NOVEL ANTI-PLATELET AGENTS AND ANTICOAGULANTS

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Dr. Frances Smith FRCA, SpR, Peninsula Deanery
Dr. Richard Telford FRCA, Consultant, Royal Devon and Exeter Hospital, UK
Correspondence: fsmith12@nhs.net

QUESTIONS

Before continuing, try to answer the following true or false questions. The answers can be found at the end of the article, together with an explanation.

1) In patients with renal dysfunction
   a) The dose of apixaban does not need to be altered
   b) The dose of dabigtran must be reduced
   c) The half life of rivaroxaban is not significantly prolonged provided creatinine clearance exceeds 50ml/min
   d) Fondaparinux does not accumulate
   e) Surgery may be scheduled 24 hours after the last dose of rivaroxaban and apixaban

2) Regarding anti platelet drugs:
   a) Prasugrel and ticagrelor are both pro-drugs requiring metabolism to the active component
   b) Aspirin exhibits less variability of response than clopidogrel
   c) Ticagrelor irreversibly inhibits the platelet adenosine P2Y12 receptor
   d) Dual anti platelet therapy is always stopped prior to elective surgery and bridging treatment instituted if necessary
   e) The effects of prasugrel may be reversed with a platelet transfusion

3) Regarding anticoagulants:
   a) Rivaroxaban and apixaban are both reversible thrombin inhibitors.
   b) P-gp inhibitors such as amiodarone can lower the bioavailability of dabigatran
   c) Apixaban has a plasma half-life of 12 hours and is given twice daily
   d) Fondaparinux may be administered iv and orally
   e) Dabigatran activity may be quantified by measuring the prothrombin time

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INTRODUCTION

This tutorial is written to compliment ATOTW 143 "Anticoagulation, an Overview"; the reader is directed to this text initially[1].
Patients are prescribed drugs which influence coagulation in order to prevent the thromboembolic complications of inherited or acquired disease. The limitations of antiplatelet agents (inter-individual variability in response), warfarin (variable response and requirement for monitoring) and heparin (heparin induced thrombocytopenia, necessity for parenteral administration) have driven the development of newer anticoagulants. The National Institute for Health and Care Excellence (NICE) in the UK have approved a number of new anticoagulants in recent years. The purpose of this tutorial is to describe the pharmacology of these new agents and their implications for anaesthesia and surgery. The following will be discussed:

- Anti-platelet agents: Prasugrel and Ticagrelor
- Anticoagulants: Direct thrombin inhibitor-Dabigatran
  Factor Xa inhibitors-Rivaroxaban, Apixaban and Fondaparinux

ANTI-PLATELET AGENTS

Patients are prescribed antiplatelet agents to reduce the thromboembolic complications of arterial disease. Patients with proven arterial disease receive monotherapy as secondary prevention against thromboembolic complications. Dual antiplatelet therapy (DAPT) is indicated following acute coronary syndrome (ACS), and after coronary stent insertion to minimise the risk of in-stent thrombosis. Until recently the two drugs in common usage were aspirin and clopidogrel. Aspirin irreversibly inhibits platelet cyclooxygenase preventing the production of thromboxane A_2 (TXA_2), inhibiting platelet aggregation. Clopidogrel irreversibly inhibits platelet aggregation by specifically inhibiting the binding of ADP to the purinergic $P2Y_{12}$ receptor on the platelet surface. Since these drugs have differing mechanisms of action their effects on platelet aggregation are synergistic. Clopidogrel requires a two-step hepatic transformation to exhibit its effect. It is metabolized by a cytochrome P450-dependent pathway to form an intermediate metabolite (2-oxo-clopidogrel) that is hydrolysed to generate the active metabolite.

Variability of response refers to the observation that a drug administered in a specific dose does not lead to a uniform therapeutic response in all individuals. Both aspirin and clopidogrel exhibit variability of response. As many as 43% of patients taking aspirin do not fully respond to therapy as measured by ex-vivo parameters such as prolongation of bleeding time, platelet function tests and platelet aggregometry. Similar variability of response is seen with clopidogrel with as many as 30% of patients not responding fully when measured by the same tests. Multiple mechanisms are likely to contribute to this, including inappropriate dosing or under dosing, patient non-compliance with medication, drug - drug interactions and genetic polymorphisms.

The occurrence of in-stent thrombosis may in part be due to the variability of response and has led to the development of anti-platelet drugs which are more efficacious than clopidogrel. Two new antiplatelet agents have recently been approved by NICE for use as part of dual anti-platelet therapy with aspirin (Table 1).

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Table 1. Summary of NICE Recommendations for Prasugrel ,Ticagrelor and Clopidogrel are indicated below as part of dual therapy with Aspirin.

Drug	Indication	Dose	Duration of therapy
Prasugrel	Percutaneous Coronary Intervention – Bare Metal Stent	60mg load, then 10mg od 5mg od if >75y or < 60kg	4-6 weeks
	Percutaneous Coronary Intervention – Drug Eluting Stent	As above	12 months
Ticagrelor	Acute Coronary Syndrome requiring immediate Percutaneous Coronary Intervention	180mg load, then 90mg bd	Up to 12 months
Clopidogrel	ACS with or without PCI	300-600mg load, then 75mg od	Initially 4 weeks, Up to 12 months

Prasugrel (Efient, Lilly UK)

Prasugrel like clopidogrel, is an orally administered irreversible platelet adenosine $P2Y_{12}$ receptor antagonist. It is a prodrug and requires metabolism by a cytochrome P450-dependent pathway to its active component in the liver. Unlike clopidogrel this is a single step pathway which accounts for its quicker onset of action. Compared to clopidogrel, prasugrel exhibits a greater anti-platelet effect (90% inhibition of aggregation in vitro compared to 50%) and much less inter-individual variation in response. Recovery of platelet function takes longer for prasugrel; it takes 7 days for 75% of patients to return to baseline reactivity compared to 5 days with clopidogrel, potentially as a result of the higher degree of platelet inhibition that occurs during treatment. [2, 3] Surgical bleeding is likely to be more troublesome as a consequence.

Prasugrel in combination with aspirin is indicated:

- When immediate percutaneous coronary intervention (PCI) is necessary to treat an ST-segment-elevation myocardial infarction
- When immediate PCI is necessary to treat a non-ST-segment-elevation myocardial infarction in patients with diabetes
- When stent occlusion occurs whilst the patient is taking clopidogrel

NICE recommendations are based on the TRITON-TIMI 38 trial (Trial to assess Improvement in Therapeutic Outcomes by Optimising Platelet inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38). In this double blind, randomized controlled trial, 13,608 moderate to high risk patients with Acute Coronary Syndromes (ST-elevation myocardial infarction (STEMI), Non ST elevation Myocardial Infarction (N-STEMI) or unstable angina) scheduled for percutaneous coronary intervention (PCI) were randomized to receive either prasugrel + aspirin or clopidogrel + aspirin. The dosages used were either a 300 mg loading dose of clopidogrel followed by 75mg daily maintenance, or a 60mg loading dose of prasugrel then 10mg daily as maintenance. It is worth noting that the loading dose of clopidogrel used in this study was less than is often used in UK practice. Primary outcome measures were: death from cardiovascular causes, non-fatal MI and non-fatal stroke, with a safety end

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point of major bleeding. The rate of primary outcomes was lower at 15 months for prasugrel (9.9% compared to 12.2% for clopidogrel, p<0.001), and the rate of in-stent thrombosis was lower with prasugrel (1.1% vs. 2.4% clopidogrel, p<0.001). However higher rates of bleeding were observed, (2.4% prasugrel vs. 1.8% for clopidogrel, p=0.03), particularly in patients with previous CVA, those aged over 75years, and those weighing less than 60kg, therefore a lower maintenance dose of 5mg is advised for these patients.[4]

Ticagrelor (Brilique, Astra Zeneca)

Ticagrelor is an orally administered ADP analogue which changes the conformation of the platelet adenosine $P2Y_{12}$ receptor inhibiting the binding of ADP without the need for metabolic activation. Unlike clopidogrel and prasugrel, this inhibition is reversible. The drug has a rapid offset of action with a half- life of 12 hours, mandating a twice daily dosing regimen (90 mg bd). It too exhibits a greater level of platelet inhibition than clopidogrel (50-60% in vitro). The ONSET/OFFSET study examined 123 patients with stable coronary artery disease on aspirin therapy. It compared the addition of either clopidogrel (600mg load followed by 75mg/day) or ticagrelor (180mg load followed by 90mg bd) or placebo. 2 hours after a loading dose, 90% of patients receiving ticagrelor achieved >70% platelet inhibition, compared to just 16% of patients receiving clopidogrel; greater platelet inhibition was also seen at 6 weeks with ticagrelor.[5]

Ticagrelor is recommended by NICE as a treatment option in conjunction with low dose aspirin for up to 12 months in adults with acute coronary syndrome i.e. STEMI, NSTEMI or unstable angina that cardiologists intend to treat with immediate PCI.

These recommendations are based on the PLATO trial (Platelet Inhibition and Patient Outcomes) which compared ticagrelor + aspirin to clopidogrel + aspirin in over 18,000 patients with ACS (with or without ST elevation). It demonstrated a lower mortality at twelve months from MI, stroke and cardiovascular causes (9.8% ticagrelor vs. 11.7% clopidogrel, p<0.001) and mortality from any other cause was lower for ticagrelor (4.5% vs. 5.9%, p<0.001). There was a similar risk of major bleeding in both groups (~11%, p=0.43), however the rate of intracranial bleeding was higher in the ticagrelor group, both for fatal intracranial haemorrhage (0.1% ticagrelor vs. 0.01% clopidogrel p=0.02), and non-fatal intracranial haemorrhage (0.3% ticagrelor vs. 0.2% clopidogrel, p=0.06).[6]

There is a mortality benefit when comparing ticagrelor with clopidogrel, but is possible that patients requiring acute surgery who have recently taken ticagrelor may experience troublesome bleeding and require platelet transfusion.

ANTICOAGULANTS

There are approximately 500,000 individuals taking anticoagulants in the UK as prophylaxis against or treatment of:

- The thromboembolic complications associated with atrial fibrillation (AF)
- Venous thrombosis and pulmonary embolism
- The thromboembolic complications associated with heart valve replacement

The majority of these patients will be taking warfarin. In some patients adequate anticoagulation with warfarin may be difficult. There are a number of reasons for this, such as interactions with drugs and food, slow onset and offset, narrow therapeutic range and the requirement for frequent monitoring and dose adjustment. As a consequence a number of new anticoagulants have been introduced and approved for use. These include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban and fondaparinux.

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Table 2. Summary of NICE Recommendations for the use of novel anticoagulants in venous thromboembolism (VTE) prophylaxis, stroke prevention and NSTEMI/Unstable angina.

Drug	Indication	Dose	Duration of therapy
Dabigatran etexilate	Primary VTE prophylaxis post hip and knee replacement surgery	110mg 1-4 hours post-op, then 220mg od. Or 75mg 1-4 hours post-op, then 150mg od if >75years or taking amiodarone or verapamil	10 days post elective TKR 35 days post elective THR
	Prevention of stroke and systemic embolisation in non-valvular AF (see text)	150mg bd Or 110mg bd if >75 years	
Rivaroxaban	VTE prophylaxis post hip and knee surgery	10mg od 6-10 hours post-op then 10mg daily	14 days post elective TKR 35 days post elective THR
	Prevention of stroke and systemic embolisation in non-valvular AF with 1 or more $CHADS_2$ risk factors	20mg od	
	Treatment of DVT and prevention of recurrent DVT	15mg bd 21days, then 20mg od	Individual dependent: 3 months for transient DVT risk factors, longer term for permanent risk factors
	Treatment of PE and prevention of recurrent PE	15mg od if CrCl 30-50 mls/min	
Apixaban	VTE prophylaxis post hip and knee replacement surgery	2.5mg bd 12-24 hours post-op	10-14 days post TKR 32-38 days post THR
	Prevention of stroke and systemic embolisation in non-valvular AF with 1 or more $CHADS_2$ risk factors	5mg bd 2.5mg bd if >80years or <60kg	
Fondaparinux	NSTEMI and unstable angina in patients without a high risk of bleeding, unless PCI planned within 24h	2.5mg od	Up to 8 days or until discharge
	VTE prophylaxis post-elective lower limb orthopaedic surgery	2.5mg 6 hours post-op, then 2.5mg od	At least 30 days (max 45)
	VTE prophylaxis medical patients	2.5mg od	
	Treatment of DVT/PE	5mg if <50kg 7.5mg if 50-100kg 10mg >100kg	

Abbreviations: DVT = Deep Vein Thrombosis, PE = Pulmonary Embolism, AF= Atrial Fibrillation, THR = Total Hip Replacement, TKR = Total Knee Replacement, $CHADS_2$ = Congestive Heart Failure, Hypertension, Age>75 years, Diabetes Mellitus, Previous Stroke or Transient Ischaemic Attack

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Advantages of novel anticoagulants	Disadvantages of novel anticoagulants
• Rapid onset of activity • Short half-lives • Similar or improved efficacy • Fewer drug interactions • Fixed dose guidelines • No requirement for monitoring	• No antidote • No widely available measure of activity • Limited knowledge and experience • Drug interactions • Effect of renal impairment on pharmacokinetics

Dabigatran Etexilate (Pradax, Boehringer Ingelheim)

Dabigatran etexilate is an orally administered pro-drug of dabigatran, a reversible thrombin inhibitor. It has received NICE approval for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation with one or more of the following risk factors:

- Previous stroke, transient ischaemic attack or systemic embolism
- Left ventricular ejection fraction below 40%
- Symptomatic heart failure (NYHA Class 2 or more)
- Age 75 or older
- Age 65 or older with one of the following: diabetes mellitus, coronary artery disease or hypertension

It also has NICE approval for primary prevention of VTE in adults who have undergone elective total hip or knee replacement.

Dabigatran is renally excreted with a half- life of 14 – 17 hours. The recommended daily dose is one 150 mg capsule twice daily. People aged 75 years or above should be treated with one 110 mg capsule twice daily due to the increased prevalence of renal impairment in this population. Dabigatran etexilate is a substrate for the transporter P-glycoprotein (P-gp); dabigatran itself is not. P-gp is an extensively distributed trans-membrane glycoprotein responsible for the efflux of many substrates. It is expressed in the intestine, liver, kidney and capillary endothelium. Drugs that inhibit P-gp lead to a higher bioavailability of dabigatran; as a result a lower dose of dabigatran is recommended in those patients taking P-gp inhibitors (e.g. verapamil or amiodarone). Staggering the administration of these drugs will limit this effect.[7]

The RE-LY trial (Randomised Evaluation of Long-term Anticoagulation Therapy) compared two doses of dabigatran (110mg bd and 150mg bd) with warfarin for non-inferiority in prevention of stroke or systemic embolus in patients with AF. Compared with patients warfarinised to a target INR of 2-3, both doses of dabigatran significantly decreased the annual rate of stroke or systemic embolus (1.11% with 150mg, 1.53% with 110mg and 1.69% with warfarin, $p<0.001$). There was a lower annual risk of haemorrhagic stroke with dabigatran (0.1% with 150mg, 0.12% with 110mg, 0.38% with warfarin, $p<0.001$). The rates of major bleeding, life-threatening bleeding, intracranial bleeding and minor bleeding were all significantly higher for warfarin than both doses of dabigatran. However, there was a higher incidence of gastrointestinal bleeding with the 150mg dose of dabigatran (1.51% vs. 1.02% for warfarin, $p<0.001$). The rate of discontinuation of drug was also higher for dabigatran (21% vs. 17% warfarin), predominantly due to its dyspeptic side effects.[8]

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Rivaroxaban (Xarelto, Bayer)

Rivaroxaban is a direct free and bound Factor Xa inhibitor, preventing the formation of thrombin from prothrombin. It is approved for stroke prevention in AF and for VTE prophylaxis following orthopaedic surgery. It is administered orally and commenced at a dose of 10mg once daily 6-10 hours post-operatively and continued for two weeks post knee replacement and five weeks post hip replacement. When used for prevention of stroke and systemic embolus in patients with AF, 20mg rivaroxaban once daily is advocated when creatinine clearance (CrCl) exceeds 50 mls/min.

Rivaroxaban has predictable pharmacokinetics and exhibits a high bioavailability of 80% with peak plasma levels at 2-3hours. Its half-life of 7-9hours is not significantly prolonged in moderate renal impairment, but warrants dose reduction to 15mg and close monitoring if GFR is 30-50 mls/min.[9] No clinical data is available in patients with CrCl less than 30 mls/min or patients on dialysis. It is highly protein bound to albumin and approximately 70% undergoes hepatic elimination, mainly via cytochrome p450, of which half is renally excreted. The remaining 30% is excreted unchanged in the urine. The plasma half-life can be prolonged to up to 13 hours in the elderly. Due to its hepatic elimination it should not be used in patients with moderate or severe hepatic impairment. It should also be avoided in patients who are taking concomitant P-gp or CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) or inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's Wort). Cytochrome P450 3A4 is a mixed function oxidase with a large number of substrates and is involved in the metabolism and/or bioactivation of many common medications.

The ROCKET-AF trial (Rivaroxaban-once daily, Oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in AF) was a non-inferiority trial that compared rivaroxaban 20mg once daily with warfarin for stroke prevention in 14,264 patients with AF. As with the RE-LY trial, the primary end points were stroke and systemic embolisation, the rates of which were lower in the rivaroxaban group (2.1% per year vs. 2.4% for warfarin, $p<0.001$). Whilst the overall rates of bleeding were similar for both drugs, (14.9% per year with rivaroxaban vs. 14.5% with warfarin, $p=0.44$), the rates of intracranial haemorrhage (ICH) and fatal bleeding were both lower in the rivaroxaban group. (ICH 0.5% vs. 0.7%, $p=0.02$, fatal bleeding 0.2% vs. 0.5%, $p=0.003$).[9]

Apixaban (Eliquis, Bristol-Meyers Squibb)

Apixaban has an identical mechanism of action to rivaroxaban and has similar indications, namely stroke prevention in AF and VTE prophylaxis post major lower limb joint replacement surgery.

It is administered orally in a dose of 5mg twice daily with a lower dose of 2.5mg bd recommended in patients aged 80 years and above, those weighing less than 60kg, and those with a serum creatinine > 133 micromol/L. It has high oral bioavailability of 85% and a short time to peak effect of 3 hours. Plasma half-life is approximately 12 hours hence a twice daily dosing regime is required, 50% is excreted into faeces and 25% is renally excreted with the parent drug responsible for half of the recovered dose.[10] Apixaban is also a substrate for both P-gp and CYP3A4.

The ARISTOTLE trial (Apixaban for Reduction In Stroke and other Thromboembolic events in AF) was a non-inferiority trial comparing apixaban 5mg bd with warfarin (target INR 2-3) for prevention of stroke and systemic embolisation in AF in 18,206 patients followed up for 12 months. Apixaban was associated with a significantly lower rate of stroke and systemic embolism than warfarin (1.27% vs. 1.60%, $P<0.001$), including haemorrhagic stroke (0.24% vs., 0.47%, $p<0.001$) with a lower risk of major bleeding (2.13% vs. 3.09%, $p<0.001$). There was also a non-significant reduction in MI, DVT and PE plus fewer all cause deaths overall.[11]

Meta-analysis of data comparing apixaban with rivaroxaban and dabigatran showed a similar incidence of stroke, systemic embolisation and all-cause mortality. There was a lower incidence of MI in the apixaban group when compared to dabigatran and a lower incidence of bleeding and discontinuation when apixaban was compared to both dabigatran and rivaroxaban. Currently this meta-analysis is not considered by NICE to be robust enough to differentiate between these three agents.

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Fondaparinux (Arixtra, GlaxoSmithKline)

Fondaparinux is a synthetic pentasaccharide that inhibits factor Xa selectively by inducing an irreversible conformational change in antithrombin. It is licensed for the prevention of thromboembolic events after major lower limb orthopaedic surgery, for the treatment of DVT and PE, and also for use in Acute Coronary Syndrome (ACS) as an alternative to Low Molecular Weight Heparin or Unfractionated Heparin where immediate PCI is not offered. It is administered subcutaneously but can also be given intravenously, with a rapid onset to peak effect within 2 hours. It has a plasma half-life of 17 hours permitting single daily dosing. When used for DVT prophylaxis post-orthopaedic surgery, fondaparinux is given initially 6 hours post-op at a dose of 2.5mg once daily. Higher doses, adjusted for body weight, are required for the treatment of DVT and PE: 5mg od for patients less than 50kg, up to 10mg od for those exceeding 100kg.

It is largely excreted unchanged in the urine and accumulates in renal failure, consequently a dose reduction to 1.5mg is advocated for an Estimated Glomerular Filtration Rate (eGFR) of 20-50 mls/min, and its use is not recommended when eGFR is less than 20 mls/min.[12] It is structurally similar to heparin and, as with heparin, may be associated with idiosyncratic elevations in ALT and AST. This is usually self-limiting and does not require dose adjustment or cessation.

Fondaparinux 2.5 mg has been compared with enoxaparin 40mg od for prevention of VTE post surgery for hip fracture. The study showed a relative risk reduction of 56.4%, with no increase in bleeding complications.[13]

Table 3. Summary of the pharmacokinetics of novel anticoagulants. Note, all are orally administered with the exception of Fondaparinux which is given sub-cutaneously (but also can be given intravenously).

Drug (Substrate of action)	Dose (mg)	T_{max} (h)	Protein binding	Renal clearance	Elimination half-life (CrCl>80)	Dialysable ?
Dabigatran (IIa)	110/150 mg bd	1-3	35%	80%	13.8 hours	Yes
Rivaroxaban (Xa)	20mg od	1-3	92-95%	33%	8.3 hours	No
Apixaban (Xa)	2.5/5mg bd	1-3	84%	25%	15.1 hours	No
Fondaparinux (Xa)	1.5-10mg od	2	94%	64-77%	17 hours	No

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MANAGEMENT OF PATIENTS PRESENTING FOR ELECTIVE SURGERY

Approximately 10% of patients taking antithrombotic agents are likely to undergo surgery or an invasive procedure each year, yet little evidence exists to guide management of these new medications around the time of surgery. Large inter-individual variability exists in drug handling, and residual agent concentrations following treatment cessation are unpredictable. Therefore a risk assessment balancing the risk of thromboembolic events if antithrombotic agents are withheld, against the likelihood, and consequence, of bleeding needs to take place for individual patients.
If a patient is at increased risk of thrombotic complications, and is undergoing an operation associated with a low risk of bleeding or minor bleeding, then antithrombotic therapy can potentially be continued. Similarly if a patient is at low risk of thrombosis undergoing a procedure usually associated with high blood loss, then treatment can potentially be suspended. The problem arises when patients with an increased risk of thrombosis present for surgery with a moderate-high risk of bleeding.

Dual Antiplatelet Therapy (DAPT)

DAPT is generally prescribed for patients post ACS, with or without coronary stents. Approximately 100,000 patients per annum undergo PCI in the UK. The majority of these procedures involve the placement of coronary stents, the vast majority of which are drug-eluting. PCI causes trauma to the vessel wall, rendering the endoluminal surface thrombogenic until the vessel has healed or the stent re-endothelialised. Stent thrombosis causing myocardial infarction has a high mortality exceeding 50%. Elective surgery should be delayed and dual anti-platelet therapy continued where possible in these patients for the recommended period of DAPT: 12 months for drug eluting stents (DES), 4-6 weeks for bare metal stents (BMS), and 12 months after ACS irrespective of type of stent.[14,15,16] The risk of in-stent thrombosis is highest for BMS in the first 6 weeks after insertion and for DES within the first 6 months.

Five per cent of patients undergoing PCI will require non-cardiac surgery in the proceeding twelve months; dealing with this poses challenges. Withdrawal of DAPT is associated with stent thrombosis (myocardial infarction, cardiac death) whilst peri-operative continuation increases the risk of surgical bleeding. If surgery cannot be postponed for this period of time *and* is associated with a low risk of bleeding, there is potential for DAPT to be continued throughout the peri-operative period. It has been suggested that a 'low-risk procedure' is one associated with a rate of bleeding of 1.5% or less, and does not involve 'special' areas i.e. intracranial, intraspinal, intraocular, pericardial and neuraxial locations where bleeding may have devastating consequences.[16] However a consensus does not exist for grading of bleeding severity. If surgery must proceed, aspirin should be continued. The platelet $P2Y_{12}$ agent should be stopped for as brief a period as possible. Bridging the patient with a short-acting platelet glycoprotein IIb/IIIa inhibitor (GPIIb/IIIa), (i.e. tirofiban or eptifibatide), has been recommended.[17] Surgery should take place in a centre that offers 24 hour interventional cardiology as angioplasty of a thrombosed stent may limit the extent of myocardial damage.

Management of Bleeding

The newer antiplatelet agents exhibit short plasma half-lives but are associated with prolonged biological effect.[18] No reversal agents exist therefore the mainstay of treatment is cessation of anti-platelet medication and general supportive measures. In extreme cases platelet transfusion may be advocated, and these have been shown to be effective in vitro although higher quantities than those used to reverse aspirin may be required, and there is a potentially increased risk of thrombosis. Platelets should be available when patients taking DAPT present for surgery in case bleeding becomes problematic. Once bleeding is controlled, consideration should be given to restarting DAPT as soon as possible.

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Anticoagulants

The same principles of balancing thrombotic and bleeding risk apply peri-operatively to the novel anticoagulants. The safety of novel anticoagulants is suggested in part to be due of their rapid offset, but unlike warfarin no antidote currently exists. The $CHADS_2$ and CHA_2DS_2-VASc scores were introduced to assess the risk of thrombosis in patients with atrial fibrillation. They can be used as part of the decision making process regarding the necessity for bridging prior to elective surgery. For major surgery with a high risk of bleeding, patients can be managed in a similar manner to those taking warfarin: assess the likelihood of thrombosis using $CHADS_2$ (score of 2 or above) or CHA_2DS_2VASc (score of 5 or above) and bridge with therapeutic low molecular weight heparin (LMWH). Stop the anticoagulant 5 days prior to surgery, commence treatment dose LMWH three days prior to surgery and convert this to a prophylactic dose LMWH the evening before surgery.

For minor surgery with a low bleeding risk in a patient with normal renal function, stop the anticoagulant 2 days prior to surgery and administer prophylactic LMWH the evening before surgery. If the patient has impaired renal function (eGFR < 80 mls/min) treat as for major surgery.

Provided haemostasis is achieved and there is no ileus, the oral anticoagulants may be restarted at a half dose 4-6 hours post-operatively.[19]

Table 4. The CHA_2DS_2VASc Score

C	CHF / LV dysfunction	1
H	Hypertension	1
A	Age > 75	2
D	Diabetes mellitus	1
S	Stroke / TIA / Embolism	2
V	Vascular disease	1
A	Age 65-74	1
Sc	Sex-Female	1

A patient with a score of 5 or greater, (maximum 9), stroke or TIA within three months, cancer or a prosthetic valve is felt to be at high risk of stroke, approximately 12-18 per 100 patients per year. When $CHADS_2$ alone is used, a score greater than 2 is associated with increased risk of stroke.

MANAGEMENT OF PATIENTS PRESENTING FOR EMERGENCY SURGERY

Good communication between surgical and anaesthetic teams is vital to coordinate optimal timing of surgical intervention. Ideally emergency surgery should be started at least 1-2 elimination half-lives after the last dose of anticoagulant if possible. Our local hospital guideline suggests starting surgery >12 hours after dabigatran, and >24 hours for rivaroxaban and apixaban. Conventional coagulation tests give limited information and cannot be used quantitatively to establish anticoagulant effect.[22] If the APPT is not elevated the effect of dabigatran is likely to be low. The same applies to rivaroxaban if the PT is normal but a degree of anticoagulation cannot be excluded.[23]

Timing of neuraxial block

The European Society of Anaesthesiologists (ESA) recommends that 2 elimination half-lives need to elapse between administration of the last dose of drug and performance of the neuraxial block.[20]

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Table 5. Timing of Central Neuraxial Block in patients taking novel anticoagulants

Therapy	Time from dose to insertion / removal	Time from insertion / removal to next dose
Dabigatran	2 days if Creatinine Clearance (CrCl) > 50 mls/min, 5 days if CrCl < 50 mls/min[21]	The first dose of dabigatran may be given two hours following the removal of an epidural catheter, but concomitant use is contraindicated
Rivaroxaban	22-26 hours	6 hours (24 hours if traumatic puncture)
Apixaban	26-30 hours	4-6 hour
Fondaparinux	36-42 hours	6-12 hours

Management of Bleeding

Treatment is largely supportive and centres around cessation of drug therapy as these drugs have relatively short half-lives. If bleeding becomes troublesome, local advice is to consider tranexamic acid (TXA), prothrombin complex concentrate (PCC) and recombinant activated factor VII (rFVIIa), but there is little supporting evidence for this. PCC and rVIIa are pro-coagulant and may lead to an increased risk of arterial thrombosis, particularly in arteriopathic patients.

Table 6. Summary of management of bleeding [24, 25]

Multidisciplinary approach
Withhold drug-maybe sufficient for mild bleeding
General haemostatic and resuscitation measures: large bore iv access, bloods and clotting assays, mechanical pressure, fluid and / or blood administration
Mild: as above plus TXA 15-25mg/kg orally
Moderate - severe: as general plus FFP 20 ml/kg + platelet transfusion (if < 70 x10^9/L), TXA 15mg/kg iv, consider PCC, e.g. Octaplex® 30iu/kg[(a)]
Life-threatening: as above plus PCC; consider charcoal (if within 2 hours of drug administration) / CVVHF for dabigatran [26]

(a) Octaplex ® is a second generation human prothrombin complex concentrate.
Abbreviations: TXA: tranexamic acid. FFP: fresh frozen plasma, PCC: prothrombin complex concentrate, CVVHF: Continuous veno-veno haemofiltration

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ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. FTTFT. A: 5mg bd reduced to 2.5mg bd if Cr> 133; C: half life is 7-9 hours

2. FFFFT. A: ticagrelor is not a prodrug; B: 43% of patients receiving aspirin do not respond as predicted compared with 30% for clopidogrel; C: ticagrelor exhibits reversible inhibition

3. FFTFF. A: rivaroxaban and apixaban are Xa inhibitors; B: bioavailability will be higher; D: fondaparinux is administered subcutaneously or iv; E: conventional clotting studies cannot reliably quantify dabigatran but a normal APTTR value implies plasma concentration of dabigatran is low

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