Review Article

Anticoagulation drugs in the perioperative period

Ben Morrison[1,2], Leigh Kelliher[1,2], Chris Jones[1,2]

[1]Department of Anaesthetics, Royal Surrey County Hospital, Guildford, Surrey, UK; [2]Surrey Peri-operative Anaesthesia and Critical Care Collaborative Research Group (SPACeR), Guildford, Surrey, UK

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study material or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ben Morrison. Department of Anaesthetics, Royal Surrey County Hospital, Guildford, Surrey, UK; Surrey Peri-operative Anaesthesia and Critical Care Collaborative Research Group (SPACeR), Guildford, Surrey, UK. Email: benmorrison@doctors.org.uk.

Abstract: Perioperative consideration of the management of anticoagulation medications is an integral part of any successful enhanced recovery after surgery (ERAS) programme. Patients can present for surgery on one or more of a number of different classes of anticoagulant each of which must be considered on an individual basis to ensure these drugs are withheld, if appropriate, in sufficient time preoperatively and recommenced in a timely manner postoperatively. Many indications for anticoagulation exist and patient suitability for certain classes of drug can be assessed using risk scores such as the CHA_2DS_2-VASc score for atrial fibrillation patients. Preoperative risk assessment of a patient's risk of developing a thromboembolism forms a vital part of this management in order to balance the risks of thrombus formation against the risk of bleeding. Venous thromboembolism (VTE) can confer a considerable risk of morbidity and mortality for patients perioperatively but risk can be significantly reduced with appropriate assessment and management of a patient's risk. The classes of drug discussed in this article are the antiplatelet drugs—aspirin, clopidogrel and dipyridamole; heparins whether unfractionated or low-molecular weight heparin; the heparin alternatives without risk of heparin-induced thrombocytopaenia—fondaparinux and danaparoid; the coumarins, namely warfarin; and direct oral anticoagulants (DOACs). It is important for perioperative physicians to be aware of the method of action and pharmacological effects of these drugs and how these affect their management perioperatively.

Keywords: Enhanced recovery after surgery (ERAS); enhanced recovery; anticoagulation; pharmacology

Received: 01 August 2019; Accepted: 27 August 2019; Published: 24 September 2019.
doi: 10.21037/dmr.2019.08.10
View this article at: http://dx.doi.org/10.21037/dmr.2019.08.10

Introduction

The wide variation in indications, pathology, comorbidities and ongoing medical treatments with which patients present for surgery creates a myriad of challenges for the perioperative team, not least in regard to anticoagulation. Indications for anticoagulation are broad and alongside the traditional medications used to achieve this, a range of novel therapies are increasingly being employed. As such, clinicians must remain up to date with their knowledge of anticoagulant therapies and their perioperative management. Anticoagulation and further prevention of complications such as venous thromboembolism (VTE) constitutes a vital element of enhanced recovery after surgery (ERAS) via reducing perioperative thromboembolic complications—principally deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE prevention through the use of anticoagulants must be balanced against the risk of perioperative bleeding thus guidelines exist to help healthcare professionals best manage these medications.

Anticoagulant medications work by either inhibiting platelet aggregation or factors involved in the coagulation process and are some of the most commonly prescribed medications in the UK (1). They also have a high adverse

Table 1 Common indications for pharmacological anticoagulation

Congenital/acquired	Cardiac arrhythmias	Implanted devices
Previous VTE	Atrial fibrillation	Metallic heart valves
Previous CVA/TIA	Atrial flutter	Temporary devices, e.g., IABP
Previous MI		Coronary stents
Active malignancy		
Peripheral ischaemia		
Trauma		
Factor V Leiden		

VTE, venous thromboembolism; CVA, cerebrovascular accident; TIA, transient ischaemic attack; IABP, intra-arterial blood pressure; MI, myocardial infarct.

drug reaction rate both in hospital and in the community (1,2). The more traditional anticoagulants, namely enteral coumarins (warfarin) and parenteral heparin are increasingly making way for novel medicines falling under the category of direct oral anticoagulants (DOACs).

VTE is one of the more common perioperative complications, causing considerable morbidity and mortality (2). Undergoing major surgery is an independent risk factor for developing VTE, acting in synergy with a host of other risk factors (3). Virchow's Triad describes the three broad categories of factors that contribute to the formation of thrombosis — hypercoagulability, vascular wall injury and venous stasis. The perioperative period will, at various points, deliver all three of these.

This article will detail the common indications for anticoagulants and give current best practice guidance on how to manage their use as part of an ERAS programme. It should be remembered that non-pharmacological methods of VTE prophylaxis are vital to any ERAS programme. Early postoperative mobilisation should be encouraged by means of patient education, physiotherapy support and suitable analgesia. Patients should be assessed for suitability of graduated compression stockings or pneumatic compression devices.

Indications for anticoagulation

The indication for commencing anticoagulant therapy is to prevent pathological intravascular thrombus formation. The reasons for increased risk of thrombus can be broadly divided into four categories: idiopathic, congenital or acquired thrombophilias, cardiac arrhythmias and implanted prostheses. More common indications are shown below in *Table 1*.

Various scoring systems exist to help stratify the need for anticoagulation in certain patient populations. The CHA_2DS_2-VASc score, for example, is a guideline for suitability of anticoagulants in certain atrial fibrillation patient populations balancing the risks of VTE against bleeding (3). The National Institute for Clinical Excellence in the UK provide a risk assessment tool for all patients admitted to hospital in order to facilitate decisions regarding VTE prophylaxis (4). Since the original publication of the guideline and combined with incentives for completion the rate of inpatient VTE risk assessment climbed from fewer than 50% of patients to over 95% in five years. Analysis of data following this provided strong evidence suggesting the incidence and mortality of VTE had decreased significantly (5,6).

Pharmacological methods of anticoagulation

Antiplatelets

Antiplatelet agents (APA) include aspirin, clopidogrel and dipyridamole and can be used in the prevention of cardiovascular thrombotic events. Aspirin, a non-steroidal anti-inflammatory drug (NSAID) irreversibly inhibits the enzyme cyclo-oxygenase (COX) and the production of thromboxane. Clopidogrel is an adenosine diphosphate (ADP) receptor antagonist causing irreversible inhibition of platelet aggregation. Dipyridamole is an adenosine reuptake inhibitor also resulting in inhibition of platelet aggregation. As sole agents in VTE prophylaxis the role of APAs is controversial, as they may be less effective than low molecular weight heparin (LMWH) and may have little or

no benefit. Combining LMWH with an APA increases the bleeding risk and current European, UK, and US guidelines all recommend that the risk of bleeding must be balanced against the risk of thrombosis. If the risk of VTE outweighs the risk of bleeding, then pharmacological VTE prophylaxis may be used alternatively mechanical VTE prophylaxis should be considered (7-9).

Unfractionated heparin (UFH) and the low-molecular-weight heparins (LMWH)

UFH produces its anticoagulant effect through the inhibition of two essential proteases necessary for thrombus formation—factor Xa and thrombin. It achieves this via induction antithrombin III. Its most common use is for treatment rather than prevention of VTE as its pharmacokinetics mean it must be given intravenously as an infusion and monitored with serial activated partial thromboplastin times (aPTT). Its main perioperative use is for "bridging" anticoagulation in those patients already taking anticoagulants who are at high risk of VTE. UFH can be acutely reversed with protamine, a specific reversal agent.

The LMWH, such as enoxaparin, dalteparin, tinzaparin, are derivatives of UFH produced by fractionating polymeric heparin with the result being the creation of smaller functional molecules (average molecular weight of less than 8,000 Da). Similarly to UFH, these act via inhibition of factor Xa, but notably not thrombin. The ability to administer these agents subcutaneously without the requirement for therapeutic drug monitoring, has led to them becoming the commonest agents used for prevention of VTE and LMWH are integral to many thromboprophylaxis guidelines across the world (5,7,8,10). However, they have their limitations, perhaps most significantly that they can accumulate in patients with renal impairment and increase the risk of bleeding—a problem compounded by the fact that, unlike UFH, LMWHs are only partially reversed by protamine. Both LMWH and UFH can cause heparin-induced thrombocytopenia (HIT).

Heparin alternatives

Fondaparinux is a factor Xa inhibitor related to heparin. It can be administered subcutaneously and has predictable pharmacokinetics, but is not known to cause HIT. It currently has no specific reversal agent and its major risk is bleeding, particularly in patients with renal impairment.

Danaparoid is a low-molecular-weight heparinoid which inhibits both factor Xa and, to a lesser degree, thrombin and it chemically distinct from heparin. It has been used widely for VTE prophylaxis in specialities such as orthopaedic surgery and, again, is not known to cause HIT thus a suitable alternative to heparin. As with fondaparinux, there is no specific reversal agent and the bleeding risk is increased in those patients with hepatic or renal dysfunction.

Coumarins

This class of oral anticoagulants work by inhibiting the enzyme vitamin KO reductase leading to a reduction in the function of vitamin K dependent clotting factors II, VII, IX and X. The most notable drug in this class is warfarin. Owing to the many interactions with other drugs and some foods dosing of warfarin can be difficult as there can be large variation in its efficacy. As a result, regular blood monitoring of the international normalized ratio (INR) and appropriate dose adjustments are required to maintain therapeutic levels of the drug. Warfarin is effective for VTE prophylaxis and is used in some centres for extended thromboprophylaxis following orthopaedic surgery (11). Largely owing to the logistical problems with dosing and blood monitoring it does not feature in ERAS, UK, or European guidelines (7,10).

DOACs

Previously termed "novel oral anticoagulants" (NOACs), DOACs include a group of agents all licensed internationally for DVT prophylaxis following lower limb arthroplasty. Apixaban, rivaroxaban and edoxaban are all examples. The mechanism of action for these drugs is via direct inhibition of factor Xa. Dabigatran, also a DOAC, differs in that it's mechanism of action is thrombin. They are an appealing option for anticoagulation as they can be given orally, do not require therapeutic drug monitoring, and have predictable pharmacokinetics meaning dosing is relatively simple. However, dabigatran aside, there is currently no specific antidote and their anticoagulant action is terminated principally by renal clearance, thus limiting their usage in patients with renal impairment and also presenting a problem in the context of major postoperative bleeding. Dabigatran, though, may be reversed with the recently licensed specific monoclonal antibody idarucizumab.

Patients already taking anticoagulants

So called "bridging" therapy—the planned cessation of

regular treatment with possible conversion to a shorter-acting alternative—may be required for patients already taking anticoagulant medications perioperatively. Withholding warfarin therapy and converting to heparin perioperatively is the most common example of "bridging". The safest method of managing anticoagulant therapy perioperatively in patients who are already at high risk of VTE but who may also be at significant risk of bleeding (if anticoagulation is not sufficiently reversed/suspended appropriately) remains controversial. As patients receive anticoagulation for a variety of indications, and the risk of thrombosis if anticoagulation is suspended varies dependent on a variety of factors, bridging is not always required. In fact, there is growing evidence that major bleeding is significantly more prevalent in patients receiving bridging therapy. Conversely there is no decrease in thrombotic events for patients who would otherwise be considered low risk (12-15). After assessing and balancing all risk factors including the original indication for anticoagulation, a decision should be made on an individual basis as to whether bridging therapy is required. A haematology specialist opinion should be sought or local guidelines consulted where doubt remains.

For patients receiving anticoagulation following cardiac procedures such as drug-eluting coronary artery stent insertion separate guidance exists. Elective surgery should be postponed until after dual antiplatelet therapy (usually aspirin and a thienopyridine such as clopidogrel) is complete. This is currently six weeks with bare-metal stents and six months with drug-eluting stents. Where surgery cannot be avoided within this period it should be assumed dual antiplatelet therapy is to be continued throughout the perioperative period unless otherwise directed by a cardiologist. Those who are at a high risk for cardiac events but without coronary stents aspirin should be continued perioperatively but thienopyridines stopped 5 days preoperatively and recommenced 24 hours postoperatively assuming adequate haemostasis is achieved. Patients who are low risk for cardiac events should stop antiplatelet therapy 7–10 days preoperatively (12). Where any doubt remains cardiology opinion should be sought.

When to stop current anticoagulation therapy varies base on the prescribed medication. Warfarin should be stopped at least five days preoperatively and the INR checked before surgery in order to take any necessary steps to further correct the INR (usually ≤1.4) where required. With sufficient time preoperatively a persistently raised INR can be treat with low-dose oral vitamin K. If the INR remains persistently elevated, and surgery cannot be delayed, further reversal therapies include intravenous (IV) vitamin K, fresh frozen plasma, or prothrombin complex concentrate. Administration of these therapies may result in difficulty in restoring a therapeutic INR with warfarin postoperatively. Assuming successful surgery with no further anticipated procedures and satisfactory haemostasis patients at low risk of VTE can usually restart their warfarin the day after surgery. Warfarin can be recommenced 12–24 hours postoperatively and patients who have received bridging should continue their bridging therapy in addition to recommencing their warfarin as patients can become paradoxically hypercoagulable. The bridging therapy can be stopped once the INR is at a therapeutic level.

APA vary in their therapeutic half-life and thus require bespoke management. Most have the effect of irreversibly inhibiting platelet function antiplatelets need to be stopped 7–10 days preoperatively (12). Aspirin, having a relatively weak effect is often safe to continue throughout the perioperative period and decisions on its continuation should be made on a risk/benefit basis. Aspirin need not be withheld prior to regional or neuraxial blockade, as is also the case with antiplatelet drugs with reversible platelet inhibition, for example: dipyridamole (16).

Decisions regarding when to withhold heparins depends upon whether LMWH or UFH is being administered and their intended effect, be it prophylactic or therapeutic anticoagulation. UFH should be stopped around 4-6 hours preoperatively and the aPTT can be measured to monitor its reduction in effect preoperatively. Prophylactic and therapeutic subcutaneous LMWH should be stopped 12 and 24 hours respectively before surgery. If a nerve or neuraxial block is performed, or before removing an epidural catheter, further doses of UFH should not be given until at least one hour postoperatively for subcutaneous administration, or at least four hours for LMWH medications (16) with other guidelines suggesting even longer time periods (12).

DOAC timings also vary perioperatively depending upon which guidelines are followed. These times can also be affected by renal dysfunction (12,16). Dabigatran, rivaroxaban, apixaban and edoxaban should be stopped two to three days preoperatively unless the patient has renal dysfunction in which case three to four days for dabigatran. Bridging is rarely indicated unless the patient has a severely high thromboembolic risk and these medications can be restarted as soon as the surgical team are satisfied haemostasis has been achieved (17).

Orthopaedic surgery

VTE prophylaxis is a key aspect of any successful ERAS pathway for orthopaedics, especially in major surgery where VTE risk is particularly high (18). However, agreement over a universal approach in this speciality has remained elusive.

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) recommends prophylaxis for 28 days following hip arthroplasty and 14 days following knee arthroplasty (7). They suggest the responsible clinician choose between 1 of 3 options for hip arthroplasty:

- LMWH for 10 days followed by aspirin for a further 28 days;
- LMWH for 28 days combined with thromboembolism-deterrent (TED) stockings until discharge;
- rivaroxaban for 5 weeks.

In cases where none of the above are favourable options, then either apixaban or dabigatran could be considered. Similarly, for knee arthroplasty, they recommend one of the following:

- aspirin for 14 days postoperatively;
- LMWH for 14 days;
- rivaroxaban also for 14 days.

In the United States there are competing guidelines produced by two different colleges. The American College of Chest Physicians (ACCP) suggest that the responsible clinician choose one of the following pharmacological agents compared to no anticoagulation:

- LMWH;
- a DOAC (either a direct thrombin inhibitor or factor Xa inhibitor);
- low-dose UFH;
- warfarin;
- aspirin plus mechanical prophylaxis with an intermittent pneumatic compression device.

They do suggest the use of LMWH in preference to the other options and recommend a minimum of 10 to 14 days treatment, which can be extended to 35 days (8).

The American Academy of Orthopedic Surgeons (AAOS) recommend a combined approach using mechanical devices and pharmacological prophylaxis, but were unable to recommend one particular regimen (19).

Most current guidelines recommend pharmacological prophylaxis for all patients undergoing hip and knee arthroplasty. As many guidelines are based upon evidence produced prior to the widespread introduction of ERAS programmes it may soon become routine only to provide pharmacological prophylaxis to high-risk patient groups as patient are encouraged to mobilise earlier postoperatively. Data from Danish ERAS programs have found that only giving in-hospital pharmacological prophylaxis for these patients has not had the effect of leading to higher rates of VTE in the community, and so only high-risk groups are given ongoing pharmacological prophylaxis (20,21). Again in Denmark, with a comprehensive ERAS programme for colorectal surgery offering only VTE prophylaxis as an inpatient, they found a 0.2% rate of non-fatal symptomatic VTE at 60 days, thus further questioning the benefit of prolonged use of VTE prophylaxis beyond hospital discharge (22).

Summary

The increasing variety of available anticoagulant medications means clinicians must remain vigilant and up to date as to how best to manage their use perioperatively in order to ensure the risk of pathological thrombus formation is kept to a minimum whilst not interfering with surgical haemostasis.

A risk assessment should be undertaken for each patient and those at higher risk should have interruption of their usual anticoagulation minimised. In certain cases, such as recent CVA or MI, delaying surgery should be strongly considered. Risk assessment should include bleeding risk as well as thromboembolic risk and where bleeding risk is low anticoagulant medications may be continued in certain cases. Consideration must be made of anaesthetic procedures with bleeding risk, such as neuraxial blockade, when deciding if, and when, to pause anticoagulant medications.

More guidelines pertaining to specific patient groups and surgical specialities are likely to emerge in the near future which will help steer surgical teams towards the best, evidence-based practice.

Patients must be educated as to when they must stop taking anticoagulant medication preoperatively and whether or not they are required to commence an alternative—which may itself require further patient education, such as in the case of heparin self-injection.

Surgical teams must recommence anticoagulant medication as soon as possible postoperatively in order to best restore patients to their usual drug regimen. Appropriate and well-planned management of anticoagulant medications will help reduce the incidence of potentially severely debilitating complications and death and improve

their overall surgical journey.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Digestive Medicine Research* for the series "Enhanced Recovery After Surgery (ERAS) Program in General Surgery". The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr.2019.08.10). The series "Enhanced Recovery After Surgery (ERAS) Program in General Surgery" was commissioned by the editorial office without any funding or sponsorship. CJ served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004;329:15-9.
2. Davies EC, Green CF, Taylor S, et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One 2009;4:e4439.
3. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962.
4. Recommendations | Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism | Guidance | NICE. Cited 2019 Jul 12. Available online: https://www.nice.org.uk/guidance/ng89/chapter/Recommendations#risk-assessment
5. Rowswell HR, Nokes TJC. Significant reduction in hospital-acquired thrombosis: impact of national risk assessment and real-time feedback. Open Heart 2017;4:e000653.
6. Roberts LN, Porter G, Barker RD, et al. Comprehensive VTE prevention program incorporating mandatory risk assessment reduces the incidence of hospital-associated thrombosis. Chest 2013;144:1276-81.
7. Overview | Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism | Guidance | NICE. Cited 2019 Jul 16. Available online: https://www.nice.org.uk/guidance/ng89
8. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. Chest 2012;141:e278S-e325S.
9. Karthikeyan G, Eikelboom JW, Turpie AG, et al. Does acetyl salicylic acid (ASA) have a role in the prevention of venous thromboembolism? Br J Haematol 2009;146:142-9.
10. Venclauskas L, Llau JV, Jenny JY, et al. European guidelines on perioperative venous thromboembolism prophylaxis: Day surgery and fast-track surgery. Eur J Anaesthesiol 2018;35:134-8.
11. Dager WE. Warfarin for venous thromboembolism prophylaxis after elective hip or knee arthroplasty: exploring the evidence, guidelines, and challenges remaining. Ann Pharmacother 2012;46:79-88.
12. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e326S-50S.
13. Oprea AD, Noto CJ, Halaszynski TM. Risk stratification, perioperative and periprocedural management of the patient receiving anticoagulant therapy. J Clin Anesth 2016; 34:586-99.

14. Mar PL, Familtsev D, Ezekowitz MD, et al. Periprocedural management of anticoagulation in patients taking novel oral anticoagulants: Review of the literature and recommendations for specific populations and procedures. Int J Cardiol 2016;202:578-85.
15. Ayoub K, Nairooz R, Almomani A, et al. Perioperative heparin bridging in atrial fibrillation patients requiring temporary interruption of anticoagulation: evidence from meta-analysis. J Stroke Cerebrovasc Dis 2016;25:2215-21.
16. Working Party, Association of Anaesthetists of Great Britain & Ireland, Obstetric Anaesthetists' Association et al. Regional anaesthesia and patients with abnormalities of coagulation: the Association of Anaesthetists of Great Britain & Ireland The Obstetric Anaesthetists' Association Regional Anaesthesia UK. Anaesthesia 2013;68:966-72.
17. Perioperative management of patients receiving anticoagulants - UpToDate. Cited 2019 Jul 18. Available online: https://www.uptodate.com/contents/perioperative-management-of-patients-receiving-anticoagulants?search=anticoagulation-&source=search_result&selectedTitle=4~150&usage_type=default&display_rank=4
18. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. Chest 2001;119:132S-75S.
19. Mont MA, Jacobs JJ, Boggio LN et al. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. J Bone Joint Surg Am 2012;94:673-4.
20. Jørgensen CC, Jacobsen MK, Soeballe K, et al. Thromboprophylaxis only during hospitalisation in fast-track hip and knee arthroplasty, a prospective cohort study. BMJ Open 2013;3:e003965.
21. Jørgensen CC, Kehlet H, Lundbeck Foundation Centre for Fast-track Hip and Knee replacement collaborative group. Early thromboembolic events ≤1week after fast-track total hip and knee arthroplasty. Thromb Res 2016; 138:37-42.
22. Vendler MMI, Haidari TA, Waage JE, et al. Incidence of venous thromboembolic events in enhanced recovery after surgery for colon cancer: a retrospective, population-based cohort study. Colorectal Dis 2017;19:O393-O401.

doi: 10.21037/dmr.2019.08.10
Cite this article as: Morrison B, Kelliher L, Jones C. Anticoagulation drugs in the perioperative period. Dig Med Res 2019;2:26.

