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Proximal femur fractures in patients taking anti-coagulants: has anything changed?

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- With an ever-ageing population, the incidence of hip fractures is increasing worldwide. Increasing age is not just associated with increasing fractures but also increasing comorbidities and polypharmacy.
- Consequently, a large proportion of patients requiring hip fracture surgery (HFS) are also prescribed antiplatelet and anti-coagulant medication. There remains a clinical conundrum with regards to how such medications should affect surgery, namely with regards to anaesthetic options, timing of surgery, stopping and starting the medication as well as the need for reversal agents.
- Herein, we present the up-to-date evidence on HFS management in patients taking blood-thinning agents and provide a summary of recommendations based on the existing literature.

Keywords
- anticoagulants
- antiplatelets
- hip fracture
- proximal femur

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Introduction

With an ever-growing population in age, the rates of hip fractures are also increasing. The highest rates of hip fractures are seen in North Europe and the United States, whereas the lowest have been reported in Latin America and Africa (1).

Patients presenting with hip fractures are usually frail with a diminished bone stock, reduced functional capacity and having several comorbidities (2, 3). For this reason, specific protocols have been developed to optimise their medical condition prior to surgery and to facilitate their post-operative recovery. This approach has contributed to the overall reduction of morbidity and mortality seen in this special group of patients during the past 5 years, particularly in the United Kingdom (4).

Interestingly, approximately 30–40% of the patients sustaining a hip fracture in the United Kingdom are also on anticoagulation or antiplatelet medication due to their underlying medical condition. When considering DOACs (direct oral anticoagulants) in particular, approximately 2% of patients requiring HFS are taking DOACs (5). However, the intake of anticoagulation and antiplatelet medication can have an impact on the patients requiring hip fracture surgery (HFS). The need for reversal will cause a delay in the execution of surgery. Historically, there have been concerns regarding increased risk of bleeding, development of haematoma, wound break down and development of infection (6).

Overall, the issues with anticoagulation in patient requiring HFS are multiple as anticoagulation can not only affect timing of surgery and perioperative care but can also affect patient's comorbidities, namely cardiovascular which require such medications to be administered (5).

In the herein study, therefore, we examine the latest evidence on the management of elderly patients with hip fractures requiring surgery taking anticoagulants in terms of reversal protocols, their impact on the timing of surgery and outcomes.

Platelet inhibitors

Platelet inhibitors constitute some of the most frequently prescribed medications in patients aged 65 and over (7). Their aim is to prevent thrombotic complications, but this must be balanced with an increased risk of bleeding.

Platelet inhibitors have been associated with an increased risk of adverse events in the elderly population when compared to their younger counterparts. This is due to changes in the pharmacokinetics and pharmacodynamics within the ageing population, as well as the higher risk of drug interactions (7, 8, 9, 10).

Noteworthy, multiple subtypes of platelet aggregation inhibitors exist as shown in Table 1 (11).

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Aspirin

This is the most widely used antiplatelet agent worldwide (11). It is rapidly absorbed through the enteric mucosa, with a peak plasma level being reached at 30–40 min. Due to the irreversible nature of its inhibition of COX-1, the antithrombotic effects of aspirin can affect platelets throughout their lifespan (7–10 days) and even lead to slow recovery of overall platelet function of 10% per day due to new platelet formation (12).

Thienopyridines/ADP receptor inhibitors

The first to be on the market was ticlopidine, but this is now rarely used due to the association with bone marrow suppression and thrombocytopaenia (12).

Clopidogrel, prasugrel and ticagrelor

Clopidogrel requires conversion to an active metabolite that irreversibly binds the ADP receptor. Prasugrel is a newer version of this subgroup of drugs which is a prodrug that irreversibly inhibits the ADP receptor for the lifespan of the platelet. Conversely, ticagrelor's mechanism of action is slightly different in that it is a reversible, non-competitive antagonist of the ADP receptor. Ticagrelor's popularity is ever-increasing among prescribers due to its high safety profile and its quality of not being affected by genetic polymorphism hence making it less prone to response variability (an issue with clopidogrel) (12).

GP IIb/IIIa inhibitors

These agents work to antagonise platelet function by inhibiting cross-linking of platelets and subsequent aggregation (13).

Meinhausen *et al.* have highlighted the difficulty in making a conclusion from the available literature regarding the efficacy of using anticoagulants for a range of comorbidities due to the lack of available data for the elderly population. In their systematic review of the existing literature, they suggested the following:

(1) To discontinue aspirin for primary prevention of CVD in adults without DM as the benefit outweighs the risk of haemorrhagic stroke, GI and extracranial bleeds. (This was however a 'weak recommendation' based on low-quality evidence.)
(2) In older adults with AF, they suggested stopping aspirin and instead considering the use of oral anticoagulants. (This was again a 'weak recommendation' based on low-quality evidence.)
(3) The discontinuation of aspirin in adults with high-risk vascular events with recent transient ischaemic attacks or ischaemic stroke who are also taking clopidogrel and who do not have another indication for dual therapy (including first-year post-acute coronary syndrome, coronary stenting or limb ischaemia). This is because dual antiplatelet therapy (DAPT) compared to clopidogrel alone increases the risk of bleeding complications and may not be beneficial in reducing vascular events, especially in those aged 65 or over (7).

Such data emphasise that with no set rules regarding the prescribing and continuation of antiplatelets it can be even harder to implement rules regarding these medications and orthopaedic surgery.

In a retrospective review of over 300 patients with neck or femur fractures pre-operative (pre-op), use of both aspirin and clopidogrel was not associated with increased mortality. The authors concluded that the risks of delaying surgery outweigh the perioperative bleeding risk (14). However, in a large meta-analysis of the data by Yang *et al.*, which included over 5000 patients, the use of antiplatelet agents (both aspirin and clopidogrel) prior to surgery were associated with a higher rate of haemoglobin drop and hence increased transfusion rates.

Table 1 **A summary of commonly prescribed platelet aggregation inhibitors and their properties** (7, 8, 9, 10, 11, 12, 13).

Platelet inhibitor group/ examples	Mechanism of action	Use in clinical practice	Route of administration	Time to peak plasma duration	Route of excretion
Cyclooxygenase inhibitors					
Aspirin	Irreversibly inhibits cyclooxygenase enzyme in the prostaglandin synthesis pathway.	ACS, CVD, PVD, analgesia	Oral/rectal	30-40 min	Hepatic
Thienopyridines	Selectively inhibit the ADP-induced platelet aggregation		Oral		
Clopidogrel		ACS		2 h	Faeces
Ticagrelor		CVD		2 h	Urine
Prasugrel		TIA		30 min	Urine
Ticlopidine		PVD		2 h	Faeces
Glycoprotein platelet inhibitors	Inhibit glycoprotein IIb/IIIa receptors on platelets and therefore decrease platelet aggregation	Short term ACS treatment	Intravenous		
Abciximab				Immediate	Renal
Eptifibatide				15 min	Renal
Tirofiban				5 min	Biliary

ACS, acute coronary syndrome; CVD, cerebrovascular disease; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

Nonetheless, early surgery was associated with a shorter length of hospitalisation (15).

Lin *et al.* have also published similar findings in their retrospective study of 176 patients admitted to their local unit requiring HFS. They reviewed the admissions of patients on aspirin and dipyridamole either in combination with each other or as solitary medications and a final group comprised patients not on antiplatelet therapy. They reported that patients on DAPT were prone to increase intraoperative blood loss, compared to those on single or no therapy. Just as before, they described no significant difference in total blood loss, transfusion rate or 1 year mortality amongst the four groups (16). Noteworthy, DAPT is considered a contraindication to spinal anaesthesia (17).

A new method of monitoring platelet function has been described by Tescione *et al*. (18). They report the use of thromboelastography (TEG) with an ADP platelet mapping kit to aid in the assessment of platelet aggregation in patients taking clopidogrel. Their study comprised very small sample size, just nine patients, of which five were found to have normal values of platelet aggregation. They proposed that in those patients with deranged function a mortality risk assessment tool can be performed to distinguish patients requiring general anaesthesia to those that can wait for normalisation of platelet aggregation (18).

A recently published Spanish randomised control trial, similarly, investigated the use of measuring functional platelet counts to guide the timing of surgery compared to patients with no monitoring. They report increased times to surgery in patients in the platelet monitoring arm compared to those without. Interestingly, there were no differences in perioperative blood loss between the two groups (19). Whilst this remains very novel, the results are encouraging and may lead to greater implementation of the technique in the future.

Vitamin K antagonists

The most widely known vitamin K antagonist (VKA) is warfarin. Other similar medications include acenocoumarol and phenprocoumon. They all work to target factors II, VII, IX, X, protein S and C (20). In particular, they work to block the function of the vitamin K epoxide reductase complex in the liver. This results in the depletion of the reduced form of vitamin K that serves as a cofactor for gamma-carboxylation of vitamin K-dependent coagulation factors (21).

With the invention of DOACs, VKAs are becoming less commonly used. The regular monitoring, narrow therapeutic index and numerous drug, and drug–food interactions are some of the issues surrounding the ongoing prescribing of such agents (20). Furthermore, an important measure of efficacy in such agents is the duration of time a patient spends within their desired therapeutic range (INR). In most patients, the target INR will be 2–3, however, in some, it may be as high as 3–4. Worryingly, the data suggest that suboptimal therapy, that is, time spent in a non-therapeutic INR can be as high as 40%. This in itself is associated with a higher risk of ischaemic bleeding or conversely, haemorrhagic stroke (20, 22, 23).

A recent review of the UK's anticoagulation prescribing policies for stroke prophylaxis showed that between 2014 and 2019, 53–99% of all anticoagulation prescriptions were for DOACs, with slight variation amongst different regions countrywide. Furthermore, in only 16% of cases was warfarin recommended as a first-line agent (24). There are, however, certain cardiovascular pathologies in which only VKAs are licensed. These include atrial fibrillation anticoagulation in patient with end-stage chronic kidney disease or with underlying valvular pathology, for the treatment of venous thromboembolism (both PE and VTE) in patients with chronic kidney disease as well as for stroke prevention in patients with metallic heart valves (20, 25).

DOAC sceptics would be right in suggesting that VKAs could be considered safer, as a missed dose of these agents has less associated risk of a thrombotic event. Furthermore, they are cheaper and the need for regular monitoring ensures higher patient–clinician interaction (20). Though in the current times of the COVID-19 pandemic, the latter point is less likely to be relevant.

With regards to the hip fracture population, there is an estimated prevalence of 5–10.3% of warfarin usage (5, 26). A high admission INR can result in patients waiting for surgery for prolonged periods of time, sometimes with no reversal of the agent (27). An observational study by Al-Rashid *et al.* did not reveal any increased bleeding complications either intra- or post-op within this population (27). In their published cohort study, Cohn *et al.* describe similar findings, with the requirement of blood transfusion being no different in patients on or off warfarin. Similarly, there was no statistically significant difference in the quantity of blood loss or complication rates (28).

Van Rijckevorsel *et al.*, have published their observational cohort study, in which they reported an increased incidence of haematomas associated with VKAs compared to antithrombotic agents (29). Overall, the literature supports the view that patients on warfarin are more likely to have a delayed time to surgery (27, 28, 29). However, delayed surgical treatment is associated with increased post-operative mortality (30, 31).

Current management suggests that surgery be performed only when the INR is 1.5 or below (17, 28, 32). Interestingly, a warfarin group sub-analysis showed that patients who had surgery with an INR at or above 1.5 had

similar transfusion rates, blood loss and complication rates to those patients with an INR <1.5 (28).

A case–control study investigating the safety and efficacy of rapid reversal on warfarin to allow for early surgery (within 24 h) for the warfarinised hip fracture population revealed no increased adverse events (including infections, myocardial infarcts and stroke), mortality or need for transfusions (33).

Importantly, bridging with treatment using low-molecular weight heparin should be considered in patients with mechanical heart valves or recent history of stroke, deep vein thrombosis or pulmonary embolism (17).

Caruso *et al.* reported that patients on warfarin are at a higher risk of death within 1 year from surgery (31). Nonetheless, what is unclear remains whether this is related to the surgery itself or the fact that these patients are generally multi-morbid at baseline.

Where is required, warfarin can be reversed by administering vitamin K or fresh frozen plasma prior to the operation. Alternatively, warfarin can be withheld and with time allowance given for the INR to drop naturally (17, 34). The benefit of reversal of VKAs should be balanced with a possible increased risk of thrombotic complications. Vitamin K can be administered either orally or intravenously (IV), though the IV route works quicker due to its increased bioavailability (35). Once administered INR can be rechecked in 6–12 h (36). Historically doses as low as 1–2 mg of vitamin K have been proposed (37, 38). However, newer studies suggest starting at a dose of 5 mg and repeating as appropriate (39). Of note, warfarin can be restarted on the first-day post-theatre, provided no concerns exist regarding uncontrollable bleeding and adequate haemostasis had been achieved during the operation (40).

Direct oral anticoagulants

The previously mentioned limitations of the anticoagulation agents led to the creation of the DOACs. Their other benefits include high efficacy and safety profile, oral administration, immediate onset of action and minimal need for monitoring.

Their mechanism of action falls into two main groups, inhibition of factor Xa and inhibition of thrombin (10).

Factor Xa inhibitors include apixaban, edoxaban and rivaroxaban. Dabigatran is the only thrombin inhibitor currently on the market (10).

Apixaban

Apixaban is an oral preparation of a direct factor Xa inhibitor that inhibits both free and clot bound factor Xa. It is rapidly absorbed and reaches maximum concentration at 3–4 h after ingestion. Its half-life has been documented at 12 h. Elimination occurs via biliary, direct intestinal and renal excretion (41). The absolute bioavailability is approximately 50% for doses up to 10 mg, but elderly patients exhibit higher plasma concentrations than younger patients (41, 42). Apixaban is typically prescribed in twice-daily dosing and can be used for both thromboprophylaxis as well as treatment of venous thromboembolism (41).

Edoxaban

Edoxaban is the last DOAC on the market and once again acts by directly inhibiting factor Xa. It reaches peak plasma concentrations very quickly at only 1.5 h and has a half-life of 10–14 h (43). Edoxaban is mostly eliminated through the faecal route, with a small amount being excreted in the urine (44). It is once-daily administrative regime and lack of interaction with cytochrome P-450 enzymes makes it a favourable prescribing option. It is licensed for use in non-valvular atrial fibrillation for stroke prevention as well as treatment for acute venous thromboembolic disease (42). Care must be taken in the prescribing of patients with low body weight (<60 kg) and renal impairment (42, 44).

Rivaroxaban

Rivaroxaban is another direct inhibitor of factor Xa which targets both free and clot bound factor Xa. It is rapidly absorbed and reaches maximum plasma concentration at 2–4 h after oral ingestion. Typically, it is considered that rivaroxaban should only be taken alongside a high-calorie meal; however, this is only true in doses of 15–20 mg. Oral bioavailability is high (80–100%) at doses of 10 mg irrespective of calorific intake. The half-life of the drug is 5–9 h in healthy adults and can rise to up to 13 h in elderly patients. The drug is eliminated in two ways; one-third in its unchanged active drug form in the urine. The remaining two-thirds are subject to metabolic degradation and consequently eliminated by both the renal and hepatobiliary routes (45, 46, 47).

Dabigatran

Dabigatran is a competitive direct thrombin inhibitor. If the capsule is swallowed whole, the oral bioavailability of the drug is only 3–7%, but this can nearly double if the shell is violated prior to ingestion. Peak plasma concentrations are reached after 2 h. Unlike rivaroxaban, a concomitant food intake can result in delayed plasma concentrations. The half-life of the drug is 12–17 h and it too undergoes renal excretion (48, 49).

Routine monitoring of these drugs is currently not validated given their predictable pharmacokinetic and pharmacodynamic properties. One can measure the plasma concentrations of the agents or consider recording thrombin time, direct thrombin time (dTT) or ecarin clotting time (ECT), especially for dabigatran (50). The current gold standard however for all agents is liquid chromatography-

mass spectrometry (LC-MS/MS). This is not routine in clinical practise as it is costly and time consuming (51).

Reversal agents

One of the long-standing benefits of VKAs over DOACs was the availability of vitamin K as a reversal agent. However, there are now two licensed reversal options on the market. Idarucizumab (Praxbindm Boehringer Ingelheim) for dabigatran and Andexanet Alfa (Andexxa, Portola) for apixaban and rivaroxaban reversal. Where direct reversal options are not available, alternatives include prothrombin complex concentrate (PCC) and activated PCC (52).

Idarucizumab is a monoclonal anti-dabigatran antibody. In the REVERSE-AD trial multicentre trial investigating the use of the agent in both life-threatening bleeding and patients requiring surgery or invasive procedures 68% of participants had cessation of bleeding within 24 h (52, 53).

Andexanet alfa is a modified recombinant factor Xa. The ANNEXA-4 trial investigated the efficacy of the agent's ability to reverse anti-factor Xa activity and mean reduction was reported at 92% in patients with major bleeding (defined as plasma DOAC level of >75 ng/mL). However, its safety profile is still undergoing investigation given its high associated risk with thromboembolic events including stroke and transient ischaemic attacks (52, 54).

PCC is a plasma-derived concentrate of vitamin K-dependent clotting factors (52). To date, there have been no studies directly comparing the use of DOAC antidotes to PCC and APCC (55). Such agents have therefore been typically used in an off-label fashion prior to the invention of the direct antidotes and currently when such antidotes are not clinically available. The aim is to boost factor levels, but it cannot directly inhibit the DOAC or affect factor Xa levels (56).

Whilst such agents are available, guidance still suggests that they should only be administered if bleeding is life threatening into a critical organ, or not controlled with maximal supportive measures, which given DOAC short half-lives is usually enough (52, 56). Furthermore, prior to invasive procedures, DOACs should not be reversed unless the bleeding risk associated with the procedure is sufficiently high when balanced with the risk of prothrombotic events and high costs. (Andexanet alfa costs £11,100/pack in the UK and $5500 per 200 mg vial in the United States, whereas Idarucizumab costs £2400 per 5 g and $3500 per 5 g kit, respectively) (52, 56, 57).

Interestingly DOACs have been investigated in several phase 3 trials for thromboprophylaxis in major orthopaedic surgeries. Not only have they been found to be effective and not pose an increased risk of bleeding, but they are also an attractive option for allowing for early discharge post-op (58). Such results have been replicated by King *et al.* in a retrospective study of HFS in a tertiary centre (59).

However, the optimal timing of surgery is a recurring conundrum for surgeons and anaesthetists alike. Leer-Salvesan *et al.* in their retrospective study investigating how DOAC users who had suffered a hip fracture were affected reported that there was no significant delay to surgery between DOAC and non-DOAC users (60). However, the patients already on DOACs were more likely to have delayed surgery if regional anaesthesia was to be used compared to general anaesthetic (60). There were no significantly increased risks of bleeding intra-op, need for blood transfusions or increased in hospital mortality between the two groups. Of note, hip fracture patients using DOAC were more likely to have a high ASA grade (3–5) compared to patients who did not use DOACs.

Following their systematic review of the data Shah *et al.* suggested that if patients are deemed suitable for general anaesthetic their optimal surgical time should be within 24 h of last ingested DOAC dose (42).

A retrospective review of data looked into the timing of surgery in patients on DOACs, dividing it into two groups early (first 48 h of admission), and late (>48 h of admission). Patients with late surgery had higher 90-day mortality, though no difference in hospital or 30 mortality rates were found. Surprisingly, increased blood loss was associated with the late intervention DOAC group compared to the early group (59).

Suggestions have been made that time to surgery should depend on patients' kidney function given the renal clearance of these agents. In patients with up to moderate chronic kidney disease, defined as a creatine clearance of >30 mL/min surgery at 24 h post last ingested dose is considered safe. In patients with severe chronic kidney disease, a risk vs benefit discussion is needed regarding bleeding risk vs increased mortality with delayed surgery. When surgery is performed, the team may consider the use of a PCC, or tranexamic acid intra-operatively (42).

The Perioperative Anticoagulation Use of Surgery Evaluation (PAUSE) study prospectively evaluated outcomes of individuals with atrial fibrillation who underwent elective surgery. Importantly they had no anticoagulation testing pre-op. They suggested that in patients with low/moderate risk of bleeding DOAC to be omitted 1 day before and commenced 1 day after. Whereas in patients at high risk of bleeding such timelines are doubled (omission 2 days prior to surgery and restarted 2days after) (61, 62).

Discussion

Within UK clinical practice, the National Institute of Clinical Excellence (NICE) in their last published guidelines in 2017 suggested that all HFS be performed within 24 h of admission to the hospital (63). Furthermore, from a

financial view 'early surgery', defined as performed within 36 h, forms a key component of the best practice Tariff for HFS that is paid to NHS providers in England (64). We have already discussed that delayed surgery is associated with increased morbidity and mortality.

To date, there appears no consensus with regards to the management of antiplatelets and anticoagulants in patients with HFS both pre-op and post-op. A lack of level 1 evidence data is likely secondary to the patient population most likely affected by HFS, being old and/or frail. Such comorbid patients, make prescribing these agents difficult due to high risks of bleeding, drug interactions and pharmacodynamic issues including the ability for drug clearance in chronic kidney disease.

Unfortunately, they have been no updated guidance by NICE, the American Academy of Orthopaedic Surgeons or the British Orthopaedic Association. This is most likely due to the COVID-19 pandemic and an overall decline in research during this time because of this. Ultimately, this means that there is no guidance from NICE with regards to perioperative management of anticoagulants and antiplatelets with proximal femoral fractures (63). Since their 2014 guidelines the American Academy of orthopaedic surgeons has released updated guidance bringing forward their timing of surgery, now suggesting that HFS should be performed as soon as possible and ideally within 24 h of admission (instead of at 48 h). Furthermore, they now suggest that there is no optimal surgical approach (a change from the 2014 guidance which suggested the avoidance of the posterior surgical approach was due to higher dislocation rates) (65). No change has been suggested since the 2014 guidelines in which aspirin and clopidogrel were documented as having some evidence that perioperative cessation of each or both is not needed (66).

There remains a debate with regards to the optimal method of anaesthesia, and to date, there appears to be no significant difference in mortality or morbidity between regional and general anaesthetic for patients undergoing HFS (67). Consequently, there are no mass contraindications to the use of antiplatelet or anticoagulation from an anaesthetic point of view. Single antiplatelet therapy in particular is posed to have no increased risk of vertebral canal haematoma (5). With recent concerns among cardiology colleagues that aspirin is associated with a high risk of major bleeding, however, such guidance may soon change (68, 69, 70). DAPT requires more consideration not just due to the increased risk of bleeding but the underlying inference that such patients usually have acute or extensive cardiovascular comorbidities. In such instances, risk vs benefit of stopping medication and consideration of general anaesthesia is required by the team (5).

In patients taking warfarin, it is advised that vitamin K is given at hospital presentation and regular INR checks are performed after this. An INR of <1.8 is considered safe for surgery, but anaesthetists and surgeons alike would aim for <1.5 (certainly <1.5 is considered safe for neuraxial anaesthesia). If an immediate reversal is required, PCC can be administered at the presentation after discussion with the haematology team and blood bank (5).

Reversal of the anticoagulation action of DOACS is warranted in both trauma and emergency surgery (55). As previously mentioned, administration of such agents must be balance the risk of bleeding to the risk of thromboembolism and greater cost. Current guidance suggests that surgery

Table 2 Summary of recommendations regarding antiplatelet and anticoagulant management in patients with proximal femoral fractures.

Antiplatelet: anticoagulant agent	Anticoagulation monitoring	Durations of pre-operative drug cessation (hours)	Bridging	Re-instatement	Level of evidence	
					Reference	Level
Antiplatelets: aspirin, clopidogrel, ticagrelor, prasugrel	Consider functional platelet counts (18, 19)	Consider cessation of 1 agent if on DAPT (7, 17)	N/A	N/A	7	V
					17	V
					18	II
					19	II
VKAs: warfarin	INR <1.5 (17, 28, 32)	Administer 5 mg of vitamin K, recheck to review if more needed (39). Repeat INR in 6–12 h (36).	Pre+post-op LMWH if primary indication is for treatment of VTE (17).	24–36 h post-op (40)	17	V
					28	IV
					32	V
					39	IV
					36	IV
					40	V
Factor Xa inhibitor DOACs: apixaban, rivaroxaban, edoxaban	Consider DOAC plasma concentrations or LC-MS (50)	24–48 h (in moderate to severe renal impairment) (42, 61, 62)	N/A	24–36 h post-op (61, 62)	50	V
					42	V
					61	V
					62	V
Thrombin inhibitor DOAC: dabigatran	Consider DOAC plasma concentrations or LC-MS (50)	24–48 h (in moderate to severe renal impairment) (42, 61, 62)	N/A	24 h post-op (61, 62)	50	V
					42	V
					61	V
					62	V

DOACs, direct oral anticoagulant; INR, international normalised ratio; LC-MS, liquid chromatography-mass spectrometry; LMWH, low molecular weight heparin; N/A, not applicable; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

should be considered after 24-48 h of the last dabigatran dose (thrombin time or dabigatran assays can be used for reassurance). Factor Xa inhibitor administration could preclude surgery for 12-24 h after the last dose, especially if there is no renal impairment. In patients with creatine clearance of <30, current advice is to wait until 48 h post last dose. Once again DOAC-specific assays can be used, and if ≤ 50 ng/mL surgery may be performed. In cases where the assays are found to be >50 DOAC reversal is recommended (5). However, DOAC assays can be difficult to perform, as not all hospitals have them readily available. Furthermore, caution must be administered when interpreting a clotting screen in patients on DOACs, as prothrombin time and activated prothrombin time are variably affected depending on a reagent's sensitivity (71, 72).

Upon review of the current literature, we have highlighted an ongoing gap in the evidence with regards to anticoagulation and antiplatelet treatment in patients with proximal femoral fractures, particularly with regards to optimisation for surgery and post-op recovery. With the ageing population, we will see an increasing incidence of polypharmacy, chronic kidney disease, cardiac pathologies (both ischaemic and arrhythmia driven) and hence a need for the urgent development of international guidelines on how to manage patients undergoing HFS who are taking antiplatelet and anticoagulant medications. A summary of recommendations based on the existing literature is shown in Table 2.

The evidence presented in this article is based on the currently available evidence, but we suggest that each patient is reviewed individually and has a surgical and anaesthetic plan tailored to their needs and comorbidities.

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Author contribution statement

M G and P V G contributed to the study design. M G constructed the database of manuscripts selected for review guided by P V G. M G and P V G contributed to writing the manuscript. All authors read and approved the final manuscript.

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