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REGIONAL ANAESTHESIA

New oral anticoagulants and regional anaesthesia

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Editor's key points

- Novel oral anticoagulants have been approved recently that impact the performance of regional anaesthesia.
- Recommendations differ in their guidance on timing for regional anaesthesia relative to anticoagulant discontinuation and resumption.
- Anaesthetists must balance the risks of bleeding with thrombotic complications based on drug pharmacokinetics and patient-dependent risk factors.

Summary. The new oral anticoagulants are approved for a variety of clinical syndromes, including the prevention of stroke in atrial fibrillation, acute coronary syndromes, treatment of venous thromboembolism (VTE), and prevention of venous thrombosis after total joint surgery or hip fracture. Published guidelines have differing recommendations on the safe interval between discontinuation of the anticoagulant and performance of neuraxial procedures and between the interventional procedure and redosing of the drug. While two to three half-life intervals might be acceptable in patients who are at high risk for VTE or stroke, an interval of four to six half-lives between discontinuation of the drug and neuraxial injections is probably safer in most patients at low risk of thrombosis. In those with renal disease, the interval should be based on creatinine clearance. After a neuraxial procedure or removal of an epidural catheter, anticoagulants can be resumed within 24–48 h in most patients, but they can be taken sooner in patients who are at higher risk for VTE or stroke, that is, 24 h minus the time to peak effect of the drug. The new antiplatelet drugs prasugrel and ticagrelor should be stopped 7 or 5 days, respectively, before a neuraxial injection and can be restarted 24 h later. In selected situations, laboratory monitoring of the anticoagulant effect is appropriate, and reversal agents are suggested when there is a need to rapidly restore haemostatic function.

Keywords: anaesthesia, regional; blood, anticoagulants; drug, safety

In 2010, the American Society of Regional Anesthesia (ASRA) and the European and Scandinavian Societies of Anaesthesiology published guidelines for regional anaesthesia in patients on anticoagulants.[1–3] However, several new oral anticoagulants have been approved by the US Food and Drug Administration (FDA) since these guidelines appeared: dabigatran in 2010; rivaroxaban and ticagrelor in 2011; and apixaban in 2012. Dabigatran is a direct thrombin inhibitor, rivaroxaban and apixaban are factor Xa inhibitors, while ticagrelor is a platelet adenosine diphosphate (ADP) P_2Y_{12} receptor inhibitor. Recent reviews of these anticoagulants discuss the development and risk of venous thromboembolism (VTE), options for thromboprophylaxis, and indications and pharmacokinetics of the drugs.[4–8] The European Society of Anaesthesiology discussed the new anticoagulants in their guidelines and their recent review of severe perioperative bleeding.[2 9] A Working Group on perioperative haemostasis and the French Study Group on thrombosis and haemostasis suggested adjustments to the interval between discontinuation of the drugs and performance of neuraxial procedures, based on the degree of risk of thrombosis.[10] Four reviews published

this year focused on creatinine clearance (CrCl) in determining the interval between discontinuation of anticoagulant and subsequent neuraxial procedures.[11–14] Other recent reviews examined laboratory monitoring of anticoagulant activity of new anticoagulants and their reversal.[15–20]

In this review, we discuss topics related to the perioperative management of patients treated with the new anticoagulants. Our discussion will include efficacy of the drugs in specific clinical syndromes, the basis for the interval between discontinuation of anticoagulant and neuraxial procedures and between neuraxial injections and resumption of anticoagulant, laboratory monitoring of anticoagulant effect, and reversal of anticoagulant in the case of emergency interventions. Understanding clinical indications for the drugs will make the anaesthesiologist more aware of the risks of discontinuation. Knowledge of appropriate coagulation assays and agents available for drug reversal is required in cases of emergency surgery, haemorrhage, overdose, or planned neuraxial injections. We include the new antiplatelet drugs prasugrel and ticagrelor, since these were not discussed in recent reviews of new anticoagulants.

Approval for clinical use of new anticoagulants

The US FDA has approved new oral anticoagulants for prevention of VTE after total joint surgery and hip fracture, prevention of embolism in patients with atrial fibrillation, and treatment of active VTE (Table 1). Warfarin therapy has traditionally been used in these conditions but has the limitation that only 60% of patients have an international normalized ratio (INR) of 2.0–3.0, the recommended therapeutic range, at any given time during treatment.[21]

Reduction of bleeding and thrombotic complications when neuraxial procedures are planned

In all patients, evaluation for bleeding and thrombotic risk is essential. A bleeding tendency is suspected if there is a previous history of surgical or trauma-related haemorrhage, hepatic or renal disease, nutritional deficiency, or treatment with dual anticoagulant therapy (oral anticoagulant and antiplatelet agent). The use of a scoring system such as HAS-BLED[22] or HEMORR$_2$-HAGES[23] might be helpful. Patients with a CHADS$_2$ score >2 are at increased risk of thrombosis.[24] Deciding when to discontinue an anticoagulant should take these risk factors into consideration.

To reduce the risk of bleeding or thrombotic complications in patients receiving new oral anticoagulants, it has been recommended that elective procedures requiring neuraxial anaesthesia should be delayed if[24]

(i) A thrombotic event [VTE, myocardial infarction, transient ischaemic attack (TIA), or stroke] has occurred within the previous 3 months;

(ii) A major haemorrhage, defined as a decrease in haemoglobin of 2 g dl^{-1}, transfusion of 2 units of packed red blood cells, or bleeding into an organ, has occurred within the previous 3 months; or

(iii) The patient is pregnant or <6 weeks post-partum.

Pharmacokinetics of drugs in relation to drug discontinuation and redosing

For older anticoagulants, the interval between discontinuation of anticoagulant and performance of a neuraxial injection was based on published studies. These include the time for synthesis of clotting factors after warfarin is discontinued,[25] risk factors for development of spinal haematoma after lumbar puncture and resumption of heparin,[26] and absence of spinal haematoma after neuraxial injection in patients treated with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs),[27–30] or subcutaneous heparin.[31]

For the new oral anticoagulants, the time between drug discontinuation and neuraxial injection is based on pharmacokinetic half-life. It has been recommended that two half-lives are an adequate compromise between safety, that is, avoidance of spinal haematoma and prevention of VTE.[32] The European and Scandinavian guidelines adopted two half-life intervals between discontinuation of the drug and neuraxial injection.[2 3] There are several reasons for this recommendation. The presence of residual anticoagulation facilitates transition to full anticoagulation after the procedure.[5] Because subclinical deep vein thrombosis occurs in ~15–20% of patients soon after surgery[33] and pulmonary embolism has been noted during the initial phase of warfarin therapy,[34] having residual anticoagulant might prevent perioperative VTE. It is, therefore, important to identify the earliest safe interval between discontinuation of drug and neuraxial injection or epidural catheter placement and between catheter removal and subsequent drug administration.[35]

Are two half-life intervals between discontinuation of anticoagulant and subsequent neuraxial injection adequate to provide protection against thrombosis, but not provoke bleeding? When a drug is discontinued, its disappearance from plasma depends on its half-life. After 1–6 half-lives, the following

Table 1 New anticoagulant drugs approved by the US FDA. AF, atrial fibrillation; VTE, venous thromboembolism; DVT, deep venous thrombosis. *Approved indication, references: Garcia and colleagues,[16] Siegal and Cuker,[17] and Siegal and Crowther.[18] †Efficacy of dabigatran in studies not uniform (see text). ‡Efficacy when added to antiplatelet therapy. ¶Apixaban is non-inferior to conventional therapy (subcutaneous enoxaparin followed by warfarin) in the treatment of acute VTE (from Agnelli and colleagues)[107]

Drug	Mechanism of action	Efficacy in clinical syndromes	Approved indications*
Dabigatran (Pradaxa®)	DTI	Prevention of postoperative VTE after total joint surgery† Prevention of stroke in AF Treatment of acute VTE	Prevention of stroke in patients with non-valvular AF (USA, Canada, and Europe) Prevention of VTE after knee or hip arthroplasty (Europe and Canada)
Rivaroxaban (Xarelto®)	Factor Xa inhibitor	Prevention of postoperative VTE after total joint surgery Prevention of stroke in AF Treatment of acute VTE Acute coronary syndromes‡	VTE prophylaxis and stroke prevention in non-valvular AF (USA, Canada, and Europe) Treatment of VTE (USA, Europe, and Canada) Prevention of VTE after orthopaedic surgery (USA, Europe, and Canada)
Apixaban (Eliquis®)	Factor Xa inhibitor	Prevention of postoperative VTE after total joint surgery Prevention of stroke in AF Treatment of acute VTE¶	Stroke prevention in patients with non-valvular AF (USA, Europe, and Canada) VTE prophylaxis after hip and knee arthroplasty (Europe and Canada)

percentages of drug remain in the circulation: 50%, 25%, 12%, 6.2%, 3.1%, and 1.6%, respectively (Table 2).[36] This recommendation for two half-lives is based on studies in young healthy persons but fails to take into consideration differences between the subjects in the studies and a non-research patient population. Some of the pharmacokinetic studies of new anticoagulants were based on single doses and not during steady-state conditions after chronic intake. Drug half-lives can be longer in the elderly (who typically have total joint surgery) or in patients with renal disease or other comorbidites. Most participants in the clinical trials were younger, specifically selected for having a lower risk of bleeding, having less medically complex illnesses, and were not on antiplatelet agents.[37] Concomitant antiplatelet therapy was discouraged in some of the total joint surgery trials. In a study on the efficacy of rivaroxaban in preventing VTE after major orthopaedic surgery, patients with severe renal impairment or those with a CrCl $\leq$30 ml min^{-1} were excluded.[38] There has been no post-marketing surveillance on the new anticoagulants except for dabigatran. Of note, a specific antidote for the new oral anticoagulants is not yet available.[10 12]

Discontinuation of anticoagulant before neuraxial injection or removal of epidural catheter

In patients with atrial fibrillation, risk factors for thrombosis include age $\geq$65 yr, congestive heart failure, hypertension, diabetes mellitus, vascular disease, and previous thromboembolism.[39] In patients with such risk factors, two to three half-life intervals might be appropriate, recognizing that haemostatic safety is not assured. When neuraxial procedures are performed under these conditions, safety measures should be observed including avoidance of multiple catheter insertion attempts and cessation of the procedure if excessive bleeding is noted. The conscientious follow-up of these patients and a heightened awareness for bleeding complications should be observed. For patients without thrombotic risk factors, an interval of four to six half-lives between the last dose of anticoagulant and neuraxial injection assures a more complete elimination of drug and less risk of bleeding (Table 2).[13 16] The European guidelines recommended two half-life intervals, but also state that the 'neuraxial procedure should coincide with the lowest anticoagulant level'[2]—this corresponds to five to six half-lives. It should be noted that 'lowest level' does not mean zero level of anticoagulant or that discontinuation of the drug be unnecessarily prolonged, thus increasing the risk of VTE. A compromise between the conservative recommendations of four to six half-lives[13 16] and two to three half-lives[2 3] is an interval of five half-lives. Bridge therapy with low molecular weight heparin (LMWH) can be performed during this time to prevent thrombosis.[14] With this arrangement, there is a low level of anticoagulant and the effect of LMWH is basically gone at the time of neuraxial block. There is very little risk of spinal haematoma

Table 2 Half-lives of new anticoagulant drugs and recommended interval between discontinuation and surgery or neuraxial procedure. Percentage of drug eliminated after several half-lives: 2 half-lives=75%; 3 half-lives=87.5%; 4 half-lives=93.8%; 5 half-lives=96.9%. For five half-lives, we took the upper limit of the half-life of the drugs in calculating the 3–5 half-lives, for example, 17 h for dabigatran, 13 h for rivaroxaban, and 15 h for apixaban. *From Sie and colleagues.[10] Recommendations of Levy and colleagues[11] regarding dabigatran in procedures with high bleeding risk: 2–4 days with CrCl >80 ml min^{-1}, 2–4 days with CrCl 50–80 ml min^{-1}, >4 days with CrCl 30–50 ml min^{-1}, and >5 days with CrCl <30 ml min^{-1}. Recommendations of Liew and Douketis[14] for mild-to-moderate anticoagulant effect at surgery (two to three drug half-lives): dabigatran: 2 days with CrCl >50 ml min^{-1}, 3 days with CrCl 30–50 ml min^{-1}; rivaroxaban/apixaban: 2 days with CrCl >50 ml min^{-1}, 3 days with CrCl 30–50 ml min^{-1}. For comparison, the French Study Group recommended a 24 h interval in patients undergoing procedures with low risk of haemorrhage and a 5 day interval in cases of medium or high haemorrhagic risk.[10] The European guidelines were based on two half-lives of the drugs: 34 h for dabigatran, 22–26 h for rivaroxaban, and 26–30 h for apixaban.[2] The Scandinavian guidelines recommended 18 h for rivaroxaban and had no recommendations for dabigatran and apixaban because data were not available when the guidelines were written.[3] There are no ASRA guidelines for the dabigatran, rivaroxaban, and apixaban

Drug	Metabolism, renal, and faecal/biliary elimination*	Elimination half-life	Five half-lives	Baron and colleagues:[12] recommendations	Connolly and Spyropoulos:[13] high bleeding risk (4–5 half-lives between dose and surgery)	Liew and Douketis:[14] no or minimal anticoagulant effect at surgery (four to five half-lives)
Dabigatran	Renal 80%, faecal 20%	12–17 h 28 h (end-stage renal disease)	85 h (4 days) 140 (6 days) (end-stage renal disease)	1–2 days with CrCl $\geq$50 ml min^{-1}; 3–5 days with CrCl <50 ml min^{-1}	3 days with CrCl>50 ml min^{-1}; 4–5 days with CrCl 30–50 ml min^{-1}	3 days with CrCl>50 ml min^{-1}; 4–5 days with CrCl 30–50 ml min^{-1}
Rivaroxaban	Metabolism 33%, renal 33% (33% inactive metabolites)	9–13 h	65 h (3 days)	$\geq$1 day with normal renal function; 2 days with CrCl 60–90 ml min^{-1}; 3 days with CrCl 30–59 ml min^{-1}; 4 days with CrCl 15–29 ml min^{-1}	3 days with CrCl>50 ml min^{-1} and CrCl 30–50 ml min^{-1}; 4 days with CrCl 15–29.9 ml min^{-1}	3 days with CrCl>50 ml min^{-1}; 4–5 days with CrCl 30–50 ml min^{-1}
Apixaban	Renal 25%, metabolism and faecal elimination 75%	15.2 (8.5)	75 h (3–4 days)	1 or 2 days with CrCl >60 ml min^{-1}; 3 days with CrCl 50–59 ml min^{-1}; 5 days with CrCl<30–49 ml min^{-1}	3 days with CrCl>50 ml min^{-1}; 4 days with CrCl 30–50 ml min^{-1}	(Same as rivaroxaban)

and the possibility of thrombosis is diminished by bridge therapy.

Resumption of drug after neuraxial injection or removal of epidural catheter

The incidence of spinal haematoma is the same with both catheter placement and catheter removal,[40] so it has been recommended that the same guidelines apply to both neuraxial injection or epidural catheter placement and catheter removal.[41] Like the interval between discontinuation of anticoagulant and subsequent neuraxial injection, the ASRA guidelines on subsequent redosing of drug are based on published studies. For heparin, the 1 h interval was based on a publication that evaluated development of spinal haematoma after lumbar puncture.[26] For warfarin, recommendations are based on the known initial effect of the drug on factor VII and anticoagulant protein C, and its delayed effect on prothrombin.[34] The very rare occurrence of spinal haematoma in patients on aspirin or NSAIDs is the reason these drugs can be immediately resumed after removal of the catheter.[27–30]

For the new anticoagulants, ASRA did not make recommendations on the resumption of drug after a neuraxial procedure or removal of an epidural catheter. The Scandinavian guidelines were based on the recommendation of Rosencher and colleagues[32] of 8 h minus the time it takes for the anticoagulant to reach peak effect. Rosencher and colleagues cited the work of Bouma and Mosnier[42] who apparently stated that it takes ∼8 h for a platelet plug to become a stable clot. Although Bouma and Mosnier did not categorically state that the clot is stable after 8 h, the 8 h value may have some basis. Analysis

of the efficacy of *thrombolytics* to lyse a cerebral embolic clot within 6 h[43] showed the benefit to be largely driven by patients who were treated within 3 h of stroke onset.[44] This implies that *anticoagulants* do not contribute to clot lysis after 8 h. For example, giving enoxaparin 24–48 h after intracerebral haemorrhage does not lead to enlargement of the haematoma.[45]

Other experts recommend a more conservative approach on the timing of resumption of anticoagulants because the reinstitution of antithrombotic therapy within 24 h after a major procedure might increase the risk of periprocedural bleeding.[12] Liew and Douketis[14] recommend a minimum of 24 h in patients with low bleeding risk, and 48 h in those with a high bleeding risk, before resuming dabigatran, rivaroxaban, or apixaban.

Therefore, options range from 8 h as recommended by the Scandinavian guidelines, or 24 h minus the time to peak effect of the drug (Table 3). The clinical risks involved with these two options are probably minimal in terms of VTE, stroke, or acute coronary syndrome. This is especially true since the time to peak effect of the new anticoagulants is short.

For older anticoagulants, guidelines recommend shorter intervals. The ASRA suggested a 1–2 h interval between dural puncture and resumption of i.v. heparin,[1] although the anticoagulant effect of heparin is immediate. It takes 3 h for the peak anti-factor Xa (anti-FXa) plasma activity of enoxaparin,[46] yet the ASRA recommended a 2 h interval between catheter removal and subsequent redose. These recommendations on heparin and enoxaparin have been followed in thousands of patients with no reports of spinal haematoma, although this might represent underreporting and not proof of safety of the guidelines. Resumption of the new anticoagulants is listed in Table 3.

Table 3 Resumption of anticoagulant based on the peak effect and onset of action. *Rosencher and colleagues[32] recommended 8 h (assumed for the clot to be stable) minus the peak effect of drug, a recommendation adapted by the Scandinavian guidelines. Although the European guidelines did not quote Rosencher and colleagues, their recommended intervals appear to follow Rosencher's recommendations. The Scandinavian guidelines recommend that prasugrel and ticagrelor can be administered after catheter removal. †The 24 h value is based on a study that showed no enlargement of intracranial haematoma when enoxaparin was given within 24–48 h after an intracranial haemorrhage (Tertri and colleagues).[45] The French Study Group recommended a 24 h interval before resumption of the oral anticoagulants[10]

Drug	Time to peak effect of drug	Resumption of drug based on 8 h minus the time to peak anticoagulant effect*	Resumption of drug based on 24 h minus the time to peak anticoagulant effect†	Baron and colleagues:[12] recommendations (high-risk procedures)	Connolly and Spyropoulos:[13] high bleeding risk	Liew and Douketis[14]
Dabigatran	2 (1.5–3) h	6 h	22 h	48 h	24 h, half of the usual dose for first 2 days	24 h after operation for cases with low bleeding risk, 48–72 h for high bleeding risk
Rivaroxaban	2.5–4 h	5.5 h	21.5 h	48 h	24 h, half of the usual dose for first 2 days	Same as dabigatran
Apixaban	1–2 h	7 h	23 h	48 h	24 h, half of the usual dose for first 2 days	Same as dabigatran
Prasugrel	1 h	7 h	23 h	Caution (recommended within 24 h for aspirin and clopidogrel)		
Ticagrelor	2–4 h	6 h	22 h	(Same as for prasugrel)		

Dabigatran

Dabigatran etexilate is a prodrug that is hydrolysed by esterases in the stomach to active drug. Dabigatran is a direct thrombin inhibitor (DTI) that blocks the interaction of thrombin with various substrates (Fig. 1).[47] Thrombin plays a dominant role in the clotting process by converting fibrinogen to fibrin, activating factors V, VIII, and XI, and stimulating platelets.[47] DTIs act independently of antithrombin.

Dabigatran etexilate has a bioavalability of 7.2%.[48 49] Peak plasma concentrations are attained 1.5–3 h after intake of the prodrug.[50 51] It has a half-life of 14–17 h in healthy volunteers, in patients undergoing orthopaedic surgery, and in healthy elderly volunteers.[50–53] Dabigatran is not metabolized by cytochrome P450 isoenzymes and has a low potential for drug–drug interactions.[48] Although the average bioavailability of dabigatran is decreased slightly by pantoprazole, other antacids and H_2 receptor blockers do not affect its absorption and dose adjustment is not considered necessary.[52] The pharmacokinetic profile of dabigatran is not affected by sex, body weight or obesity, ethnic origin, or mild-to-moderate hepatic impairment.[51] Intra- and interindividual variability is low, indicating that dabigatran has a predictable pharmacokinetic profile. Renal clearance accounts for 80% of the clearance: reduced renal function results in up to a six-fold increase in plasma concentration and a prolonged half-life.[54 55] In cases of end-stage renal disease, elimination half-life doubled from 14 to 28 h.[55 56] In healthy elderly subjects, concentrations are 40–60% higher than in younger subjects, which is primarily a reflection of reduced renal clearance with increasing age.[52] The drug is contraindicated in patients with CrCl <30 ml kg^{-1} min^{-1}.[57] Low body weight has also been identified as a risk factor for increased bleeding.
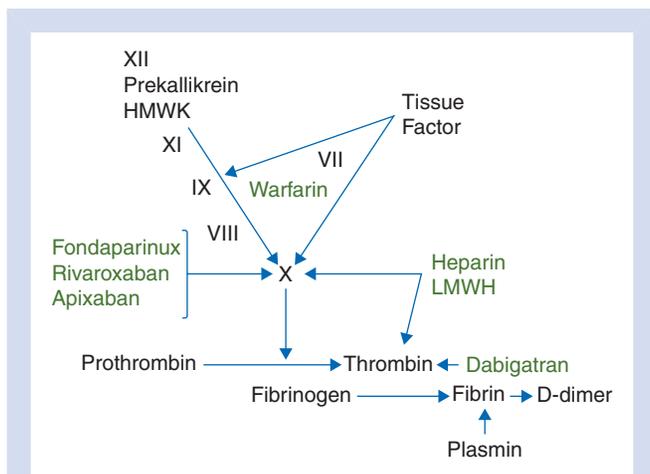

Fig 1 Sites of action of anticoagulant drugs. Clotting factors are indicated by Roman numerals. Warfarin reduces production of factors VII, IX, X, and prothrombin. Heparin and LMWH inhibit factor Xa and thrombin. Fondaparinux, rivaroxaban, and apixaban are direct factor Xa inhibitors. Dabigatran is a DTI. HMWK, high molecular weight kininogen; LMWH, low molecular weight heparin.

In patients with atrial fibrillation, dabigatran was noted to reduce rates of stroke and systemic embolism to a degree similar to that of warfarin; rates of major haemorrhage were also similar, but intracranial haemorrhage was significantly less frequent.[58] For treatment of acute VTE and prevention of recurrent VTE, dabigatran was as effective and had a safety profile similar to that of warfarin.[59] When added to dual antiplatelet therapy in patients with acute coronary syndromes, dabigatran increased the rate of bleeding events without decreasing the incidence of cardiovascular ischaemic events.[60]

The efficacy of dabigatran in preventing VTE after total joint surgery is not uniform. A recent Japanese study found dabigatran to be effective in preventing VTE after total knee arthroplasty compared with placebo.[61] Earlier studies showed it to be either more effective,[62] non-inferior,[63 64] or inferior to enoxaparin.[65] Meta-analysis of the trials noted no differences between dabigatran and enoxaparin in any of the endpoints analysed.[66] The superiority of dabigatran over enoxaparin in a European study[62] but not in the North American study[65] is probably the reason the drug is approved for VTE prophylaxis after total joint surgery in Europe and Canada but not in the USA (Table 1).

We reviewed the use of regional anaesthesia in patients undergoing total joint replacement and receiving dabigatran for VTE prophylaxis (Table 4). The range of drug dosing was 12.5 and 300 mg twice daily.[67] Epidural anaesthesia, spinal anaesthesia, or both were used in 1122 (71%) of the 1576 patients, and NSAIDs with half-lives <12 h, low-dose aspirin, or COX-2 inhibitors were allowed.[61] There was no comment on the interval between removal of catheters and subsequent dosing of dabigatran, but no instances of spinal haematoma were noted. The RE-MODEL study also permitted the use of concomitant low-dose aspirin and COX-2 inhibitors.[63] Like the previous trial, there was no comment on timing of epidural catheter removal in relation to ongoing treatment or subsequent dosing of dabigatran after removal of catheters. In the RE-NOVATE trial,[64] the same dosing of dabigatran and use of low-dose aspirin was followed as in the RE-MODEL trial.[63] In the RE-MOBILIZE study, the initial dose was one-half of subsequent doses and administered 6–12 h after surgery.[65] Most patients had spinal anaesthesia (796), while nine patients had 'other anaesthesia'. In the study by Fuji and colleagues,[61] 'indwelling catheters' (it was not clear whether these were epidural catheters) were removed before initiation of dabigatran. However, only 95 of 512 patients had 'non-general' anaesthesia. Overall, the number of patients in studies on dabigatran who had neuraxial anaesthesia was 4785. Although there were no instances of spinal haematoma, this small number, relative to the incidence of this rare complication,[68] does not permit firm conclusions about the safety of dabigatran in patients having neuraxial anaesthesia. The manufacturer states that epidural catheters should not be placed in patients receiving dabigatran.[2] A 2 h minimum interval between 'indwelling catheter' removal and dabigatran administration observed in the study by Fuji and colleagues[61] has also been recommended by Levy and colleagues.[5] This interval is shorter than the difference between 8 and 2 h time to reach peak effect of the drug (6 h). Recommended intervals between

Table 4 Neuraxial anaesthesia and drug administration in studies of total joint surgeries. *Combination (RE-MODEL trial): peripheral nerve block+general or neuraxial anaesthesia. †Combination (RE-NOVATE trial): peripheral nerve block+general or neuraxial anaesthesia. ‡Other anaesthesia (RE-MOBILIZE): not stated but not general or spinal. The total number of patients in the dabigatran studies who had neuraxial anaesthesia (included patients who had 'combination anaesthesia' but may have had peripheral nerve block): 4794. The total number of patients in the apixaban studies who had spinal anaesthesia: 6550. The total number of patients in the rivaroxaban RECORD studies who had 'regional anaesthesia' with or without general anaesthesia: 4622

Trial, drug	Neuraxial procedure	Initiation of drug	Interval between drug discontinuation and neuraxial injection or epidural catheter placement	Subsequent drug dose after catheter removal	Incidence of spinal haematoma
BISTRO I trial, dabigatran, and THR[67]	Not stated, 289 patients (dose-escalating efficacy study)	4–8 h after surgery	Type of anaesthesia not stated	Not stated	No major bleeding noted
BISTRO II trial, dabigatran, and THR/TKR[62]	Epidural, spinal, or both—1122	1–4 h after surgery, second dose on the same day if dosing interval≥8 h	Dabigatran given after surgery, not clear if epidural used	Not stated	No spinal haematoma
RE-MODEL trial, dabigatran, and TKR[63]	Neuraxial alone—656 Combination*—399	First dose half of (75 or 110 mg) subsequent dose, given 1–4 h after surgery. Full dose if administered the day after surgery	Dabigatran given after surgery, not clear if epidural used	Not stated	No spinal haematoma
RE-NOVATE trial, dabigatran and THR[64]	Neuraxial alone—1512 Combination†—205	Dabigatran (75 or 110 mg) 1–4 h after surgery. Full dose if given the next day	Dabigatran given after surgery, not clear if epidural used	Not stated	No spinal haematoma
RE-MOBILIZE trial, dabigatran, and TKR[65]	Spinal anaesthesia—796 Other anaesthesia‡—9	First dose (75 or 110 mg) half of subsequent doses, administered 6–12 h after surgery. Full dose (150 or 220 mg) if given the day after surgery	Dabigatran given after surgery	Not applicable, patients had spinal anaesthesia	No spinal haematoma
Fuji and colleagues, dabigatran, and TKR[61]	'Non-general' anaesthesia—95	Dabigatran (110, 150, and 220 mg) started day after surgery, at least 2 h after removing of 'indwelling catheter'	Dabigatran given after surgery	Not stated	No spinal haematoma
RECORD 1 trial, rivaroxaban, and THR[91]	Regional only—1308 General and regional—223	Rivaroxaban 10 mg 6–8 h after surgery	Rivaroxaban given after surgery	Not clear, number of patients who had postoperative epidural catheter not stated	No spinal haematoma
RECORD 2 trial, rivaroxaban, and THR[92]	Regional only—794 General and regional—77	Rivaroxaban 10 mg 6–8 h after surgery	Rivaroxaban given after surgery	Same as RECORD 1	No spinal haematoma
RECORD 3 trial, rivaroxaban, and TKR[93]	Regional only—786 General and regional—188	Rivaroxaban 10 mg 6–8 h after surgery	Rivaroxaban given after surgery	Same as RECORD 1 and 2	One patient of haemorrhagic spinal puncture with no neurological signs or symptoms of spinal cord compression. Two patients occurred in the enoxaparin group (40 mg given 12 h before surgery)
RECORD 4 trial, rivaroxaban, and TKR[94]	Regional only—885 General and regional—361	Regional 10 mg 6–8 h after surgery	Rivaroxaban given after surgery	Same as RECORD 1–3	No spinal haematoma. In the enoxaparin group, one patient had intracranial bleed while another patient with a catheter had 'intraspinal bleeding'

Continued

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Table 4 *Continued*

Trial, drug	Neuraxial procedure	Initiation of drug	Interval between drug discontinuation and neuraxial injection or epidural catheter placement	Subsequent drug dose after catheter removal	Incidence of spinal haematoma
Apixaban and TKR[112]	Spinal anaesthesia—475	Apixaban, 5, 10, or 20 mg per day	Apixaban started 12–24 h after surgery	Patients had spinal anaesthesia	No spinal haematoma
ADVANCE study, apixaban, and TKR[113]	Spinal anaesthesia—1643	Apixaban, 2.5 mg twice daily	Apixaban started 12–24 h after surgery	Patients had spinal anaesthesia	No spinal haematoma
ADVANCE-2 study, apixaban, and TKR[114]	Spinal—1561	Apixaban, 2.5 mg twice daily	Apixaban started 12–24 h after surgery	Patients had spinal anaesthesia	No spinal haematoma
ADVANCE-3 study, apixaban, and THR[115]	Spinal—2871	Apixaban, 2.5 mg twice daily	Apixaban started 12–24 h after surgery	5 h	No spinal haematoma

discontinuation of drug and neuraxial procedures, and subsequent resumption of the drug, are given in Tables 2 and 3.

There have been reports of increased bleeding after dabigatran. An audit of bleeding events done in collaboration with the Haematology Society of Australia and New Zealand identified 78 bleeding episodes, mostly gastrointestinal, in ~7000 patients over a 2 month period.[69] A more recent audit by the FDA, however, using Mini-Sentinel analysis, did not notice an absolute increase in bleeding with dabigatran compared with warfarin.[70]

Laboratory monitoring of new anticoagulants is required when neuraxial anaesthesia is to be performed in patients failing to discontinue the agents at the times specified by the various guidelines. Other scenarios include patients with extensive ecchymoses or other evidence of bleeding, patients with renal impairment, cachexia, or poor nutritional status, uncertainty about when the last dose was taken, or patients taking more than the recommended dose. For dabigatran and the other novel anticoagulants, coagulation tests should be interpreted relative to the last administered dose, drug pharmacokinetics, and renal function.[17] The activated partial thromboplastin time (aPTT) is prolonged after dabigatran, but there is a greater than linear increase at lower concentrations (at or <200 ng ml^{-1}) and a linear relationship at higher concentrations (>200 ng ml^{-1}) (Table 5).[15 16] Another study showed that the aPTT, prothrombin time (PT), and activated thrombin time (ACT) were insensitive to therapeutic levels of dabigatran.[71] The thrombin time (TT), also known as thrombin clotting time (TCT), is highly sensitive to the effects of dabigatran (Table 4).[16 17 72] The TCT is more appropriately used for detecting the presence of the anticoagulant effect of dabigatran rather than quantifying the effect of the drug.[72] A dilute TT (Hemoclot Thrombin Inhibitory assay) has become available recently and has linearity across pharmacologically relevant plasma dabigatran concentrations.[15 17] Ecarin is a commercially available snake venom that converts prothrombin to meizothrombin.[15] The ecarin clotting time (ECT), which directly measures thrombin generation, is prolonged by dabigatran[50 72 73] (Table 4), and is linearly and dose-dependently related to dabigatran concentration.[15] It is the most sensitive assay for dabigatran, but very few institutions have the test available.[19] The anti-factor IIa assay can be used to measure the effect of dabigatran, but clinical experience is limited, unlike the anti-Xa assay, which is currently used to monitor effects of LMWH and unfractionated heparin.[72] PT is the least sensitive test. Dilute TT and ECT are the tests of choice for dabigatran.[15]

Reversal of anticoagulant effect might be necessary before neuraxial anaesthesia in cases where such a technique is absolutely indicated or when the patient insists. It may also be necessary before an epidural catheter is removed in the presence of coagulopathy, for example, after a liver resection. Coagulation tests return to 30% of their maximum value 12 h after dabigatran discontinuation.[49] This observation in healthy subjects has been used to support the rationale for the two to three half-life intervals recommended by the European and Scandinavian

Table 5 Utility of coagulation assays and reversal of new anticoagulants. *There is no specific antidote for dabigatran, rivaroxaban, and apixaban. PCC, prothrombin complex concentrate; PT, prothrombin time; PTT, partial thromboplastin time; TEG, thrombelastography; TT, thrombin time. The authors have no experience with multiple electrode platelet aggregometry (Multiplate)

	Dabigatran	Rivaroxaban	Apixaban	Prasugrel	Ticagrelor
Recommended coagulation assay	Dilute TT, also called TCT—sensitive aPTT—sensitive (relationship not linear) and readily available ECT—sensitive but not readily available Anti-factor II assay	PT Anti-Xa assay	Anti-Xa assay Dilute PT	$P2Y_{12}$ assay Platelet mapping portion of the TEG Multiple electrode platelet aggregometry (Multiplate)	$P2Y_{12}$ assay Platelet mapping portion of the TEG Multiple electrode platelet aggregometry (Multiplate)
Reversal*	Dialysis Activated charcoal (within 1–2 h of ingestion) Dabigatran-neutralizing antibody in development	Activated charcoal (within 8 h of ingestion) Four-factor PCC	Activated charcoal (within 3 h of ingestion)	Platelets	Platelets

guidelines, but might not apply to patients with renal failure or other conditions delaying drug metabolism or excretion.

There is no antidote to reverse the effect of dabigatran or other new oral anticoagulants. Activated charcoal prevents absorption of the drug from the intestine, but it needs to be given within 2 h of ingestion (Table 5). Dialysis might speed drug elimination. To control haemorrhage, activated recombinant factor VIIa (rFVIIa) has been recommended,[50] but there is little clinical experience using this agent and it is thrombogenic. Prothrombin complex concentrates (PCCs) are concentrated pooled plasma products that contain either three (II, IX, and X) or four (II, VII, IX, and X) clotting factors (see Tanaka and colleagues, this issue). While the use of four-factor PCCs has been suggested,[17 72] a trial of this concentrate did not reverse the *in vitro* anticoagulant effect of dabigatran in healthy volunteers.[74] In addition, there is a risk of thrombosis with the use of PCCs. It should be noted, however, that patients developing thrombotic events were severely ill and potentially in a prothrombotic state.[75] A dabigatran-directed neutralizing antibody is under development.[73 76] There are no studies on the efficacy and safety of fresh-frozen plasma (FFP) for the reversal of the new oral anticoagulants.[17] It is unlikely that FFP would be effective in the reversal of dabigatran since the levels of circulating procoagulants are not decreased.[19]

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor (Fig. 1). Its onset of action is rapid and peak plasma concentrations are observed within 2.5–4 h.[38 77] Maximum inhibition of factor Xa, which ranges from 22% to 68%, occurs ∼3 h after dosing and is maintained for at least 12 h,[77] or 24–48 h when higher doses were given to elderly Chinese subjects.[78] Rivaroxaban has a terminal half-life of 5.7–9.2 h,[38 77] but can be as long as 11–13 h in elderly patients secondary to age-related decline in renal function.[49 79] One-third of the drug is eliminated by the kidneys, one-third by the faecal/biliary route, and one-third is metabolized to inactive metabolites.[38 80] Co-administration with food increases the C_{max} by 30–40% and the t_{max} to 4 h. The effect of

age and body weight on the pharmacokinetics of rivaroxaban is moderate.[38 81] The maximum concentration is not affected by obesity (patients weighing ≥120 kg) but is increased by 24% in patients weighing ≤50 kg.[81] Renal clearance of rivaroxaban decreases with increasing renal impairment.[82] Because rivaroxaban is partly metabolized by the liver, its use should be avoided in patients with moderate-to-severe liver disease.[79 83]

Concomitant use of rivaroxaban and aspirin is an independent risk factor for bleeding,[83] although no additive effects on platelet aggregation were noted when the drug was administered with aspirin or naproxen.[84] A porcine model of stent thrombosis showed that rivaroxaban caused a dose-dependent inhibition of platelet aggregation induced by FXa, tissue factor, or thrombin.[85] When added to aspirin and clopidogrel, rivaroxaban enhanced the inhibition of ADP-induced platelet aggregation.[85] Drugs that induce (carbamazepine, phenytoin, and rifampin) or inhibit (ketoconazole and ritonavir) P-glycoprotein and CYP 3A4 should not be given with rivaroxaban.[83]

Rivaroxaban was reported to be as effective as enoxaparin in the treatment of symptomatic VTE.[86] It was non-inferior to warfarin for prevention of embolic stroke during atrial fibrillation.[87] In patients with a recent acute coronary syndrome, the addition of rivaroxaban to standard antiplatelet therapy reduced the composite endpoint of death from cardiovascular causes, myocardial infarction, or stroke.[88] This is in contrast to the lack of additional salutary effect with either dabigatran or apixaban in the same conditions.[61 89] The benefit of rivaroxaban in this setting occurs at the expense of an increase in major bleeding and intracranial haemorrhage, but not in fatal bleeding. For thromboprophylaxis in acutely ill medical patients, rivaroxaban is non-inferior to enoxaparin for standard-duration prophylaxis but is associated with increased risk of bleeding.[90]

Rivaroxaban was reported to be as effective or superior to enoxaparin in preventing VTE after total joint surgery.[91–95] In the RECORD 1–4 studies,[91–94] rivaroxaban was a more effective thromboprophylactic agent than enoxaparin, with a similar safety profile (Table 3). In the RECORD 1–3 studies,[91–93] 40 mg enoxaparin was started 12 h before surgery, restarted 6–8 h

after wound closure, and then given every 24 h. In the RECORD 4 study,[94] 30 mg enoxaparin was started 12–24 h after surgery and then given every 12 h. The protocol for enoxaparin dosing in the RECORD 4 study is the one commonly used in the USA, while the protocol for the RECORD 1–3 studies is the dose and regimen approved for Europe.[93] The number of patients who had neuraxial anaesthesia or postoperative indwelling epidural catheters was not stated in the published RECORD studies (Table 3). At any rate, there were no spinal haematomata in the 4622 patients who received rivaroxaban and had 'regional anaesthesia', while there were two cases of spinal haematoma among the 4630 patients who received enoxaparin. Epidural catheters were not removed until at least two half-lives after the last dose of rivaroxaban, and the next rivaroxaban dose was given 4–6 h after catheter removal.[96] None of the 1141 patients who were given rivaroxaban and had neuraxial anaesthesia developed spinal haematoma.[96] This small number of patients does not provide assurance as to the safety of the 24 h interval observed in the RECORD studies. This concern pertains especially to elderly, low body weight, and renal insufficiency patients. There is a black-box warning about the risk of spinal/epidural haematoma in patients receiving rivaroxaban. Factors that increase the risk are indwelling epidural catheters, concomitant use of drugs that inhibit platelet function, traumatic or repeated epidural or spinal punctures, and a history of spinal deformity or surgery.[83]

The Scandinavian Society guidelines recommend a minimum of 18 h between the last dose of rivaroxaban and removal of an indwelling catheter, and a minimum of 6 h before the next dose.[3] The European Society guidelines recommend an interval of 22–26 h between the last dose of rivaroxaban and removal of an indwelling catheter, probably based on the prolonged half-life of rivaroxaban in elderly patients (11–13 h), and an interval of 4–6 h between epidural catheter removal and the next dose of rivaroxaban.[2] These two recommendations represent two half-life intervals between rivaroxaban discontinuation and epidural catheter placement or removal. The 4–6 h interval before resumption of the next dose is also in agreement with the recommendation of Rosencher and colleagues,[32] as rivaroxaban takes 2.5–4 h to reach peak effect. Expert recommendations on the intervals between discontinuation of rivaroxaban and surgical or neuraxial procedures, and resumption of the drug, are noted in Tables 2 and 3.

A linear correlation was observed between the effects of rivaroxaban and the PT, especially when neoplastin was used as the test reagent (Table 5).[16 38 72] The effect on the PT, however, can be short-lived, because prolongation was seen only during peak concentrations of the drug and minimal increases were noted at clinically relevant concentrations.[49] Because there is marked variability in the sensitivity of PT reagents to rivaroxaban, it has been recommended that each laboratory should calibrate the PT specifically for rivaroxaban to determine its effect on the test.[20] The INR should not be used to monitor rivaroxaban because the INR is very dependent on the thromboplastin reagent, and thromboplastins vary greatly in their sensitivity to rivaroxaban.[15] The aPTT lacks

sufficient sensitivity to determine the anticoagulant effect of rivaroxaban.[16 49 72] Rivaroxaban does not prolong the ECT.[72] The inhibition of factor Xa might also be a surrogate for plasma concentrations of rivaroxaban.[97 98] Overall, PT and anti-FXa are the tests best suited for monitoring the effects of rivaroxaban.[15]

Removal of rivaroxaban by activated charcoal has been suggested, but it must be given within 8 h of rivaroxaban ingestion.[72] In contrast to its lack of effect on dabigatran, a four-factor PCC has been shown to reverse the *in vitro* anticoagulant activity of rivaroxaban in healthy volunteers.[72 74] The use of rFVlla is effective in reversing the effect of fondaparinux,[72] but none of the new oral anticoagulants.[18] Because of the risk of thrombogenicity in non-haemophiliac patients, the FDA issued a black-box warning on the use of rFVIIa outside approved indications.[18] Rivaroxaban (and apixaban) might not be dialysable because of their high protein binding.[18]

Apixaban

Apixaban is a highly specific factor Xa inhibitor (Fig. 1). It is rapidly absorbed, attaining peak concentrations in 1–2 h. An earlier single 20 mg dose study showed apixaban to have a half-life of 13.5 (9.9) h.[99] More recent studies showed the terminal half-life to be 15.2 (8.5) h after a single 5 mg dose and 11.7 (3.3) after multiple 5 mg doses.[100 101] Administration of a high fat, high calorie meal did not affect the kinetics of drug uptake. When given twice a day, steady-state concentrations are reached by day 3.[101] Maximum plasma concentration is affected by body weight (higher concentrations of apixaban in subjects with low body weight), and plasma anti-Xa activity shows a direct linear relationship with apixaban plasma concentration.[101]

Apixaban has an oral bioavailability >45%. The major metabolic pathways include *O*-demethylation, with *O*-demethyl apixaban as the significant metabolite.[99] It is effectively eliminated via multiple elimination pathways and direct renal and intestinal excretion.[102] After oral administration, 24–29% of the dose is excreted via the kidneys, and 56% is recovered in the faeces.[49 99] More than half of apixaban is excreted unchanged, lessening the risk of metabolic drug–drug interactions. With low clinically effective concentrations and multiple clearance pathways, the drug–drug interaction potential of apixaban and co-administered drugs is probably low.[103] Famotidine does not affect the pharmacokinetics of apixaban.[104] However, inhibitors of CYP 3A4, such as ketoconazole or ritonavir, increase apixaban plasma levels, so it should be avoided in patients receiving these drugs.

A clinical trial of apixaban added to antiplatelet therapy in patients with recent acute coronary syndrome, in the absence of atrial fibrillation, was terminated prematurely because addition of apixaban did not reduce the incidence of ischaemic events but led to a significant increase in major bleeding events.[105] The lack of superiority of added apixaban[105] or dabigatran combined with standard antiplatelet therapy[60] is in contrast to the efficacy of rivaroxaban when added to antiplatelet therapy.[88] Apixaban is not more effective

than enoxaparin in preventing thromboembolism in medically ill patients (with congestive heart failure, respiratory failure, or other medical disorders and at least one additional risk factor for VTE).[106] For the treatment of acute VTE, apixaban was found to be non-inferior to conventional therapy (subcutaneous enoxaparin followed by warfarin) and was associated with significantly less bleeding.[107] Apixaban was also noted to reduce the risk of recurrent VTE without increasing the rate of major bleeding.[108]

For patients with atrial fibrillation who are not candidates for vitamin K antagonists, apixaban is superior to aspirin in reducing stroke or systemic embolism without increasing the risk of bleeding.[109] Compared with warfarin, apixaban at 5 mg daily is superior in preventing stroke or systemic embolism, with lower mortality and less bleeding.[110] The better efficacy of apixaban, rivaroxaban, and dabigatran compared with warfarin is considered a major breakthrough in the treatment of patients with atrial fibrillation.[111]

Apixaban, at 5–20 mg daily, has been noted in a clinical trial to provide effective thromboprophylaxis in total knee arthroplasty, comparable with enoxaparin or warfarin.[112] In that trial, 475 patients had spinal anaesthesia, and apixaban was given 12–24 h after surgery (Table 4). When apixaban, 2.5 mg b.i.d. after total knee arthroplasty was compared with enoxaparin 30 mg b.i.d.[113] or 40 mg daily,[114] apixaban was equally efficacious in preventing VTE while having a lower[113] or similar[114] rate of major bleeding. In a trial of total hip surgery, apixaban 2.5 mg b.i.d. was noted to be more effective than enoxaparin 40 mg daily in preventing VTE without increased bleeding.[115] Like the other studies, apixaban was given 12–24 h after surgery (Table 3). Patients in the apixaban group who did not have general anaesthesia had spinal anaesthesia (2871 of 3556), regional anaesthesia (327), or 'other' anaesthesia (358). In the latter trial, the authors stated, 'devices in connection with intrathecal or epidural anaesthesia were removed at least 5 h before the first dose' of apixaban.[115] In all studies of apixaban, the drug was started 12–24 h after surgery, so recommendations on the time interval between discontinuation of the drug and neuraxial procedures have to depend on the pharmacokinetics of the drug (Table 2). The number of patients who had intrathecal or epidural catheters were not stated, but were probably not adequate for definite recommendations on resumption of drug after catheter removal. As in the cases of dabigatran and rivaroxaban, experts made recommendations on the intervals between discontinuation of apixaban and neuraxial procedures, and resumption of the drug (Tables 2 and 3).[12–14]

Compared with rivaroxaban, apixaban has little effect on PT when given in approved doses.[16] Similar to rivaroxaban, each laboratory should specifically calibrate the sensitivity of their PT assay to apixaban. On the other hand, the dilute PT assay, wherein the thromboplastin reagent is diluted 16-fold, has improved sensitivity over conventional PT.[16] Apixaban can also be evaluated with the anti-FXa assay,[116] and there is linear correlation between anti-FXa activity and low-, intermediate-, and high-plasma concentrations of apixaban (Table 5).[117] The anti-FXa assay is more sensitive than PT and

as sensitive as the dilute PT assay,[18 118] and appears to be the best choice for clinical monitoring of the anticoagulant effect of apixaban.[15] While the drug prolongs aPTT, its effect is minimal and variable,[118] so aPTT is not an appropriate test for monitoring factor Xa inhibitors.[16] There are no data on the effect of apixaban on the ECT.[72]

Activated charcoal, given within 3 h of ingestion, reduces absorption of apixaban. Whether PCCs are effective in controlling bleeding due to apixaban has not been adequately assessed.[72]

Antiplatelet agents

The use of aspirin and a $P2Y_{12}$ receptor inhibitor, so-called dual antiplatelet therapy, has dramatically reduced atherothrombotic events in patients with acute coronary syndromes and those who undergo percutaneous coronary interventions.[119 120] Clopidogrel is the commonly used antiplatelet drug but has several limitations. Prasugrel is a prodrug similar to clopidogrel, while ticagrelor is a direct-acting $P2Y_{12}$ receptor inhibitor (Fig. 2).[6 121 122] Both drugs have rapid onset of antiplatelet effect. The median time to peak effect is 1 h with prasugrel compared with 4 h with clopidogrel.[123] The mean time to peak plasma concentration of prasugrel is 30 min[124] and its median half-life is 3.7 h, but this does not reflect the duration of platelet inhibition because of the irreversible inhibition of the $P2Y_{12}$ receptor.[125 126] Platelet inhibition does not normalize for 7 days.[127]

Both prasugrel and ticagrelor cause 90% inhibition of platelet function compared with 60–70% for clopidogrel.[123 128 129] The improved efficacy of prasugrel over clopidogrel is due to its improved metabolism, resulting in more active metabolites (R-138727, P-AM).[123 130 131] Platelet inhibition by prasugrel is not affected by renal or moderate hepatic impairment.[132 133] Patients more than 75 yr of age and those with a small body mass index or a history of TIA or stroke are at risk for bleeding.[134 135] The advantages of prasugrel over clopidogrel include reliable conversion of the drug to active metabolite and lack of drug interactions or susceptibility to genetic polymorphisms.[136–139] Disadvantages are the increased incidence of bleeding events and the 7 day interval required for normalization of antiplatelet effects.[126]

Ticagrelor is an adenosine triphosphate analogue that reversibly binds to the $P2Y_{12}$ receptor to block ADP-mediated receptor activation.[80] In contrast to thienopyridines, both the parent drug and active metabolite (AR-C124910XX; T-AM) exhibit antiplatelet activity. While both compounds appear to be equipotent, the parent drug is responsible for the majority of the in vivo platelet inhibition.[140 141] The antiplatelet effect of ticagrelor is rapid, with peak platelet inhibition occurring at 2–4 h after intake, compared with 24 h with clopidogrel.[128] The mean platelet inhibition by ticagrelor is 93%, compared with 58% for clopidogrel.[142] Like clopidogrel, a loading dose of ticagrelor hastens its antiplatelet effect. An initial dose of 180 mg of ticagrelor followed by 90 mg twice daily results in platelet inhibition of 41% at 30 min.[142] Platelet recovery is rapid with ticagrelor, and platelet inhibition is similar to placebo at 5 days after the last dose.[142]
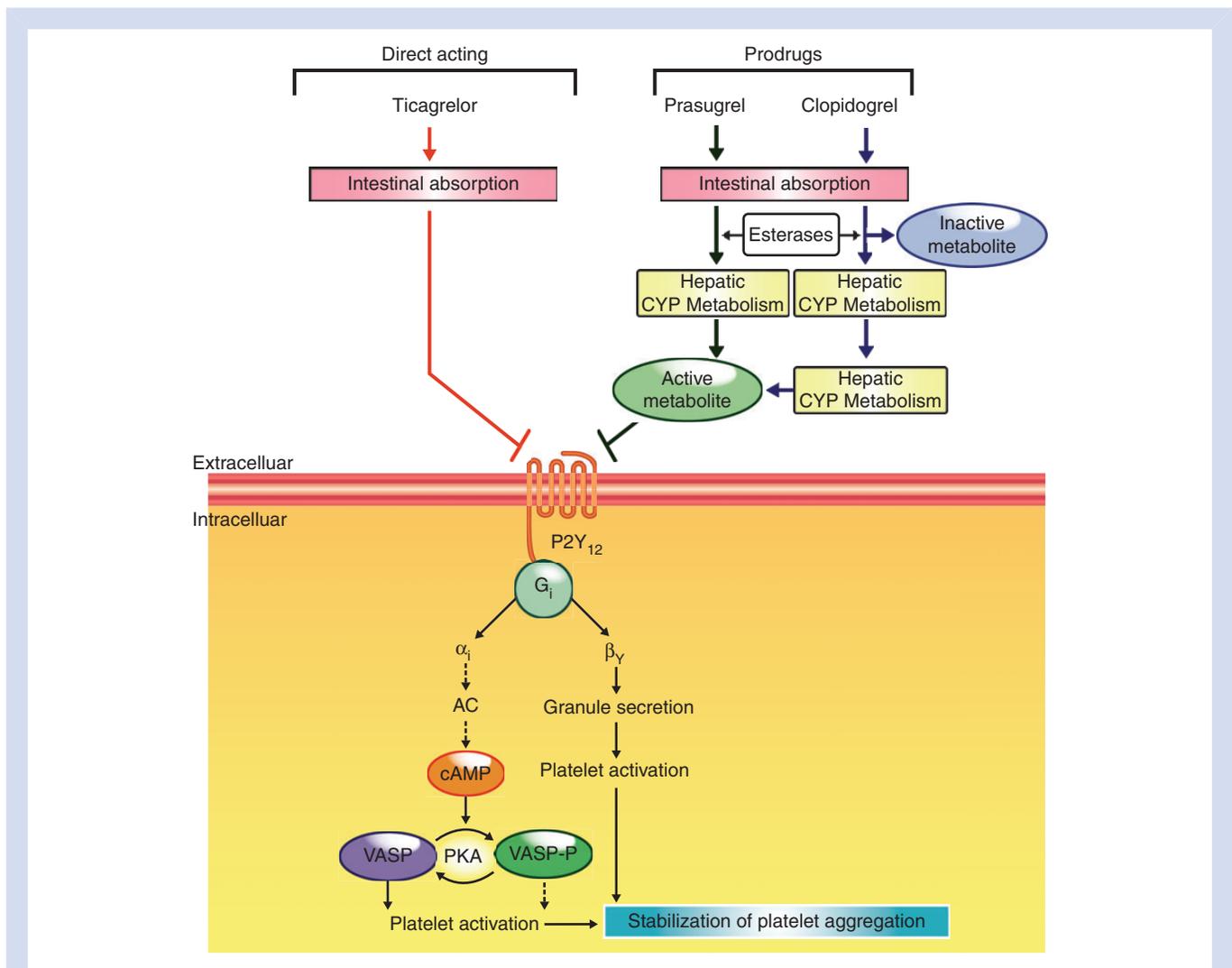
Fig 2 Inhibitors of the platelet P2Y$_{12}$ receptor. Clopidogrel must undergo two metabolic steps to form active drug, prasugrel requires only one step, and ticagrelor is a direct inhibitor. AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; VASP, vasodilator-stimulated phosphoprotein (-p=phosphorylated). Modified from Capodanno and colleagues,[122] with permission from John Wiley and Sons.

Metabolism of ticagrelor is by the liver and renal clearance is minor. Although the concentrations of ticagrelor and its metabolite were higher in the presence of hepatic impairment, the percentage inhibition of platelets and pharmacodynamics were not different from subjects without hepatic impairment.[143] Ticagrelor has predictable pharmacokinetics that are not affected by genetic polymorphisms and there are no known drug interactions.[126] Its faster onset of effect is an advantage, but its twice-daily dosing may present problems with patient compliance.[144 145] There has been no head-to-head comparison between prasugrel and ticagrelor.

Time between discontinuation/resumption of antiplatelet drug and neuraxial injection

Like the new oral anticoagulants, residual anticoagulation is probably acceptable, especially in patients at high risk for VTE or stroke, since arterial occlusions can occur soon after antiplatelet therapy is discontinued. For example, acute coronary syndromes have appeared 4–8 days after discontinuation of clopidogrel,[146] and myocardial infarction occurred in three of 24 (12.5%) patients during the 5 days after preoperative discontinuation of clopidogrel.[147] In addition, coronary and carotid stent occlusion in the perioperative period have been reported after the discontinuation of antiplatelet agents.[148] ASRA recommends that aspirin not be discontinued, and epidural injections have been performed in patients with no sequelae.[27–30]

The degree of platelet inhibition and platelet turnover are important factors in determining the interval between drug discontinuation and neuraxial injection (Table 5). As noted, clopidogrel causes a maximum of 60% platelet inhibition, while prasugrel and ticagrelor cause 90% inhibition. Ten to 15% of the circulating platelet pool is formed every day,[149] resulting in new platelets comprising 50–75% of the circulating platelet pool 5–7 days after discontinuation of the drug.[35] An interval of

5–7 days has been recommended for ticagrelor and 7–10 days for prasugrel.[2] These recommendations are appropriate since normalization of platelet aggregation takes 7 days after prasugrel[127] and 5 days after ticagrelor.[150]

The European Society of Anaesthesiologists recommends an interval of 6 h between removal of an epidural catheter and resumption of prasugrel and ticagrelor,[2] while the Scandinavian guidelines note that it is acceptable to start the drugs at the time of catheter removal.[3] Other experts suggest that clopidogrel can be restarted within 24 h, but recommend caution in restarting prasugrel and ticagrelor because of their rapid effect and potent antiplatelet inhibition.[12] A 24 h interval might be more appropriate.

Invasive procedures are occasionally considered for patients with coronary stents on dual antiplatelet therapy. If at all possible, such procedures should be deferred for at least 6 weeks in those with bare metal stents and 6 months in those with drug-eluting stents. For patients who require surgery within these time periods, it has been recommended that the dual antiplatelet drugs be continued around the time of surgery.[24] In these scenarios, peripheral nerve blocks or general anaesthesia might be preferable.

Monitoring of antiplatelet effects

The bleeding time was the most useful screening test until the 1990s. However, it is invasive, insensitive to mild platelet defects, time-consuming, and poorly reproducible.[29][151] Light transmission aggregometry (LTA) is considered the gold standard for testing of platelet function, but it is used mostly as a research tool because it requires experience, is time-consuming, is poorly standardized, and needs to be adjusted for platelet count.[119][120][151] The Platelet Function Analyzer-200 (PFA-200) is an update of the PFA-100 that has been in use since the 1990s. The test is simple and rapid and a whole blood assay, thereby avoiding sample preparation. It is a global test of platelet function but is insensitive to mild platelet defects.[151] The cartridges are mostly insensitive to $P2Y_{12}$ receptor inhibitors, so a third cartridge (INNOVANCE PFA P2Y) was introduced to detect the efficacy of this class of drugs.[152] Studies showed the test to be comparable with the VerifyNow, LTA, vasodilator-stimulated phosphoprotein (VASP) assay, and multiple electrode platelet aggregometry (see subsequent discussion).[152][153]

Tests that monitor $P2Y_{12}$ receptor activity include the VASP assay, the VerifyNow assay, multiple electrode platelet aggregometry (Multiplate), and the platelet mapping portion of the thromboelastograph (TEG; Table 5). The VASP assay is considered the reference standard for assessing P2Y12 antagonist therapy and is ideal for evaluating clopidogrel resistance.[120][154] However, one study showed inadequate correlation between the VASP index and $P2Y_{12}$ receptor occupancy.[155] There was also a weak correlation between LTA and VASP assays.[156]

Multiple electrode platelet aggregometry is a point-of-care, whole blood method that measures the change in electrical conductivity because of the attachment of platelets to metal electrodes.[157] It is useful for detection of both aspirin and clopidogrel effects on platelets. Other commonly used clinical tests for $P2Y_{12}$ receptor activity are the VerifyNow assay and the platelet mapping portion of the TEG. TEG provides information on clot formation and fibrinolysis. In the platelet mapping system, ADP and arachidonic acid are used to activate platelets, making it suitable to monitor antiplatelet therapy.[158][159] A cut-off value of <30% inhibition has been considered as being safe to proceed with surgery.[160] Unfortunately, one study showed that the mean percent platelet ADP receptor inhibition was 47% in a control group of patients who were not on anticoagulants.[161] The Platelet Mapping Assay[TM] on TEG was compared with its adapted version in the rotational thrombelastography (ROTEM[®]) system, using multiple electrode impedance aggregometry as a reference. The investigators noted good correlation between TEG and ROTEM ($r=0.82$).[159] However, because there was a large number of false-positive and false-negative results, the authors considered Multiplate a more clinically applicable point-of-care assay in view of its shorter test duration and lower cost. Furthermore, the test was noted to be more sensitive than optical aggregometry.[162]

The VerifyNow assay can monitor antiplatelet effects of aspirin and $P2Y_{12}$ inhibitors.[163] The results are reported as platelet reaction units (PRU) and percentage platelet inhibition. Recently, only PRU are being reported. Normal values are 194–418 PRU; high PRU values signify low platelet inhibition while low PRU values mean high platelet inhibition. Values <194 indicate an antiplatelet effect because of $P2Y_{12}$ receptor block. While the platelet mapping system of the TEG is commonly used in surgery and anaesthesiology, the VerifyNow is the predominant assay in clinical cardiology.[164] There has been no head-to-head comparison of the VASP assay, VerifyNow, or the platelet mapping system of the TEG.

The tests, as they pertain to the $P2Y_{12}$ receptor inhibitors, are being used to predict high residual platelet reactivity or enhanced response of platelets to agonists in the presence of antiplatelet therapy.[120] A statement has been published that provides the consensus cut-off values for high platelet reactivity: platelet reactivity index (PRI) >50% for the VASP assay and PRU≥235–240 for the VerifyNow assay.[165] Unfortunately, there has been no consensus on values predictive of bleeding, although a PRI <16% was noted to be predictive of bleeding events.[166] As a rule, the tests give very limited prognostic information on bleeding.[120] Reversal of the effect of $P2Y_{12}$ inhibitors usually requires administration of platelets.[12]

Regional anaesthesia

Peripheral nerve blocks can be performed, if appropriate, in patients taking antiplatelet drugs. The use of ultrasound to visualize blood vessels should decrease the incidence of intravascular injections. While the ASRA recommends the same guidelines for peripheral nerve blocks as for neuraxial procedures, the European Society of Anaesthesiology commented that the guidelines for neuraxial block do not routinely apply to peripheral nerve blocks. The Austrian Society of Anaesthesiologists suggests that superficial nerve blocks (axillary, femoral, and distal sciatic blocks) can be safely performed in the presence of anticoagulants.[167] Because of the possibility

of retroperitoneal haematoma, lumbar plexus and paravertebral blocks merit the same recommendations as for neuraxial injections.

Post-neuraxial anaesthesia monitoring

Clinicians should be vigilant in the follow-up of previously anticoagulated patients receiving neuraxial anaesthesia. They should be aware of the symptoms of spinal haematoma including back pain, numbness, motor weakness, and bowel/bladder incontinence. Computed tomography or magnetic resonance imaging should be done as quickly as possible to diagnose spinal haematoma. A neurosurgeron or neurologist should be consulted as soon as the presence of a spinal haematoma is suspected. Factors related to recovery include the degree of neurological deficit at the time of treatment and the timing of surgical intervention.[168] Surgery within 12 h of symptoms results in the best chance of full recovery, even in patients who are initially paraplegic.

Conclusions

This review discusses the efficacy of new anticoagulants in different clinical syndromes and the studies that led to their approved FDA indications. Relevant pharmacokinetics of the anticoagulant drugs provide the foundation for safe perioperative use in terms of neuraxial injections and epidural catheter placement and removal. For patients without thrombotic risk factors included in the $CHADS_2VASC_2$ algorithm, five half-life intervals between discontinuation and neuraxial procedure are recommended. This can be shortened to two or three half-lives in patients at high risk for VTE or stroke. Alternatively, five half-life intervals can be observed in conjunction with LMWH bridge therapy. Adjustments should be made for patients with reduced CrCl. Anticoagulants can be resumed 24–48 h after a neuraxial procedure. In patients who are at risk for VTE or stroke, the drugs can be taken 24 h minus the time to peak effect of the drug. Prasugrel should be stopped 7 days before neuraxial injection, while 5 days are adequate for ticagrelor, and either drug can be restarted 24 h later. Careful evaluation of the patient and knowledge of the pharmacokinetics of these drugs should help clinicians decide, together with their respective pharmacy and therapeutics committees and haematology colleagues, the safe interval between discontinuation of anticoagulants, neuraxial injection, and their subsequent readministration.

Authors' contributions

H.T.B. reviewed the literature and wrote the initial manuscript. M.J.A., D.G., and R.O.B. reviewed the manuscript, reviewed the literature, and edited and approved the final manuscript.

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