



Management of anticoagulation in hip fractures: a pragmatic approach

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- Hip fractures are common and increasing with an ageing population. In the United Kingdom, the national guidelines recommend operative intervention within 36 hours of diagnosis. However, long-term anticoagulant treatment is frequently encountered in these patients which can delay surgical intervention. Despite this, there are no set national standards for management of drug-induced coagulopathy pre-operatively in the context of hip fractures.
- The aim of this study was to evaluate the management protocols available in the current literature for the commonly encountered coagulopathy-inducing agents.
- We reviewed the current literature, identified the reversal agents used in coagulopathy management and assessed the evidence to determine the optimal timing, doses and routes of administration.
- Warfarin and other vitamin K antagonists (VKA) can be reversed effectively using vitamin K with a dose in the range of 2 mg to 10 mg intravenously to correct coagulopathy.
- The role of fresh frozen plasma is not clear from the current evidence while prothrombin complex remains a reliable and safe method for immediate reversal of VKA-induced coagulopathy in hip fracture surgery or failed vitamin K treatment reversal.
- The literature suggests that surgery should not be delayed in patients on classical antiplatelet medications (aspirin or clopidogrel), but spinal or regional anaesthetic methods should be avoided for the latter. However, evidence regarding the use of more novel antiplatelet medications (e.g. ticagrelor) and direct oral anticoagulants remains a largely unexplored area in the context of hip fracture surgery. We suggest treatment protocols based on best available evidence and guidance from allied specialties.
- Hip fracture surgery presents a common management dilemma where semi-urgent surgery is required. In this

article, we advocate an evidence-based algorithm as a guide for managing these anticoagulated patients.

Keywords: hip; fracture; coagulopathy; treatment

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Introduction

Hip fractures are common orthopaedic injuries with an estimated 60 000 to 75 000 cases each year in the United Kingdom, at an estimated annual cost of £2 billion to the NHS. This cost is growing due to the increase in the ageing population.¹

Most of these patients are elderly with polypharmacy for multiple co-morbidities.² Many are likely to be taking some form of anticoagulant. In the United Kingdom, it has been estimated that 4% to 8% of these patients are on warfarin.³ German studies demonstrate that around 15% receive phenprocoumon and over 50% are on aspirin.^{4,5}

With timing of hip fracture surgery playing an important role in reducing morbidity and mortality, adequately managing coagulopathy in this setting is a crucial aspect of overall treatment.⁶⁻⁹

In the United Kingdom, practice generally follows the Department of Health's Best Practice Tariff, suggesting surgery should be performed within 36 hours.¹⁰ The British Orthopaedic Association (BOA) similarly recommends that surgery should not be delayed by > 48 hours.¹¹

The urgency for surgical management of hip fractures specifically varies according to fracture type, morphology and patient age, with urgent (less than six hours) intervention recommended for young patients (aged < 60 years) with intracapsular fractures,¹² and semi-urgent (< 36 hours) surgery for most other patients.¹

Reversal strategies for patients receiving oral anticoagulants needing emergency orthopaedic hip surgery have largely been developed from studies addressing various other emergencies typically in the general surgical and neurosurgical fields.

In this review, we explore the background of coagulopathy in the population presenting with hip fractures and evaluate the optimal channels for assessing and managing this cohort of patients.

Vitamin K antagonists (VKAs)

VKAs such as warfarin or phenprocoumon, are widely used orally administered anticoagulants with multiple clinical indications. Their mechanism of action involves the inhibition of the synthesis of vitamin K-dependent coagulation factors in the liver. This in turn prevents the propagation of an established thrombus.¹³ Their duration of action is variable, with significant range in the half-life across the class of drugs.¹⁴ The action of warfarin, for example, lies between two and five days.¹⁵

Alcohol and other drugs can interact with VKAs by affecting their absorption or metabolic clearance. This can significantly interfere with its control and hence the risk of bleeding or thromboembolism.^{16,17}

When reversal is attempted, the timing for testing International Normalised Ratio (INR) is highly controversial. Testing at six hours is based on the half-life of factor 7 which is six hours. Hence, with vitamin K supplementation, it is assumed that its effect will start to correct the INR within six hours.¹⁸

VKAs in orthopaedic surgery

Major orthopaedic bony surgery is commonly associated with a high risk of bleeding due to the multiple soft-tissue layers breached during the surgical approaches and the associated bleeding from displaced fractures.^{19,20} VKA reversal is therefore crucial before most orthopaedic interventions. An INR > 1.5 is generally associated with an increased risk of post-operative bleeding complications.²¹⁻²³ The BOA recommends that the INR should be corrected to 1.5 or lower pre-operatively.²⁴

A primary concern with discontinuation and reversal of VKAs is the predisposition of patients to thromboembolic events. It is estimated that in high-risk patients, the absolute risk of thromboembolic events within six to eight days of stopping warfarin is approximately 0.3%.²⁵ This risk is significantly higher in patients requiring surgery and has been reported to be as high as tenfold (3%).²⁴

Reversal of VKA-induced coagulopathy is possible with the omission of the responsible agent only. This will often lead to a controlled but slow reduction in the INR over several days. A study addressing INR ranges with

warfarin omission revealed that for those with an INR in the therapeutic range, it took 2.7 to 4.7 days for the INR to reach a range of 1.2 to 1.6.²⁵ In the context of hip fractures this is deemed inappropriate due to the urgency for intervention.²⁶

We will now explore the reversal of VKA coagulopathy for hip fracture surgery, focusing on vitamin K supplementation as the predominant modality, with mention of agents to be used as a back-up or in more urgent situations.

Vitamin K (Phytonadione)

Supplementation of vitamin K (or Phytonadione) is thought to reverse the actions of VKAs through replenishment of body vitamin K stores. This, coupled with omission of the drug, results in the re-activation of existing vitamin K-dependent clotting factors.

The use of vitamin K to reverse both warfarin and phenprocoumon anticoagulation has been shown to be safe and effective in the context of hip fracture surgery.^{5,27}

There is no widely accepted consensus on the absolute indications, dosage and route of vitamin K treatment in the context of hip fracture. Doses as low as 1 mg orally have been shown to significantly reduce the INR in anticoagulated patients over a 24-hour period.²⁸ This study, however, only revealed correction of the INR back to a near therapeutic range. The role of small oral doses remains controversial, with a study demonstrating that up to 66% of patients failed to reach a safe INR of ≤ 1.5 following a 1 mg dose, 24 hours pre-operatively.²⁹ Studies addressing higher doses of oral vitamin K (5 mg to 10 mg) are sparse, with these doses recommended when complete reversal is required or in the presence of active bleeding.¹⁸

The greater bio-availability and rate of onset are thought to be advantages with intravenously (IV) administered vitamin K. Concerns with the administration of IV vitamin K include: anaphylaxis, acute thrombosis and later warfarin resistance.^{13,30,31} The adverse reaction rate to IV vitamin K has been reported to be around 2%.³² Doses as low as 0.5 mg by the IV route have been advocated for correction of over anticoagulation into a therapeutic range.³² In the same study, a 1 mg IV dose saw a reversal of the INR to below 2 in 50% of patients at 24 hours. In all cases, there were no reported complications. In a separate study addressing warfarin reversal for elective surgery, a dose of 3 mg of IV vitamin K administered between 12 and 18 hours pre-operatively, resulted in reversal of the INR to < 1.5 in 94% of patients.³³ A higher IV dose of 5 mg to 10 mg produces a reliable correction of the INR within a 24-hour period.^{30,34} However, as the dose of vitamin K increases, the risk of complications and warfarin resistance when the drug is later restarted also rises.

A recent review directly comparing oral and IV vitamin K administration reported safe reversal using both routes,

with the IV route averaging six to 12 hours compared with 18 to 24 hours for the oral route.³⁵

In 2008, the American College of Chest Physicians recommended an oral dose of no more than 5 mg of vitamin K for warfarin reversal in semi-urgent surgery (defined as an acceptable delay of 24 to 36 hours), with further doses of 1 mg to 2 mg orally if INR normalisation had not yet occurred.¹⁸ In the event of serious bleeding, a dose of 10 mg IV is recommended with fresh frozen plasma (FFP) or prothrombin complex supplementation, depending on the overall urgency. The 2009 Scottish Intercollegiate Guidelines Network recommend using a dose of 1 mg to 2.5 mg of vitamin K to reverse the effects of warfarin, with either IV or oral routes.²⁶ The National Institute of Clinical Excellence recommended assessing and correcting coagulopathy, while performing surgery in a timely manner but did not specify any clinical protocols for achieving this.¹ Lastly in 2011, the *British Journal of Haematology* produced expert-based guidelines recommending IV vitamin K for surgery, which can be delayed for six to 12 hours, using a dose of 1 mg to 3 mg for non-major bleeding.³⁶

Several clinical studies have addressed warfarin reversal in the context of hip fractures. A dose of 1 mg IV, with a further administration of the same dose if necessary at 24 hours, resulted in an average admission to operation time of 37.7 hours in one prospective cohort study.³⁷ In a separate prospective audit, a dose of 1 mg IV was effective in correcting the INR to a level of 1.5 or less in a mean 38 hours without complications.³⁸ Current practice for reversal in hip fractures remains highly variable. However higher IV doses of 5 mg to 10 mg are still used routinely in some institutes despite the lack of evidence for such practice.³⁹

Subcutaneous administration is generally avoided due to its slow and unpredictable onset. Furthermore, intramuscular administration is associated with risk of haematoma at the site of injection and later may result in depot characteristics, which delay the re-attainment of a therapeutic INR range on re-instatement of VKA therapy.³⁰

The majority of guidance available on the use of vitamin K administration in the context of warfarin use tends to be for emergency reversal of over-anticoagulation back into a therapeutic range, rather than from therapeutic range into the sub-therapeutic range. In studies addressing complete reversal, this tends to be in the context of elective surgery when a timely reversal regime can be planned. Studies addressing semi-urgent reversal over a 36- to 48-hour period, which relates to the timeline for reversal in hip fracture surgery, are lacking. The role of oral vitamin K for semi-urgent reversal is unclear with limited evidence to suggest that it is unlikely to reliably reverse the INR within a 36- to 48-hour period. There is no evidence to suggest using higher oral doses of vitamin K to improve the speed of INR reversal. Using the IV route

seems to be more effective over a shorter period of time, with doses in the range of 1 mg to 3 mg reliably effective in reversing an INR within 48 hours.

FFP

FFP is the liquid component of blood, free from platelet, leucocyte and red blood cell constituents, while containing all of the coagulation factors normally found in blood plasma. The transfusion of FFP must be group ABO compatible while rhesus status compatibility is not essential. As FFP is a blood product, it carries all of the risks associated with whole blood transfusions.

Currently, there is no clear guidance to support the use of FFP in patients with hip fractures on the background of anticoagulation. More specifically, guidelines published by the British Committee for Standards in Haematology (BCSH) did not make reference to the peri-operative management of VKA anticoagulation in hip fracture patients but suggested, in the non-acute setting, that FFP should be reserved only for the reversal of VKA anticoagulation in the presence of severe bleeding or if correction cannot safely be achieved using vitamin K supplementation.⁴⁰ This was clarified subsequently, with the current guidelines for warfarin management published in the *British Journal of Haematology* concluding that FFP could not be recommended for use in the acute setting.³⁶

FFP is rarely used in VKA reversal in the context of hip fractures.³⁹ In the emergency setting, FFP is less favoured compared with other modalities, namely prothrombin complex concentrate (PCC), due to its delay and incomplete reversal.⁴¹

PCC

PCC is composed of varying concentrates of inactivated vitamin K-dependent clotting factors (II, VII, IX and X) as well as proteins C and S. It is prepared from donated frozen human plasma, with the overall clotting factor concentration reaching approximately 25 times that found in normal plasma.⁴²

As previously discussed, delay to surgery for treatment of hip fractures has been well established to increase mortality and complication rates. As such, PCC remains a useful tool to rapidly correct coagulopathy in individuals in whom vitamin K reversal is not possible.⁴³

PCC normally corrects coagulopathy within 30 minutes and can reduce a therapeutic INR range to an average of 1.3 in this time.³⁰ Its duration theoretically depends on the shortest half-life of its constituent coagulation factors. In most formulations, factor 7's half-life of six hours limits its effects to this time.³⁶ Clinical studies, however, have demonstrated significant ongoing effects for up to 96 hours.³⁰ Administration of vitamin K in addition to PCC is thought to prevent rebound increases in INR and provide a more sustained reversal of anticoagulation.⁴⁴

Side effects associated with PCC include: allergic reactions; heparin-induced thrombocytopenia; disseminated intravascular coagulopathy; and thromboembolic events such as deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction.

Currently, there are no specific guidelines for the use of PCC in the context of hip fractures on the background of anticoagulation. The BCSH recommends using PCC specifically for emergency anticoagulation reversal in patients with major bleeding or, when surgery cannot be delayed, PCC in combination with 5 mg IV vitamin K.³⁶ In the event when PCC is not available, FFP should be considered. There are, however, no well-designed studies proving superiority of PCC over FFP. Clinical studies addressing reversal of coagulopathy in hip fractures indicate that PCC is not routinely used.³⁸

The overall cost of PCC is dependent on the exact commercial product used but can be between £550 and £875 per treatment for a single patient. This can be offset by saving up to £1250 per patient across their hospital stay following a hip fracture.⁴⁵

The use of PCCs in the management of VKA-induced coagulopathy has been shown to be a reliable and rapid means of reversal. The literature is scarce on proving the efficacy of PCC over other forms of reversal agents available. In the context of the majority of hip fractures when a timeline in the range of 36 to 48 hours between presentation and surgery is usually advocated, the use of PCC is not usually necessary. We would, however, retain this option of reversal, particularly for younger patients sustaining intracapsular hip fractures when urgent surgery (within six hours) is crucial for preventing future complications.¹²

Direct oral anticoagulants (DOACs)

As described earlier, VKAs exhibit several drawbacks, including drug interactions, narrow therapeutic index and the need for frequent monitoring.

To date, there are three oral compounds which have been popularised by their wider therapeutic index in comparison with warfarin with less risk of bleeding complications^{46,47} and fewer interactions with other drugs and dietary components. Since 2013, apixaban, dabigatran and rivaroxaban have all received licensing for use in elective hip and knee arthroplasties, as well as in the area of stroke and systemic embolism prevention.⁴⁸

Rivaroxaban and apixaban both have their effects through the direct inhibition of activated coagulation factor 10.⁴⁶ In contrast, dabigatran competitively inhibits activated coagulation factor 2 (thrombin).⁴⁹ All agents exhibit a rapid onset of action, with peak plasma concentrations reached as early as 1.5 hours after administration for dabigatran and three to four hours for rivaroxaban and apixaban. The half-lives of all three drugs are highly

variable ranging from four hours in rivaroxaban to 17 hours in dabigatran.⁴⁶⁻⁵⁰ The effects of these have been shown to increase either the prothrombin time (rivaroxaban), the activated partial thromboplastin time (APTT) (dabigatran)⁵⁰ and the clotting time (apixaban),⁵¹ although no guidelines have suggested using these parameters to monitor their anticoagulation effects.

Human studies have demonstrated complete reversal of the prothrombin time within 15 minutes of administration of PCC in individuals treated with rivaroxaban.⁵⁰ These effects lasted for a minimum of 24 hours. The same study revealed no effect on reversal of the APTT following PCC administration in patients treated with dabigatran.

Reversal approaches for apixaban are less well understood. However, there is some evidence to suggest recombinant activated factor 7 and activated PCC corrects the clotting time in patients treated with apixaban, usually within 45 minutes.⁵¹

Haemodialysis and haemoperfusion have also been studied for their reversal potential. Up to 60% of plasma-based dabigatran was eliminated within four hours of haemodialysis, resulting in a significant reduction in its overall anticoagulant activity.⁵² This management strategy should be considered, particularly in patients with impaired renal function when renal excretion will likely be prolonged. Rivaroxaban is 95% protein bound and apixaban is 87% protein bound, making haemodialysis relatively ineffective.⁵³

An antidote received United States Food and Drug Administration approval in 2014 for the reversal of dabigatran treatment.⁵⁴ Idarucizumab, derived from a human antibody, is advocated for use specifically in cases of uncontrolled bleeding or in the event of emergency surgery.

Monitoring of the serum levels of dabigatrin has been advocated in DOAC peri-operative management by the Groupe d'Intérêt en Hémostase Périopératoire.⁵⁵

In the elective setting, the European Society of Cardiology suggests omission of DOACs for 96 hours before orthopaedic surgery or other procedures deemed high-risk for bleeding.⁵⁶ As previously discussed, hip fracture surgery necessitates more urgent management; however, as yet, the literature does not inform this decision more specifically to these patients.

Analysis of the registry data looking at the safety of DOACs in the peri-operative setting suggests low complication rates (1% major cardiovascular events, 1.2% major bleeding complications) overall after major interventions.⁵⁷ Strategies to manage the DOAC therapy peri-operatively include continuation, cessation \pm bridging heparin therapies. Involvement of the physician who initiated the DOACs is essential in guiding these strategies, however, the registry data are encouraging for these drugs, and approaches to their management peri-operatively convey relatively low risk.

While specific evidence is awaited on reversal protocols for DOACs in hip fracture, the risk/benefit decisions regarding surgical delay and anticoagulation reversal should remain multidisciplinary. Common practice is to omit the DOAC for 24 to 48 hours and undertake surgery thereafter.⁵⁶ Pending robust evidence-based protocols, we would continue to recommend this pragmatic approach.

Antiplatelet therapy

Aspirin and clopidogrel are the most commonly used antiplatelet agents, with newer agents including ticagrelor and prasugrel. They can be used in isolation or combined in order to reduce the risk of primary cardiovascular events.

Aspirin is an irreversible inhibitor of the cyclo-oxygenase enzyme, resulting in reduced platelet production of the lipid thromboxane A₂, a potent vasoconstrictor and promoter of platelet aggregation. Aspirin has a serum half-life of 20 minutes and is metabolised by the liver.⁵⁸ Clopidogrel and prasugrel both target the P2Y₁₂ receptor on platelets, covalently bonding and thus irreversibly inhibiting platelet aggregation.⁵⁹ The reversal of the effects of these antiplatelet therapies is largely dependent on the seven to ten days half-life of platelets.^{58,60} Conversely, platelet transfusion can be undertaken in the context of bleeding or emergency surgery.

Ticagrelor directly acts on the P2Y₁₂ receptors themselves, producing a reversible and concentration-dependent inhibition of the receptor. Its use has been popularised after it was shown to reduce mortality in acute coronary syndromes when compared with clopidogrel.⁶¹

However, the only reversal strategy of platelet transfusion has been shown to be ineffective for ticagrelor.⁶² A ticagrelor-binding antidote is in development.⁶³

The main concerns around the use of antiplatelet therapy in the context of hip fractures are in relation to increased bleeding risk during the procedure, as well as increased risk of haematoma formation following spinal anaesthesia. Conversely, withdrawal of antiplatelets or reversal of their effects with platelet transfusions (if appropriate) results in increased risk of thromboembolic events.⁶⁰

The literature to date on antiplatelet agents in relation to hip fracture surgery centres on aspirin and clopidogrel alone, with a lack of guidance specific to the novel antiplatelet agents. Patients suffering a delay to surgery due to these antiplatelet agents have an increased overall mortality rate.⁶⁴ A clinical study addressing the use of both aspirin and clopidogrel when surgery for hip fractures is not delayed concluded that there was no difference in bleeding complications, blood loss or transfusion requirements, when compared with those not on antiplatelets.⁶⁵

Furthermore, hospital length of stay and overall mortality were also not affected. In a separate study directly comparing early and late surgical intervention for hip fracture patients taking long-term clopidogrel, no difference was found in overall bleeding complications and mortality rate between the two groups.⁶⁶ However, the thromboembolic and infectious complications were significantly higher in the delayed group to surgery, further supporting the view of early surgery despite the use of antiplatelet therapy. A significantly increased risk of bleeding complications has been highlighted in one study with the use of either clopidogrel only or combined clopidogrel and aspirin in patients who underwent early hip fracture surgery.⁶⁷ This study confirmed no increase in mortality and advocated early surgery in such cases, corroborated by a systematic review in 2016.⁶⁸

Neuro-axial anaesthesia in the setting of hip fractures is often a preferred anaesthetic modality. Early fears around the risk of spinal haematoma following neuro-axial anaesthesia in patients on aspirin have since been alleviated following a comprehensive review of the literature.⁶⁹ It is now widely accepted that the use of aspirin in the setting of neuro-axial anaesthesia does not predispose to haematoma formation and therefore does not represent a contraindication. However, the same does not apply to the isolated use of clopidogrel, with the American Society of Regional Anaesthesia recommending the discontinuation of antiplatelet therapy by at least seven days before the use of neuro-axial anaesthesia.⁷⁰ In cases of combined aspirin and clopidogrel antiplatelet therapy, several individual case reports have described safe anaesthesia when used with platelet transfusions, if such anaesthesia is necessary.⁷¹

Bridging therapy

Bridging therapy refers to the notion of safe therapeutic short-term anticoagulation, usually in the form of low molecular weight heparin, while regular long-term oral anticoagulation is discontinued.

No universal single regime can be prescribed for all patients due to the large variation in patient indications for anticoagulation and the different haemorrhagic risks associated with various surgical interventions. Currently, the decision on whether to commence bridging therapy is made following a risk stratification process depending on the original indication for anticoagulation and departmental guidelines.⁷² The stratification process ultimately weighs up a patient's risk of thrombosis without anticoagulation against their risk of peri-operative bleeding as it is backed up by the BCSH.³⁶

In the context of hip fracture surgery, it is our opinion that bridging therapy should be considered only in particular cases at significant risk of venous thromboembolism. However, there is a lack of research in this area proving the

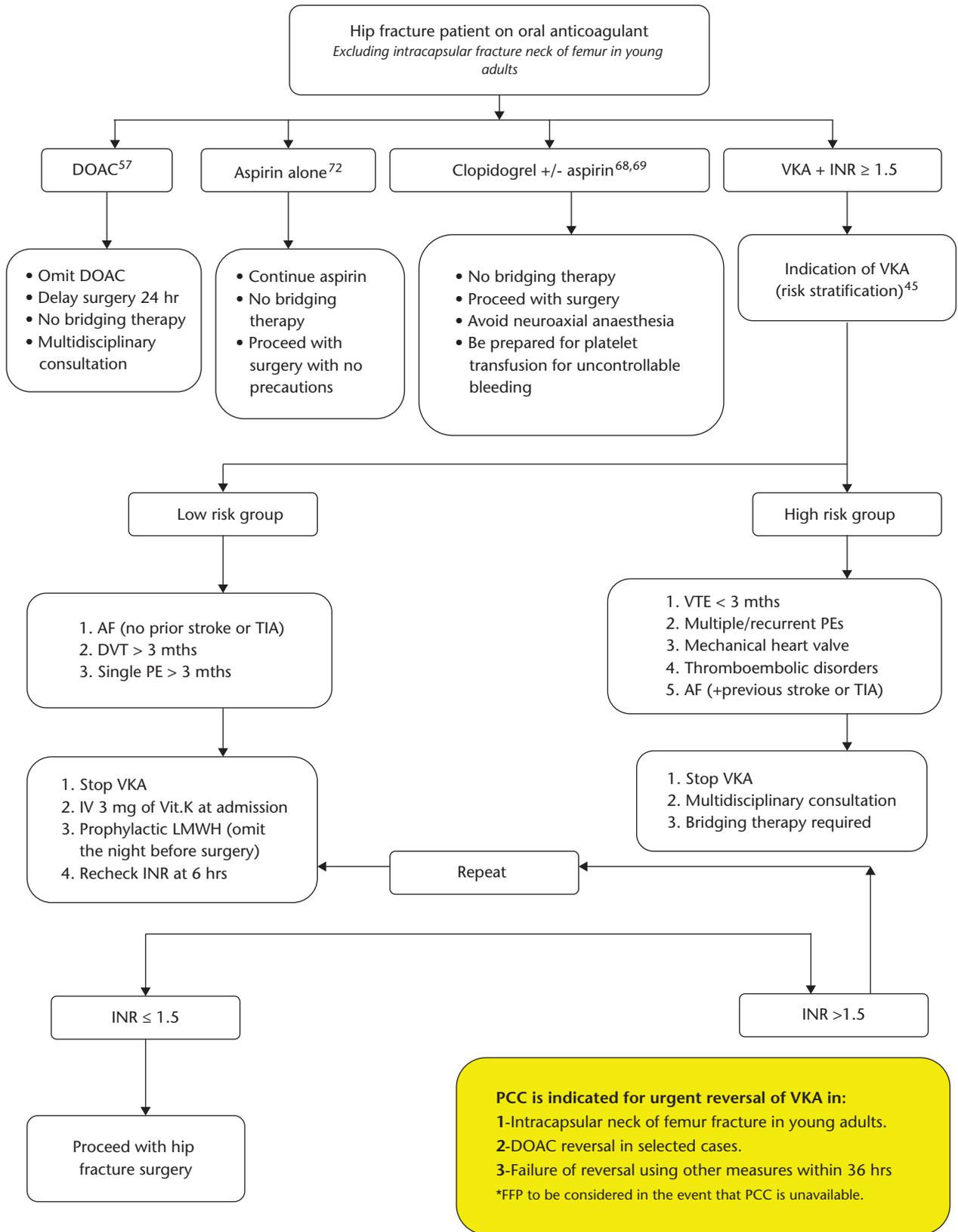


Fig. 1 Management of anticoagulation in hip fractures (DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; INR, International Normalised Ratio; AF, atrial fibrillation; TIA, transient ischaemic attack; DVT, deep vein thrombosis; PE, pulmonary embolism; IV, intravenous; Vit.K, vitamin K; LMWH, low molecular weight herapin; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma.

efficacy of bridging therapy in any scenario. The use of meticulous surgical technique by an experienced surgeon can minimise the operating time and blood loss.

Hip fracture surgery, while remaining urgent, in most cases is not truly emergent. As such, it holds a rather specific middle ground. Historically, the general medical and surgical literature concentrating on acute haemorrhage, surgical emergency or conversely non-urgent elective procedures were not completely relevant when informing our approach to the increasing number of patients with hip fracture presenting on anticoagulation therapy. As reviewed above, a body of evidence has emerged on the importance of expeditious hip fracture surgery. This, in part, was fuelled by the observations of the effects of delaying surgery in attempts to address coagulopathy.

Robust, hip fracture-specific evidence now informs our approach to VKA-induced coagulopathies and the classical antiplatelet agents (aspirin and clopidogrel). Research into novel antiplatelet agents and DOACs in the context of hip fracture is awaited. In the meantime, we provide a pragmatic approach (Fig. 1) informed by orthopaedic-specific evidence where available, evidence from allied fields and expert opinion.

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