J, Chen X, Wang J, et al. Poor prognosis after surgery for intertrochanteric fracture in elderly patients with clopidogrel treatment: a cohort study. *Medicine (Baltimore)* 2017;96:e8169.

12. Soo CGKM, Della Torre PK, Yolland TJ, Shatwell MA. Clopidogrel and hip fractures, is it safe? A systematic review and meta-analysis. *BMC Musculoskelet Disord* 2016;17:136.

13. Doleman B, Moppett IK. Is early hip fracture surgery safe for patients on clopidogrel? Systematic review, meta-analysis and meta-regression. *Injury* 2015;46:954–962.

14. Jang CY, Kwak DK, Kim DH, Lee HM, Hwang JH, Yoo JH. Perioperative antiplatelet in elderly patients aged over 70 years treated with proximal femur fracture: continue or discontinue? *BMC Musculoskelet Disord* 2019;20:124.

15. Purushothaman B, Webb M, Weusten A, Bonczek S, Ramaskandhan J, Nanu A. Decision making on timing of surgery for hip fracture patients on clopidogrel. *Ann R Coll Surg Engl* 2016;98:91–95.

16. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Thorac Cardiovasc Surg* 2016;152:1243–1275.

17. Chechik O, Thein R, Fichman G, Haim A, Tov TB, Steinberg EL. The effect of clopidogrel and aspirin on blood loss in hip fracture surgery. *Injury* 2011;42:1277–1282.

18. Benzon HT, Avram MJ, Green D, Bonow RO. New oral anticoagulants and regional anaesthesia. *Br J Anaesth* 2013;111:i96–i113.

19. Gleason LJ, Mendelson DA, Kates SL, Friedman SM. Anticoagulation management in individuals with hip fracture. *J Am Geriatr Soc* 2014;62:159–164.

20. Griffiths R, Alper J, Beckingsale A, et al; Association of Anaesthetists of Great Britain and Ireland. Management of proximal femoral fractures 2011: Association of Anaesthetists of Great Britain and Ireland. *Anaesthesia* 2012;67:85–98.

21. Lawrence JE, Fountain DM, Cundall-Curry DJ, Carrothers AD. Do patients taking warfarin experience delays to theatre, longer hospital stay, and poorer survival after hip fracture? *Clin Orthop Relat Res* 2017;475:273–279.

22. The British Orthopaedic Association. *BOA blue book: the care of patients with fragility fractures*. London: The British Orthopaedic Association, 2007.

23. Eardley WG, Macleod KE, Freeman H, Tate A. 'Tiers of delay': warfarin, hip fractures, and target-driven care. *Geriatr Orthop Surg Rehabil* 2014;5:103–108.

24. Hanley JP. Warfarin reversal. *J Clin Pathol* 2004;57:1132–1139.

25. Watson HG, Baglin T, Laidlaw SL, Makris M, Preston FE. A comparison of the efficacy and rate of response to oral and intravenous Vitamin K in reversal of over-anticoagulation with warfarin. *Br J Haematol* 2001;115:145–149.

26. Douketis JD. Perioperative anticoagulation management in patients who are receiving oral anticoagulant therapy: a practical guide for clinicians. *Thromb Res* 2002;108:3–13.

27. Ahmed I, Khan MA, Nayak V, Mohsen A. An evidence-based warfarin management protocol reduces surgical delay in hip fracture patients. *J Orthop Traumatol* 2014;15:21–27.

28. Burbury KL, Milner A, Snooks B, Jupe D, Westerman DA. Short-term warfarin reversal for elective surgery: using low-dose intravenous vitamin K: safe, reliable and convenient. *Br J Haematol* 2011;154:626–634.

29. Hanslik T, Prinseau J. The use of vitamin K in patients on anticoagulant therapy: a practical guide. *Am J Cardiovasc Drugs* 2004;4:43–55.

30. Leonidou A, Rallan R, Cox N, Pagkalos J, Luscombe J. Comparison of different warfarin reversal protocols on surgical delay and complication rate in hip fracture patients. *J Orthop Surg (Hong Kong)* 2013;21:142–145.

31. Tal A, Rubin G, Rozen N. Treatment with vitamin K in hip fracture patients receiving warfarin. *Isr Med Assoc J* 2013;15:348–351.

32. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines. Eighth ed. *Chest* 2008;133:160S–198S.

33. Cohn MR, Levack AE, Trivedi NN, et al. The hip fracture patient on warfarin: evaluating blood loss and time to surgery. *J Orthop Trauma* 2017;31:407–413.

34. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, Kitchen S, Makris M; British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin. Fourth ed. *Br J Haematol* 2011;154:311–324.

35. Keeling D, Tait RC, Watson H; British Committee of Standards for Haematology. Peri-operative management of anticoagulation and antiplatelet therapy. *Br J Haematol* 2016;175:602–613.

36. Patanwala AE, Acquisto NM, Erstad BL. Prothrombin complex concentrate for critical bleeding. *Ann Pharmacother* 2011;45:990–999.

37. DeAngelo J, Jarrell D, Cosgrove R, Camamo J, Edwards C, Patanwala AE. Comparison of 3-factor versus 4-factor prothrombin complex concentrate with regard to warfarin reversal, blood product use, and costs. *Am J Ther* 2018;25:e326–e332.

38. Gulati V, Newman S, Porter KJ, et al. Implications of anticoagulant and antiplatelet therapy in patients presenting with hip fractures: a current concepts review. *Hip Int* 2018;28:227–233.

39. Ng R, Shabani-Rad MT. Results of Octaplex for reversal of warfarin anticoagulation in patients with hip fracture. *Can J Surg* 2019;62:14–19.

40. Francis J, Girish G, Jones R. Prothrombin complex concentrate reversal of warfarin in patients with hip fracture. *Anaesthesia* 2014;69:520–521.

41. Yassa R, Khalfaoui MY, Hujazi I, Sevenoaks H, Dunkow P. Management of anticoagulation in hip fractures: a pragmatic approach. *EFORT Open Rev* 2017;2: 394–402.

42. Chai-Adisaksopha C, Hillis C, Siegal DM, et al. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal: a systematic review and meta-analysis. *Thromb Haemost* 2016;116:879–890.

43. Forster R, Stewart M. Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee replacement or hip fracture repair. *Cochrane Database Syst Rev* 2016;3:CD004179.

44. Tufano A, Coppola A, Contaldi P, Franchini M, Minno GD. Oral anticoagulant drugs and the risk of osteoporosis: new anticoagulants better than old? *Semin Thromb Hemost* 2015;41:382–388.

45. Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol* 2014;64:1128–1139.

46. Hourston GJ, Barrett MP, Khan WS, Vindlacheruvu M, McDonnell SM. New drug, new problem: do hip fracture patients taking NOACs experience delayed surgery, longer hospital stay, or poorer outcomes? *Hip Int* 2019. doi:10.1177/1120700019841351 [Epub ahead of print].

47. Vílchez JA, Gallego P, Lip GY. Safety of new oral anticoagulant drugs: a perspective. *Ther Adv Drug Saf* 2014;5:8–20.

48. NICE Implementation Collaboration Consensus. Supporting local implementation of NICE guidance on use of the non-Vitamin K antagonist oral anticoagulants (NOACs) in non-valvular atrial fibrillation. https://www.nice.org.uk/guidance/cg180/resources/nic-consensus-statement-on-the-use-of-noacs-243733501 (date last accessed 14 October 2019).

49. Leitch J, van Vlymen J. Managing the perioperative patient on direct oral anticoagulants. *Can J Anaesth* 2017;64:656–672.

50. Liew A, Douketis J. Perioperative management of patients who are receiving a novel oral anticoagulant. *Intern Emerg Med* 2013;8:477–484.

51. Douketis JD, Healey JS, Brueckmann M, et al. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure: substudy of the RE-LY trial. *Thromb Haemost* 2015;113:625–632.

52. Schulman S, Carrier M, Lee AY, et al; Periop Dabigatran Study Group. Perioperative management of dabigatran: a prospective cohort study. *Circulation* 2015; 132:167–173.

53. Schuetze K, Eickhoff A, Dehner C, Gebhard F, Richter PH. Impact of oral anticoagulation on proximal femur fractures treated within 24 h: a retrospective chart review. *Injury* 2019;50:2040–2044.

54. Schermann H, Gurel R, Gold A, et al. Safety of urgent hip fracture surgery protocol under influence of direct oral anticoagulation medications. *Injury* 2019;50: 398–402.

55. Franklin NA, Ali AH, Hurley RK, Mir HR, Beltran MJ. Outcomes of early surgical intervention in geriatric proximal femur fractures among patients receiving direct oral anticoagulation. *J Orthop Trauma* 2018;32:269–273.

56. Mullins B, Akehurst H, Slattery D, Chesser T. Should surgery be delayed in patients taking direct oral anticoagulants who suffer a hip fracture? A retrospective, case-controlled observational study at a UK major trauma centre. *BMJ Open* 2018;8:e020625.

57. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal: full cohort analysis. *N Engl J Med* 2017;377:431–441.

58. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511–520.

59. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al; ANNEXA-4 Investigators. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med* 2016;375:1131–1141.

60. Chai-Adisaksopha C, Hillis C, Lim W, Boonyawat K, Moffat K, Crowther M. Hemodialysis for the treatment of dabigatran-associated bleeding: a case report and systematic review. *J Thromb Haemost* 2015;13:1790–1798.

61. Wang X, Mondal S, Wang J, et al. Effect of activated charcoal on apixaban pharmacokinetics in healthy subjects. *Am J Cardiovasc Drugs* 2014;14:147–154.

62. NICE. Hip fracture: management. https://www.nice.org.uk/guidance/cg124 (date last accessed 9 October 2019).

63. American Academy of Orthopaedic Surgeons. Management of hip fractures in the elderly: evidence-based clinical practice guideline. https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/guidelines/hip-fractures-elderly-clinical-practice-guideline-4-24-19%20-2.pdf (date last accessed 9 October 2019).

64. VTE Prophylaxis Guidance - British Orthopaedic Association https://www.boa.ac.uk/uploads/assets/85dfa123-1985-492c-8c8f161f495e13da/vte-guidance-document-for-website.pdf (date last accessed 23 January 2020).

65. Steffel J, Verhamme P, Potpara TS, et al; ESC Scientific Document Group. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39:1330–1393.

66. Clinical Excellence Commission. Guidelines on perioperative management of anticoagulant and antiplatelet agents, 2018. http://www.cec.health.nsw.gov.au/___data/assets/pdf_file/0006/458988/Guidelines-on-perioperative-management-of-anticoagulant-and-antiplatelet-agents.pdf (date last accessed 9 October 2019).

67. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines. Fourth ed. *Reg Anesth Pain Med* 2018;43:263–309.

68. Godier A, Dincq AS, Martin AC, et al. Predictors of pre-procedural concentrations of direct oral anticoagulants: a prospective multicentre study. *Eur Heart J* 2017;38:2431–2439.