

Implications of Anticoagulant and Antiplatelet Therapy in Patients Presenting with Hip Fractures: A Current Concepts Review

Short title: Perioperative Anticoagulant and Antiplatelet Therapy

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Abstract

The increasing use of anticoagulant and antiplatelet therapy for the prevention of thromboembolic disease poses a significant challenge to orthopaedic surgeons treating elderly patients presenting with proximal femoral fractures. Early surgical intervention is known to be beneficial from a clinical perspective and has been encouraged in the UK through the introduction of best practice tariffs providing increased remuneration for prompt treatment. An understanding of the necessary delay to surgery or reversal options for each type of antiplatelet or anticoagulant agent is therefore important. A number of professional bodies have recently produced guidelines that help clinicians manage these patients during the peri-operative period.

We review the guidelines relating to antiplatelet and anticoagulant agents during the perioperative period with respect to hip fracture surgery.

Antiplatelet agents should not interfere with timing of surgery, but may affect the choice of anaesthetic performed. The action of warfarin should be reversed to expedite surgery. Newer direct oral anticoagulants are more problematic and surgical delay may be necessary, though reversal agents are becoming available.

Key words: Anti-coagulant; Anti-platelet; Surgery; Guidelines

The last decade has seen a proliferation in the number and diversity of anticoagulant and antiplatelet agents and an increase in the indications for their use.. This has helped to increase the longevity and reduce the morbidity of patients with vascular disease. An increasing number of this cohort subsequently survive to present to orthopaedic services with injuries requiring urgent surgery, most notably those with fragility hip fractures. The management of these patients represents a significant clinical challenge. Expeditious surgery is indicated both on humanitarian ground and also on the basis that it may improve survival [1]. However antiplatelet agents and anticoagulants increase the risk attendant to both surgical and anaesthetic intervention. Most have no specific antidote (table I). The decision to discontinue such medication is not always simple and can place patients at increased risk of thromboembolic sequelae. There is wide variation in clinical practice with regard to the peri-operative use of a number of anticoagulant and antiplatelet drugs [2]. Very recently, guidelines have been issued by a number of bodies providing clarification on the clinical management of patients requiring urgent surgery whilst medicated on antiplatelet and anticoagulant agents. Here we provide a review of these iatrogenic coagulopathies and how they relate to management of hip fracture patients.

Aspirin

Aspirin is widely used in primary and secondary prevention of cardio, cerebro and peripheral vascular disease. It acts by inhibiting the cyclooxygenase enzymes thereby preventing the generation of mediators, notably thromboxane, germane to the process of platelet aggregation and clot formation [3]. Guidelines from the Scottish Intercollegiate Guidelines Network (SIGN), The Association of Anaesthetists of Great

Britain and Ireland (AAGBI) and the American College of Chest Physicians (ACCP) concur that aspirin should not delay surgery for hip fracture patients [4–6]. The guidance however differs as to whether interruption of aspirin therapy is necessary in the perioperative period. The AAGBI recommend that aspirin be discontinued except in cases of unstable angina or recent/frequent transient ischaemic attack. The ACCP make a similar recommendation in that those with moderate to high risk such as those with cardiovascular disease, cerebrovascular disease or diabetes should continue aspirin. In those falling into lower risk categories where aspirin is being used for primary prevention, consideration should be given to withholding this treatment during admission. The basis for the recommendation is unclear, as evidence suggests that aspirin does not significantly increase the peri-operative blood loss for hip fracture patients [7–10].

Aspirin is uncommon amongst antiplatelet and anticoagulant agents in that it has a readily available method to reverse its effects if unexpected bleeding occurs. The British Society of Haematologists (BSH) in their 2016 guidance on the perioperative management of anticoagulant and antiplatelet agents, advises that aspirin antiplatelet activity can be reversed with 2 pools of platelets administered 2 hours after the last dose of aspirin [11].

Clopidogrel

Clopidogrel is a potent antiplatelet agent. It is a pro-drug converted to an active metabolite by the liver. It binds directly to the receptor P2Y₁₂ on platelets inhibiting ADP dependent signalling pathways involved in platelet aggregations [3]. There is little clinical consensus on the management of patients with hip fracture medicated on

clopidogrel [12]. According to SIGN and AAGBI guidelines, surgery should not be delayed due to anticoagulation with clopidogrel [4, 5]. Patients medicated on clopidogrel represent a high cardiovascular risk cohort. Hence it is advised by the AAGBI that clopidogrel therapy not be interrupted during admission for hip fracture [5]. This position is corroborated by a recent meta-analysis and large case series showing that clopidogrel cessation during admission is associated with an increased risk of cardio and cerebrovascular sequelae and does not prevent bleeding complications [12, 13]. In addition, the studies found early surgery to be safe with no increase in mortality. Doleman and Moppett in their earlier meta-analysis reported similar findings [14].

Evidence does suggest however that clopidogrel increases peri-operative blood loss for hip fracture patients [12]. However it is not clear that this difference is clinically significant with regard to patient morbidity or whether it translates into increased transfusion requirements. The meta-analysis of Soo et al suggested that there is no increase in transfusion requirements in patients receiving clopidogrel therapy [13]. However an earlier meta-analysis looking specifically at patients medicated on clopidogrel undergoing early surgery compared to controls suggested a marginal increase in risk of transfusion [15]. Clopidogrel therapy increased the odds of transfusion by 1.4 with 95% confidence interval of 1.00 to 1.99 compared to those not on this therapy [15].

Clopidogrel use does have ramifications for spinal anaesthesia. The AAGBI and the American Society of Regional Anaesthesia and Pain Medicine guidance recommend in general that clopidogrel be discontinued for 7 days prior to the administration of spinal anaesthesia [5, 11]. The same guidance suggests that the use of clopidogrel

is not an absolute contraindication for spinal anaesthesia within the 7-day window in patients with hip fracture [16].

In summary, the thrust of evidence suggests that clopidogrel should not be discontinued nor surgery delayed for patient medicated on clopidogrel. There is an increased bleeding risk and general anaesthesia is preferable to neuraxial anaesthesia.

There is no antidote to clopidogrel. The efficacy of packed platelets at mitigating its antiplatelet effect remains controversial. Studies have shown platelet infusion to correct the inhibition of platelet aggregation caused by aspirin but not clopidogrel [3]. According to the 2016 British Society of Haematologists (BSH) guidance, platelets are only effective if clopidogrel is discontinued and administered between 12 and 24 hours after the final dose. The number of pools required for reversal is not clear [11].

Ticagrelor and Prasugrel

Ticagrelor and Prasugrel both inhibit ADP dependent pathways involved in platelet aggregation [3]. Prasugrel is similar to clopidogrel in that its binding to the P2Y₁₂ receptor is irreversible. However it is more expeditious and effective at achieving platelet inhibition. It has a comparable half-life of 7 hours [3]. Hence, in principle, platelet infusion is likely to be ineffective at correcting a bleeding diathesis if administered shortly after the last dose. Ticagrelor is a reversible inhibitor of ADP mediated platelet aggregation. It is a more potent and faster in onset than clopidogrel. Ticagrelor is increasingly replacing clopidogrel in the management of acute coronary syndromes [17–19]. It may however carry a higher risk of bleeding related complications than clopidogrel. Similar to clopidogrel, a platelet infusion does not

reverse the effect of ticagrelor [20, 21]. Given the increasing use of ticagrelor, developers AstraZeneca are in the process of developing an antidote [22].

There are no explicit guidelines for the newer antiplatelet agents. The mode of action suggests patients with hip fracture should be managed in a similar fashion to those on clopidogrel.

Phosphodiesterase inhibitors

Dipyridamole and Cilostazol are antiplatelet agents that inhibit platelet aggregation by inhibiting phosphodiesterase and blocking the reuptake of adenosine by platelets. Dipyridamole is used as an adjunct to warfarin for the prevention of thromboembolism associated with metallic cardiac valves. It is also an option, often in combination with aspirin, for the secondary prevention of thrombosis in patients who have sustained a transient ischaemic attack [23]. Cilostazol is a second line drug for the treatment of vascular claudication. There are no specific guidelines on the management of fracture neck of femur patients receiving these drugs, however the antiplatelet effect of these agents is relatively weak and therefore their use should not delay surgery [24].

Dual Antiplatelet therapy (DAT)

This is commonly indicated in patients who represent high cerebrovascular and cardiovascular risk. Aspirin and ticagrelor, clopidogrel, prasugrel or dipyridamole are the most common combinations. Evidence suggests DAT is associated with an increased bleeding risk following hip fracture surgery. A modest-sized study however found surgery in fracture patients on DAT (clopidogrel and aspirin) to be safe [9]. The BSH recommend the use of tranexamic acid to control the bleeding effects associated with DAT.

Those patients who have undergone recent cardiovascular stenting are at particularly high risk of thromboembolic phenomena. Such patients are frequently on DAT. The ACCP and American College of Cardiology (ACC) guidelines suggest that these agents should be continued if possible as interruption to therapy poses a risk of stent thrombosis. If there is a need to discontinue an agent it should be the P2Y₁₂ inhibitor that is stopped [25]. The risk of stent thrombosis is highest within the first 30 days for bare metal cardiac stents or 6 months for drug eluting stents and dual therapy should be continued during this time period. In instances where there is a very high and undesirable bleeding risk for a patient with dual therapy but cessation of antiplatelet agents poses a high-risk, the P2Y₁₂ inhibitor can be discontinued and "bridging cover" provided using enteral platelet glycoprotein IIb/IIIa receptor inhibitors [3]. These agents have a short half-life and can be rapidly discontinued and restarted post-operatively.

Direct Oral Anti-Coagulants

The direct oral anticoagulants (DOACs) are increasingly being used to replace warfarin and have a wide therapeutic repertoire. There are no explicit guidelines as to the management strategy for patients requiring urgent hip fracture surgery, medicated on DOACS. More detailed guidance is available with respect to elective surgery. Given that until very recently there were no readily available reversal agents, surgeons are bound to some degree by the recommendations for elective surgery. Lai et al in their review advocated a minimum delay of 12 hours, but preferably 24 hours, from the last dose of DOAC prior to surgery [26]. The BSH advocates a delay of 48 hours before elective surgery with a major risk of bleeding in those with normal renal function [11].

Surgery can only be performed when it is safe to do so. The increasing use of DOACs will have tangible ramifications for the remuneration hospitals receive for hip fracture

surgery. The National Health Service Best Practice Tariff financial reward of £1335 per patient for hip fracture is only paid if their treatment meets certain criteria [27]. A major criterion is surgery within 48 hours of admission. There is no exemption for patients medicated on anticoagulants. The use of DOACs may make achieving this target increasingly difficult.

Rivaroxaban , Apixaban & Edoxaban

Rivaroxaban, apixaban and edoxaban are all direct inhibitors of factor Xa. The BSH recommend discontinuing these agents for 48 hours prior to elective surgery with high bleeding risk. In those with renal impairment (creatinine clearance <30ml/min) the period should be extended to 72 hours. According to the BSH, all agents should be re-introduced at 48 hours after surgery with thromboprophylaxis post-operatively as normal until full re-introduction of the DOAC [11]. There is no explicit recommendation from BSH for hip fracture surgery. The manufacturer's recommendations differ somewhat for rivaroxaban and edoxaban compared to those from BSH, recommending cessation for 24 hours prior to surgery [28, 29]. The manufacturers for all 3 agents advise reintroduction as soon as possible after the procedure (e.g. 6-10 hours for Rivaroxaban) with no specific 48 hour stipulation [25, 26, 30].

There are implications for anaesthesia. According to the AAGBI guidance neuraxial blockade should be avoided for 24-48 hours following the last dose of apixaban and 48 hours for rivaroxaban [5]. If surgery is required before this, general anaesthesia is indicated.

Dabigatran

This is a direct thrombin inhibitor. A normal thrombin time excludes any significant dabigatran activity. The BSH guidelines for elective surgery recommend that dabigatran treatment should be interrupted for 48 hours. However the interval rises with increasing renal impairment to 96 hours for those the creatinine clearance less than 50ml/hr [11]. The BSH, as with the other DOACs, recommends that dabigatran be reintroduced at 48 hours after surgery [11].

The manufacturer advise that in cases of subacute surgery, dabigatran should be stopped for at least 12 hours from the last dose before surgery, and introduced as soon as possible post procedure. The manufacturer recognises that renal impairment can cause significant delay in clearance. In those with a creatinine clearance of less than 50ml/hr, it is recommended that dabigatran be discontinued for 4 days prior to high risk elective surgery.

AAGBI guidelines for neuraxial blockade in the context of dabigatran are similar to those for major surgery. In those with creatinine clearance of greater than 80ml/hr, a 48 hour window is required. In those clearance values between 80 and 50, this rises to 72 hours and finally 96 hours, where creatinine clearance is less than 50ml/hr [5]. Clearly a delay of 4 days is unacceptably long for a patient with hip fracture. Hence in patients with renal failure for whom hip fracture surgery is necessary specific antidotes to the DOACs may be indicated.

Antidotes to DOACs

Specific antidotes for DOACs are starting to emerge:

Idarucizumab

Idarucizumab is the first specific antidote to a DOAC to be licensed in the UK and US. The agent, which is a humanised monoclonal antibody, binds to and reverses the effects of dabigatran. The uncontrolled REVERSE AD trial involving 90 patients medicated with dabigatran who had uncontrolled haemorrhage or need for emergency surgery showed that idarucizumab completely reversed the elevated dilute thrombin time and the ecarin clotting time in 88-98% of patients, with an effect that was evident in minutes after delivery of the infusion [31]. The drug is relatively expensive with a 5g dose costing £2400 but BSH advocate its use where emergency surgery is required [11, 32].

Andexanet

Andexanet is a drug that is under development but is not yet licenced for use in either the UK or US. It acts as a decoy target for rivaroxaban, apixaban and edoxaban. It has proven efficacy at reversing the activity of these DOAC in patients with bleeding episodes [33]. There are a number of unresolved issues including: the effect of the timing of the last dose of a DOAC on the dose required of andexanet, the duration of a continuous infusion to provide adequate therapy, variations in dose required depending on DOAC and the timing of reinstating anticoagulation after treatment [34]. The BSH have endorsed the use of andexanet for the reversal of the anticoagulation within emergency surgery when it becomes available [11].

Tranexamic Acid

The BSH recommend the use of tranexamic acid to mitigate the bleeding effect of both antiplatelets and DOACs. It stabilises clots by inhibiting the activation of plasminogen to plasmin. The latter is responsible for clot degradation by means of targeting fibrin, a key component of the clot. Tranexamic acid is thus an antifibrinolytic [35]. However

the British National Formulary and manufacturer summary product characteristics state its use is contraindicated in those with a history of venous or arterial thrombosis [36]. This would thus include those receiving anti-platelets and DOAC therapy. However, a recent large systematic review showed that the use of tranexamic acid in hip fracture surgery reduced transfusion requirements by 46% (95% confidence interval 35% to 85%) and increased post-operative haemoglobin levels. There was no reported increase in thrombotic events, but the authors state the quality of the evidence was low with respect to this finding [37]. Studies in elective orthopaedic surgery have not shown an increased thrombosis risk with the use of tranexamic acid [38].

Warfarin

It is estimated that 5% of hip fracture patient are medicated on warfarin [5] and warfarinised patients may endure delays to surgery. A recent large study found that patients medicated on warfarin were only a fifth as likely to undergo surgery within 36 hours even after adjustment for potential confounders, when compared those not receiving this medication [39]. Warfarin inhibits vitamin K dependent-generation of factors II, VII, IX and X. Its action is effectively reversed by vitamin K. Its anticoagulant action is monitored using the INR. The target range for surgery is less than 1.5 for spinal anaesthesia [11]. Reversal of warfarin activity is recommended for hip fracture surgery in the SIGN guidelines [4].

Beriplex is an alternative, but expensive, antidote compared to vitamin K. The mean cost of a reversal dose is £550 [40] compared to £0.19 for 5mg of intravenous vitamin K [41]. However it reverses the anticoagulant effect of warfarin within 30 minutes and lasts up to 6 hours [42]. It may be administered in conjunction with vitamin K (5mg) to

avoid rebound rises in INR once the effect of PCC is extinguished [43]. As Beriplex is much more expeditious in effect than vitamin K it may prevent the delays often seen when vitamin K is used to reverse the effect of warfarinisation.

The BSH advocate that for certain high risk patients, once the INR becomes subtherapeutic, short-acting bridging anticoagulation is required in the form of low molecular weight heparin or intravenous unfractionated heparin [11]. Such patients include

- Those with metallic heart valves.
- Patients with a history of deep vein thrombosis or pulmonary embolism within the 3 months preceding a hip fracture and patients who have developed thromboembolic disease while already on anticoagulant therapy.
- Those with atrial fibrillation who have suffered stroke or a transient ischaemic attack within 3 months of presentation with a hip fracture.

For patients with atrial fibrillation the BSH recommend that risk stratification should be performed according to the CHA₂DS₂VASC score [44]. A score of 4 or greater is indicative of high thromboembolic risk and consideration should be given to bridging anticoagulation in this group [11]. This advice was based on the study by Douketis et al. In this large prospective randomised controlled trial of surgical patients on warfarin for atrial fibrillation, it was found that bridging anticoagulation did not reduce the risk of thromboembolic disease, but did increase bleeding complications compared to those who were not given any bridging anticoagulation [45]. However, the study included very few patients with a CHA₂DS₂VASC score above 4, therefore bridging continues to be recommended for these patients.

Antithrombotics and anticoagulants have improved the survival of patients at high risk of thromboembolic diseases. Surgeons need to be conversant with the gamut of agents to ensure that surgery is performed safely and expeditiously in this vulnerable cohort. The timing of the last dose of any anticoagulant or antithrombotic agent is increasingly an important component of the clinical history of hip fracture patients. There is merit in the formulation of local guidelines in conjunction with haematologists and transfusion services regarding the management of hip fracture patients medicated on antithrombotic and anticoagulant agents. We would advocate incorporation of these guidelines into hip fracture clerking proformas to help the multidisciplinary team manage these patients efficiently and effectively.

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Table I: Summary of anticoagulant and antiplatelet agents in common use and relevant guidance on perioperative management

Agent	Target	Pharmacokinetics	Diagnostic test	Agents to restore haemostasis	Hip fracture surgery guidance
Aspirin (Acetylsalicylic acid, active metabolite salicylic acid)	Platelet aggregation Cyclooxygenase irreversible inhibitor	Elimination half-life 20 minutes (Permanent inactivation of platelets occurs meaning clinical effects reverse with natural turnover of platelets (approx. 10%/day))	Platelet function tests <i>Closure time assay</i> <i>Bleeding time</i> <i>Viscoelastometry</i> <i>Platelet aggregometry</i> <i>Flow cytometry</i>	Platelets (2 units) minimum 2 hours after last dose of drug. DDAVP	Delay of surgery or reversal rarely necessary. (SIGN, AAGBI, ACCP)
Clopidogrel	Platelet aggregation P2Y ₁₂ receptor irreversible inhibitor	Elimination half life 6 hours.	Platelet function tests	Platelets (no consensus on dose) minimum 12-24 hours after the last dose.	Hip fracture surgery delay not necessary (BSH). Spinal anaesthesia not contraindicated in hip fracture patients who have received the drug during the preceding 7 days, though general anaesthesia may be preferable. (AAGBI). General anaesthetic should be performed if on dual antiplatelet therapy (SIGN).
Ticagrelor	Platelet aggregation P2Y ₁₂ reversible inhibitor	Elimination half life: parent drug approx. 7 hours, active metabolite approx. 9 hours	Platelet function tests	Platelets	No specific guidance. SIGN advise that antiplatelet therapy should not delay surgery.
Prasugrel	Platelet aggregation	Elimination half life: active metabolite approx. 7 hours	Platelet function tests	Platelets	No specific guidance. SIGN advise that antiplatelet therapy should not delay surgery.

	P2Y ₁₂ reversible inhibitor				
Dipyridamole	Platelet aggregation Dose dependent inhibition of adenosine uptake into platelets. Phosphodiesterase inhibitor.	Elimination half life: 2 phase model. Initial decline 40minutes, terminal decline 10 hours.	Platelet function tests	Platelets	No specific guidance. SIGN advise that anti-platelet therapy should not delay surgery.
Cilostazol	Platelet aggregation Dose dependent inhibition of adenosine uptake into platelets. Phosphodiesterase inhibitor.	Elimination half-life: 11-13 hours	Platelet function tests	Platelets	No specific guidance. SIGN advise that anti-platelet therapy should not delay surgery.
Rivaroxaban	Factor Xa inhibitor	Elimination half life: 5-9 hours, longer in the elderly (11-13 hours).	PT and APTT may be abnormal. Factor Xa assays	Andexanet and Aripazine under investigation as a reversal agent. In case of severe bleeding consider prothrombin complex concentrate.	Manufacturer advises 24 hour surgical delay after last dose. BSH advise to delay surgery until 48 hours after last dose and 72 hours in renal impairment (BSH planned surgery guideline). Avoid neuraxial block for 48 hours after last dose (AAGBI)
Apixaban	Factor Xa inhibitor	Elimination half-life: 12 hours	PT and APTT may be abnormal. Factor Xa assays	Andexanet and Aripazine under investigation as a reversal agent.	BSH advise to delay surgery until 48 hours after last dose and 72 hours in renal impairment (BSH planned surgery

				In case of severe bleeding consider prothrombin complex concentrate.	guideline). Avoid neuraxial block for 24 hours after last dose (AAGBI)
Edoxaban	Factor Xa inhibitor	Elimination half-life: 10-14 hours	PT and APTT may be abnormal. Factor Xa assays	Andexanet and Aripazine under investigation as a reversal agent. In case of severe bleeding consider prothrombin complex concentrate.	BSH advise to delay surgery until 48 hours after last dose and 72 hours in renal impairment (BSH planned surgery guideline). Avoid neuraxial block for 24 hours after last dose (AAGBI)
Dabigatran	Thrombin inhibitor	Elimination half-life: 12-17 hours, longer in renal impairment (28 hours in severe renal impairment)	APTT and Thrombin time increased. Ecarin clotting time.	Idarucizumab	BSH advise to delay surgery until 48 hours after last dose and 96 hours in severe renal impairment (BSH planned surgery guideline). Avoid neuraxial block for 48 hours after last dose with normal renal function, increased to 96 hours with severe renal impairment (AAGBI)
Warfarin	Inhibits Vitamin K dependent synthesis of factors II, VII, IX and X	Elimination half-life: 20-60 hours	INR	5mg intravenous Phytomenadione (Vitamin K1) and delay surgery 6-8 hours. Lower doses for partial reversal. Prothrombin complex concentrate for more urgent reversal.	SIGN recommend partial reversal of warfarin with 1-2.5mg intravenous or oral phytomenadione. BSH advise 5 mg of intravenous phytomenadione or 25-50µg/Kg of Beriplex (prothrombin complex concentrate)