European Heart Journal Advance Access published December 7, 2012

European Heart Journal
doi:10.1093/eurheartj/ehs408

REVIEW

New drugs

Acute management of bleeding in patients on novel oral anticoagulants

Deborah M. Siegal[1] and Mark A. Crowther[1,2]*

[1]Division of Hematology and Thromboembolism, Department of Medicine, McMaster University, Hamilton, Ont., Canada; and [2]Laboratory Medicine, St Joseph's Healthcare and Hamilton Health Sciences, Hamilton

Received 18 June 2012; revised 19 September 2012; accepted 11 October 2012

Novel oral anticoagulants that directly inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban) are currently available for prevention of venous thromboembolism (VTE) after orthopaedic surgery, treatment of acute VTE, and prevention of arterial thromboembolism in non-valvular atrial fibrillation. These agents offer advantages over VKAs, including rapid onset, shorter half-lives, fewer drug interactions, and lack of need for routine monitoring. However, there are no established agents to reverse their anticoagulant effect. We review the risk of bleeding with the novel oral anticoagulants and the limitations of conventional coagulation assays for measuring anticoagulant effect. We provide an approach to the management of patients with bleeding complications with evidence for various interventions for reversal, where available.

Keywords Novel oral anticoagulants • Bleeding • Management

Introduction

Novel oral anticoagulant agents that directly inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban) are currently available for the prevention and treatment of thromboembolism and have been shown to be more effective and/or safer than warfarin and low molecular weight heparin (LMWH) for some indications. Advantages of these agents include rapid onset of action, shorter half-lives, fewer drug interactions, and predictable pharmacokinetics that preclude the need for routine monitoring. However, there are no antidotes to reverse their anticoagulant effect. In this narrative review of novel oral anticoagulants, we summarize published rates of major bleeding, present the use and limitations of coagulation testing, review potential reversal agents, and provide an approach to the management of acute bleeding associated with their use.

Mechanism of action and pharmacokinetics

Thrombin and factor Xa are targets for anticoagulant treatment due to their important role in coagulation. Thrombin catalyses the final step in the coagulation cascade with conversion of fibrinogen to fibrin.[1,2] It amplifies its own production through feedback mechanisms and is a potent platelet activator. Factor Xa is an effector in the final common pathway of coagulation which, in conjunction with factor Va, mediates activation of prothrombin to thrombin.

Following oral administration, dabigatran etexilate is rapidly converted to dabigatran, which inhibits thrombin through interaction with its active site.[3] Plasma levels peak in 1.25–3 h.[4] It is excreted predominantly by the kidneys (80%) and has a half-life of 12–14 h.[4] Rivaroxaban selectively and competitively inhibits free and prothrombinase/clot-associated factor Xa through reversible interactions with its active site.[3] It achieves peak plasma levels ~2–4 h after oral administration.[5] It has a half-life of 9–13 h and is partially excreted by the kidneys (66%).[5,6] Apixaban is an oral, reversible, direct active-site inhibitor of free and clot-bound factor Xa.[7] It achieves peak plasma levels within 1–3 h after oral administration, has a half-life of 10–14 h, and is partially excreted by the kidneys (25%).[8,9]

Novel oral anticoagulants are substrates of the P-glycoprotein (P-gp) transport protein leading to important drug interactions with P-gp inhibitors (e.g. amiodarone, verapamil, ketoconazole, quinidine, clarithromycin, grapefruit juice) and inducers (e.g. carbamazepine, rifampicin, St John's wort, trazodone).[3,10] Rivaroxaban

* Corresponding author: Tel: +1 905 521 6024, Fax: +1 905 540 6568, Email: crowthrm@mcmaster.ca

and apixaban are metabolized by the CYP3A4 enzyme and co-administration of inhibitors (e.g. azole amtimycotic agents, HIV protease inhibitors) or inducers (e.g. phenytoin, rifampin, phenobarbital, carbamazepine) of this enzyme should be avoided.[7,10,11]

Indications for use

Dabigatran is approved for the prevention of arterial thromboembolic events in non-valvular atrial fibrillation (Europe, USA, Canada) and VTE prophylaxis following hip and knee-replacement surgery (Europe, Canada). Rivaroxaban is approved for stroke prevention in non-valvular atrial fibrillation (Europe, USA, Canada), prevention of VTE following hip and knee-replacement surgery (Europe, USA, Canada) and treatment of deep vein thrombosis (Europe, Canada). Apixaban is approved for stroke prevention in non-valvular atrial fibrillation (Europe) and VTE prevention after hip and knee replacement surgery (Europe, Canada).

Bleeding risk with novel oral anticoagulant use

Comparison of bleeding rates between agents is hampered by the lack of a common definition of major bleeding. In clinical trials of novel oral anticoagulants, major bleeding rates were generally low and comparable to (or lower than) those with LMWH or warfarin (*Table 1*). Differences in indication, drug dosage, duration of treatment, and patient characteristics likely account for variability across studies. For example, the study population in ROCKET AF (rivaroxaban) had a higher baseline thromboembolic risk profile (older age, worse renal function) compared with the RE-LY (dabigatran) and ARISTOTLE (apixaban) studies.[12–14]

A recent meta-analysis examined the safety and efficacy of novel oral anticoagulants compared with warfarin for prevention of stroke and systemic embolism in atrial fibrillation.[15] Patients receiving novel oral anticoagulants had a reduced risk of stroke and systemic embolism (RR 0.78, 95% CI 0.67–0.92) and all cause-mortality (RR 0.88, 95% CI 0.82–0.95), and a similar risk of major bleeding compared with those receiving warfarin (RR 0.88, 95% CI 0.71–1.09). Intracranial bleeding was reduced in patients receiving novel oral anticoagulants (RR 0.49, 95% CI 0.36–0.66).

Systematic large-scale documentation of novel oral anticoagulant use relative to other antithrombotic therapies is required to define bleeding risk outside the clinical trial setting.[16] Currently available post-marketing reporting databases lack comparative vitamin K antagonist (VKA) data and do not reflect the total number of patients receiving novel agents thereby limiting interpretation. In November 2011, the EudraVigilance database reported 256 post-marketing episodes of serious bleeding resulting in death associated with use of dabigatran worldwide.[17] The US Food and Drug Administration (FDA) recently concluded there is no evidence that bleeding rates are higher with dabigatran than seen with other anticoagulants.[18]

Several recently published case reports highlight physician concerns regarding the management of serious bleeding due to a lack of reversal agents.[19–23] However, the clinical impact of anticoagulant reversal in the event of serious bleeding is uncertain even when reversal agents are available such as for VKAs.[24–27]

Elderly patients

Age is an established risk factor for anticoagulant-associated bleeding.[28] Data regarding the impact of age on bleeding risk with novel agents are limited to subgroup analyses of large clinical trials not adequately powered to assess safety in the elderly. Patients >75 years receiving dabigatran (150 mg daily) for VTE prophylaxis following orthopaedic surgery had a similar risk of major bleeding compared with those receiving enoxaparin (40 mg once daily).[29] In the RE-LY study, patients ≥75 years receiving dabigatran 110 mg twice daily for prevention of stroke and systemic embolism in atrial fibrillation had a similar risk of extracranial bleeding, while those receiving dabigatran 150 mg twice daily had a trend towards increased extracranial bleeding compared with warfarin.[30] Dabigatran was associated with reduced risk of intracranial haemorrhage irrespective of age. Subgroup analyses of the ROCKET AF and ARISTOTLE trials showed no effect of age on bleeding risk.[12,14] While further studies are needed, regulatory agencies in Europe and Canada recommend dose reduction when using dabigatran in patients ≥80 years.[3,30]

Renal failure

Renal function, a predictor of bleeding with anticoagulant use in general, should be assessed prior to initiation of therapy with novel oral anticoagulants and monitored during treatment.[28,31] Monitoring is particularly important for dabigatran, which is excreted by the kidneys to a greater extent than rivaroxaban or apixaban.

Well-powered studies examining the impact of renal function on bleeding risk with novel oral anticoagulants are lacking. In a subgroup analysis of the RE-MODEL and RE-NOVATE data, patients with moderate renal impairment (CrCl 30–50 mL/min) taking dabigatran for VTE prophylaxis after orthopaedic surgery had fewer major bleeding events than those receiving enoxaparin (0% vs. 4.7%).[29] In atrial fibrillation trials, patients with moderate renal dysfunction (CrCl 30–50 mL/min) had increased bleeding rates irrespective of treatment with novel oral anticoagulants or warfarin.[13,14,32] In the ROCKET AF study, a reduced dose of rivaroxaban (15 mg once daily) was used for patients with moderate renal impairment due to pharmacokinetic considerations. Subgroup analyses of patients with CrCl 30–50 mL/min in the RE-LY and ROCKET AF studies showed a similar risk of bleeding with novel agents and warfarin.[13,32] In a subgroup analysis of the ARISTOTLE study, a greater reduction in major bleeding was seen in patients with CrCl 25–50 mL/min receiving apixaban.[14] Based on RE-LY study data, dose reduction of dabigatran is not currently recommended for patients with moderate renal impairment. However, subgroup analysis may lack sufficient power to detect differences and further well-powered studies are needed to determine the safety and efficacy of reduced doses in patients with moderate renal dysfunction. Patients with severe renal impairment (CrCl < 25–30 mL/min) were excluded from large clinical trials and should not receive novel oral anticoagulants.[12–14]

Table 1 Major bleeding rates in published clinical trials of dabigatran, rivaroxaban, and apixaban

Trial acronym First author	Indication	Criteria for major bleeding events	Dose of novel oral anticoagulant	Comparator	Treatment duration	Major bleeding events		Estimate of treatment effect (95% CI)
						Novel oral anticoagulant, %	Comparator, %	
Dabigatran								
Meta-analysis (RE-MODEL, RE-MOBILIZE, RE-NOVATE) Wolowacz *et al.*[81]	VTE prevention orthopaedic surgery	Clinically overt bleeding with ≥20 g/L fall in Hb or transfusion ≥2 units packed cells or whole blood Fatal bleeding Retroperitoneal, intracranial, intraocular, or intraspinal bleeding Bleeding warranting treatment cessation or reoperation	220 mg once daily	Enoxaparin 40 mg once daily or 30 mg twice daily	6–35 days	0.6 1.4 2.0	1.4 0.9 1.6	RR 0.42 (0.15–1.19) RR 1.14 (0.46–2.78) RR 1.29 (0.70–2.37) RR 0.94[a] (0.51–1.75)
RE-LY, Connolly *et al.*[13]	ATE prevention atrial fibrillation	Reduction in Hb ≥ 20 g/L Transfusion ≥ 2 units blood Symptomatic bleeding in a critical area or organ	110 mg twice daily 150 mg twice daily	Warfarin (INR 2–3) Warfarin (INR 2–3)	2 years (median)	2.7/year 3.1/year	3.4/year 3.4/year	RR 0.80 (0.69–0.93) RR 0.93 (0.81–1.07)
RE-COVER, Schulman *et al.*[82]	VTE acute treatment	ISTH major bleeding	150 mg twice daily	Warfarin (INR 2–3)	6 months	1.6	1.9	HR 0.82 (0.45–1.48)
Rivaroxaban								
RECORD 1–4, Turpie *et al.*[83]	VTE prevention orthopaedic surgery	Clinically overt bleeding: Fatal Involving a critical organ Necessitating re-operation Outside of the surgical site and associated with a fall in Hb ≥ 20 g/L, or required ≥ 2 units of blood	10 mg once daily	Enoxaparin 40 mg once daily or 30 mg twice daily	12 ± 2 days 30–35 day	0.3 0.4	0.2 0.2	OR 1.62 (0.77–3.53) HR 1.84 (0.94–3.62)
ROCKET AF, Patel *et al.*[12]	ATE prevention atrial fibrillation	ISTH major bleeding and/or bleeding causing permanent disability	20 mg once daily	Warfarin (INR 2–3)	707 days	3.6/year	3.4/year	HR 1.04 (0.90–1.20)
EINSTEIN, Bauersachs *et al.*[84]	DVT acute treatment	ISTH major bleeding	15 mg twice daily for 3 weeks then 20 mg daily	Enoxaparin 1 mg/kg twice daily then VKA (INR 2–3)	3, 6, or 12 months	0.8	1.2	HR 0.65 (0.33–1.30)

Continued

Table 1 *Continued*

Trial acronym First author	Indication	Criteria for major bleeding events	Dose of novel oral anticoagulant	Comparator	Treatment duration	Major bleeding events		Estimate of treatment effect (95% CI)
						Novel oral anticoagulant, %	Comparator, %	
	DVT continued treatment		20 mg daily	Placebo	6 or 12 months	0.7	0	—
EINSTEIN-PE, Buller *et al.*[85]	PE acute treatment	ISTH major bleeding	15 mg twice daily for 3 weeks then 20 mg daily	Enoxaparin 1 mg/kg twice daily then VKA (INR 2–3)	3, 6, or 12 months	1.1	2.2	HR 0.49 (0.31–0.79)
Agnelli *et al.*[86]	VTE acute treatment	ISTH major bleeding	10 mg twice daily 20 mg twice daily 30 mg twice daily 40 mg daily	Enoxaparin 1 mg/kg twice daily then VKA (INR 2–3)	12 weeks	1.7 1.7 3.3 1.7	0	—
ATLAS ACS 2, Mega *et al.*[36]	ACS secondary prevention	TIMI major bleeding	2.5 mg twice daily 5 mg twice daily	Placebo	13 months (mean)	2.1 (combined)	0.6	HR 3.96 (2.46–6.38)
Apixaban								
ADVANCE-1, Lassen *et al.*[87]	VTE prevention orthopaedic surgery	Acute clinically overt bleeding with ≥1 of: Decrease in Hb ≥ 20 g/L in 24 h Transfusion ≥ 2 units of packed red cells Bleeding at a critical site (i.e. intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding) Bleeding into operated joint, requiring an additional operation or intervention Intramuscular bleeding with compartment syndrome Fatal bleeding Acute clinically overt bleeding with ≥1 of:	2.5 mg twice daily	Enoxaparin 30 mg twice daily	10–14 days	0.7	1.4	RR 0.50[c] (0.24–1.01)

ADVANCE-2, Lassen *et al.*[88]	VTE prevention orthopaedic surgery	Decrease in Hb ≥ 20 g/L in 24 h Transfusion ≥ 2 units packed red blood cells Bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding) Bleeding into operated joint, needing reoperation or intervention Intramuscular bleeding with compartment syndrome Fatal bleeding	2.5 mg twice daily	Enoxaparin 40 mg once daily	10–14 days	0.6	0.9	RR 0.65[c] (0.29–1.45)
ADVANCE-3, Lassen *et al.*[89]	VTE prevention orthopaedic surgery	Acute, clinically overt bleeding with ≥1 of: Decrease in Hb ≥ 20 g/L in 24 h Transfusion ≥ 2 units packed red cells Bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, and retroperitoneal bleeding) Bleeding into operated joint, necessitating reoperation or intervention Intramuscular bleeding with the compartment syndrome Fatal bleeding	2.5 mg twice daily	Enoxaparin mg once daily	35 days	0.8	0.7	RR 1.21[c] (0.65–2.26)
AVERROES, Connolly *et al.*[90]	ATE prevention atrial fibrillation	ISTH major bleeding	5 mg twice daily	Aspirin (81 to 324 mg daily)	1.1 year (mean)	1.4/year	1.2/year	HR 1.13 (0.74–1.75)
ARISTOTLE, Granger *et al.*[14]	ATE prevention atrial fibrillation	ISTH major bleeding	5 mg twice daily	Warfarin (INR 2–3)	1.8 years (median)	2.1/year	3.1/year	HR 0.69 (0.60–0.80)
APPRAISE-2, Alexander *et al.*[37]	ACS secondary prevention	TIMI major bleeding ISTH major bleeding	5 mg twice daily	Placebo	240 days (median)[b]	TIMI: 2.4/year ISTH: 5.1/year	TIMI:0.9/year ISTH: 2.0year	HR 2.59 (1.50–4.46) HR 2.48 (1.72–3.58)

Continued

Table 1 *Continued*

Trial acronym First author	Indication	Criteria for major bleeding events	Dose of novel oral anticoagulant	Comparator	Treatment duration	Major bleeding events		Estimate of treatment effect (95% CI)
						Novel oral anticoagulant, %	Comparator, %	
ADOPT, Goldhaber *et al.*[91]	VTE prevention medically ill patients	Fatal bleeding Overt with ≥1 of the following: Decrease in Hb ≥ 20 g/L over 24 h Transfusion ≥ 2 units of packed red cells Intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding Bleeding that occurred in an operated joint that required reoperation or intervention Intramuscular bleeding with the compartment syndrome	2.5 mg twice daily	Enoxaparin 40 mg once daily	Apixaban 30 days Enoxaparin 6–14 days	0.5	0.2	RR 2.58 (1.02–7.24)
Levine *et al.*[92b]	VTE prevention in cancer patients receiving chemotherapy	ISTH major bleeding	5 mg once daily 10 mg once daily 20 mg once daily	Placebo	12 weeks	0 0 6.3	3.4	— — RR 1.81[c] (0.25–13.5)

Major bleeding events associated with the use of dabigatran, rivaroxaban, and apixaban as published in completed clinical trials.
ACS, acute coronary syndrome; ATE, arterial thromboembolism; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; OR, odds ratio; PE, pulmonary embolism; RR, relative risk; TIMI, Thrombolysis in Myocardial Infarction; VKA, vitamin K antagonist; VTE, venous thromboembolism.
ISTH major bleeding in non-surgical patients: fatal bleeding, and/or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin levels of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.[93]
TIMI major bleeding: fatal bleeding, and/or intracranial bleeding, and/or clinically overt bleeding associated with a fall in Hb ≥ 50 g/L.[94]
[a]Random effects analysis.
[b]Trial stopped early due to slow accrual.
[c]For studies which did not report an estimate of treatment effect, relative risk and 95% CIs were calculated using previously described methods.[95,96]

Concurrent use of antiplatelet agents

Limited data suggest that aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) may not increase bleeding in patients receiving dabigatran for VTE prophylaxis; in a *post-hoc* analysis of pooled data from the RE-MOBILIZE, RE-MODEL, and RE-NOVATE studies, patients receiving dabigatran and concomitant aspirin (<160 mg/day) or NSAIDs (half-life < 12 h) had a similar risk of major bleeding as those receiving dabigatran alone.[33]

When given in addition to therapeutic doses of dabigatran in patients with atrial fibrillation in the RE-LY study, aspirin increased the risk of intracranial bleeding (RR 1.6).[34] In the phase II dose-finding PETRO trial, aspirin used in conjunction with dabigatran for stroke prevention in atrial fibrillation increased the risk of bleeding events in the group receiving doses of dabigatran higher than those currently approved (300 mg twice daily).[35] There was no increased risk of bleeding when aspirin was added to lower doses of dabigatran (50 mg or 150 mg), but these analyses were limited by small sample size.

In patients with acute coronary syndrome, the addition of apixaban and rivaroxaban to dual antiplatelet therapy (aspirin and clopidogrel) increased the risk of major bleeding.[36,37] However, there may be clinical benefit with concomitant therapy as shown by decreased cardiovascular mortality (HR 0.66; 95%CI 0.51–0.86) and all-cause mortality (HR 0.68; 95%CI 0.53–0.87) with rivaroxaban 2.5 mg twice daily compared with placebo in the ATLAS ACS 2 trial.[36]

Coagulation testing

Emergency situations (e.g. haemorrhage, overdose, urgent surgery/invasive procedure) necessitate rapid assessment of coagulation status. However, conventional coagulation assays have limitations when used to measure novel oral anticoagulant effect. Modified conventional tests and alternative assays have increased reliability and accuracy, but are not standardized or routinely available. *Table 2* shows the effect of novel oral anticoagulants on coagulation tests.

Dabigatran prolongs the activated partial thromboplastin time (aPTT) and thrombin clotting time (TCT, also known as thrombin time or TT).[38–40] However, the aPTT varies with reagents used and does not accurately reflect the amount of dabigatran present.[39,40] The TCT assay is the most effective test for detecting the presence of dabigatran, even in small quantities. It has a linear relationship with dabigatran concentration, but rapidly prolongs beyond the normal detection limits and is not routinely available.[38] The ecarin clotting time uses a viper-venom-derived metalloprotease to determine the activity of direct thrombin inhibitors, but is not standardized or widely available.[41,42] A commercial dabigatran calibrator, the Hemoclot direct thrombin inhibitor assay (HYPHEN BioMed, Neuville Sur Oise, France), provides accurate, reproducible measures of dabigatran anticoagulant activity and plasma concentrations using a dilute TT test in conjunction with a dabigatran calibration curve.[43] It is licensed and approved for clinical use in Europe and Canada, but is approved only for research purposes in the USA.[44] The prothrombin time (PT) has low sensitivity for measuring the effects of dabigatran and is not recommended for this purpose; however, a prolonged PT reliably predicts the presence of dabigatran in quantities sufficient to produce an anticoagulant effect.[4,9,41]

For rivaroxaban, the PT is useful for detecting the presence of drug if prolonged; however, the assay is not sensitive at low concentrations and the degree of prolongation does not reliably predict the amount of drug present.[45–47] The relationship between drug concentration and PT prolongation is influenced by the reagents used for testing. Commercially available chromogenic anti-factor Xa assays can be used to measure rivaroxaban levels, but sensitivity varies between assays.[41,46] When used with a rivaroxaban calibration curve, chromogenic anti-factor Xa assays are sensitive and specific for rivaroxaban plasma concentrations.[48]

Apixaban may prolong the PT, but this assay lacks sensitivity in comparison to the dilute PT test (or modified PT).[41,49] The HepTest (American Diagnostica), a commercially available clot-based anti-Factor Xa assay, is more sensitive than the PT and equally sensitive as the dilute PT to apixaban.[41,49] Chromogenic anti-factor Xa assays also provide more accurate apixaban levels compared with the PT.[46]

Levels of all of the novel agents can be determined using chemical techniques such as liquid chromatography–mass spectrometry.[8,50,51] These techniques are available only in selected biochemistry laboratories.

Despite their limitations, conventional coagulation assays may provide qualitative information regarding the presence of drug. A normal TCT in patients receiving dabigatran, normal PT in patients receiving rivaroxaban, and normal anti-factor Xa activity in patients receiving apixaban suggest very low drug levels and intact haemostatic function. Although it is less precise, aPTT can be used to determine dabigatran effect if TCT testing is unavailable. Test results should be interpreted relative to the time of drug administration and pharmacokinetics. Further research studies are required to confirm the predictive ability of these tests in the clinical setting. In the interim, procedures should be delayed, if possible, depending on procedural bleeding risk, drug pharmacokinetics, and renal function. Procedures with standard bleeding risk (e.g. uncomplicated laparoscopic procedures, colonoscopy without polyp removal) should be delayed 24 h in patients with normal renal function.[52] A longer delay should be implemented for patients with impaired renal function (2–4 days) and/or procedures with high risk of bleeding (2–6 days; e.g. major cardiac surgery, epidural or spinal anaesthesia, neurosurgery, pacemaker/defibrillator insertion).[38,52,53] Recently published data from the RE-LY study showed similar major bleeding event rates in patients requiring discontinuation of dabigatran or warfarin for invasive procedures (dabigatran 110 mg: HR 0.79, 95% CI 0.35–1.79; dabigatran 150 mg: HR 1.20, 95% CI 0.55–2.60) using a dabigatran discontinuation algorithm based on procedural bleeding risk and renal function.[54]

Anticoagulant reversal strategies

Specific reversal agents

A monoclonal antibody targeted against dabigatran is currently under development. It potently and specifically inhibited dabigatran anticoagulant activity in human plasma *in vitro* and in rats *in vivo*.[55]

Table 2 Effect of novel oral anticoagulants on commonly used coagulation tests

Novel anticoagulant	Prothrombin time (PT)	Activated partial thromboplastin time (aPTT)	Thrombin clotting time (TCT)	Ecarin clotting time	Haemoclot assay	Anti-factor Xa activity	
						Clot-based	Chromogenic
Dabigatran	↑ or no change (low sensitivity, varies with reagents)	↑ (varies with reagents)	↑	↑	↑[a]	↑	ND
Rivaroxaban	↑ or no change (not sensitive at low concentrations, varies with reagents)	↑ or no change (less sensitive than PT)	—	—	—	↑	↑[a] (sensitive and specific when calibration curve used)
Apixaban	↑ or no change (other tests more sensitive, may vary with reagents)	↑ or no change (other tests more sensitive, may vary with reagents)	—	—	—	↑[a]	↑[a]

ND, no data.
[a]Preferred test. Adapted from previously published review articles.[41,59]

Plasma-derived and recombinant factor Xa (pd-factor Xa and r-factor Xa) which lack catalytic and membrane-binding activity are being investigated as antidotes for factor Xa inhibitors.[56,57] Preliminary studies showed that both pd-factor Xa and r-factor Xa are capable of neutralizing the coagulation test abnormalities induced by rivaroxaban and apixaban *in vitro* and in animal models.[56,57]

Coagulation factor replacement

To our knowledge, there are no data regarding the use of fresh frozen plasma (FFP) in patients with novel oral anticoagulant associated bleeding. In mice receiving high-dose dabigatran, FFP reduced the volume of intracerebral haemorrhage, but had no effect on mortality.[58] FFP carries risks of volume overload and, rarely, allergic reactions, and infection.[59]

Prothrombin complex concentrates (PCC) contain high doses of vitamin K-dependent coagulation factors and variable amounts of proteins C and S. Four-factor PCC (factors II, VII, IX, X) is commercially available in Europe and Canada, while 3-factor PCC (factors II, IX, X) is licensed for use in the USA. In healthy volunteers, a high dose of 4-factor PCC (50 U/kg) reversed PT prolongation due to rivaroxaban, but did not correct aPTT prolongation due to dabigatran.[60] It is unclear whether correction of laboratory tests would correspond to amelioration of bleeding. In animal models, high-dose 4-factor PCC reduced intracranial haematoma expansion and 24 h mortality in mice pre-treated with dabigatran.[58] Administration of 4-factor PCC to rivaroxaban-treated rabbits resulted in partial correction of laboratory parameters, but no correction of bleeding.[61] PCC improved thrombin generation indices following the addition of apixaban *in vitro* to aliquots of blood from healthy donors.[62] While there is no clinical evidence to support its use, a dose of 50 IU/kg of 4-factor PCC might be reasonable for severe/life-threatening bleeding in patients taking novel oral anticoagulants.[52]

PCC use is associated with an increased risk of thrombosis. A meta-analysis of observational studies found a 1.4% incidence of thromboembolic events in VKA-treated patients receiving PCC for bleeding or urgent surgical procedures.[63]

Prohaemostatic agents

Recombinant activated factor VII (rVIIa) was developed for the treatment of bleeding episodes in haemophiliac patients with inhibitors to factors VIII and IX.[64] It has been used outside of its approved indication as a potential treatment of severe/life-threatening bleeding in non-haemophiliac patients with mixed results.[64–67] There is concern regarding thrombogenicity in non-haemophiliac patients.[67,68] In a meta-analysis, arterial thromboembolic events were increased in non-haemophiliac patients treated with rVIIa compared with placebo (4.5 vs. 2.0%).[69] As a result, the FDA issued a black box warning regarding the use of rVIIa outside its approved indications.[70]

RVIIa has no demonstrated efficacy for reversing bleeding complications associated with novel oral anticoagulants. In healthy volunteer subjects receiving the oral direct thrombin inhibitor melagatran, rVIIa had no effect on aPTT, thrombin generation, and platelet activation.[71] In an animal model, rVIIa failed to stabilize induced intracerebral haematoma expansion in mice receiving dabigatran.[58] Similarly, a randomized controlled animal model showed that rVIIa did not reverse bleeding and only partially corrected laboratory abnormalities induced by rivaroxaban.[61] RVIIa improved thromboelastometry parameters after the addition of apixaban *in vitro* to blood from healthy donors.[62] These results provide little support for the use of rVIIa to reverse bleeding associated with the novel oral anticoagulants. Because no human studies have been conducted to date, it is unclear whether this therapy is of benefit in emergent anticoagulant reversal.

Activated PCC [aPCC, commercially available as factor eight inhibitor bypassing activity (FEIBA), Baxter Bioscience, Vienna, Austria] is a coagulation complex containing factors II, VII, IX, and X which are activated during the manufacturing process.[72] Like rVIIa, aPCC was developed for haemostatic control in haemophiliac patients with inhibitors to factors VIII or IX.[72] Activated

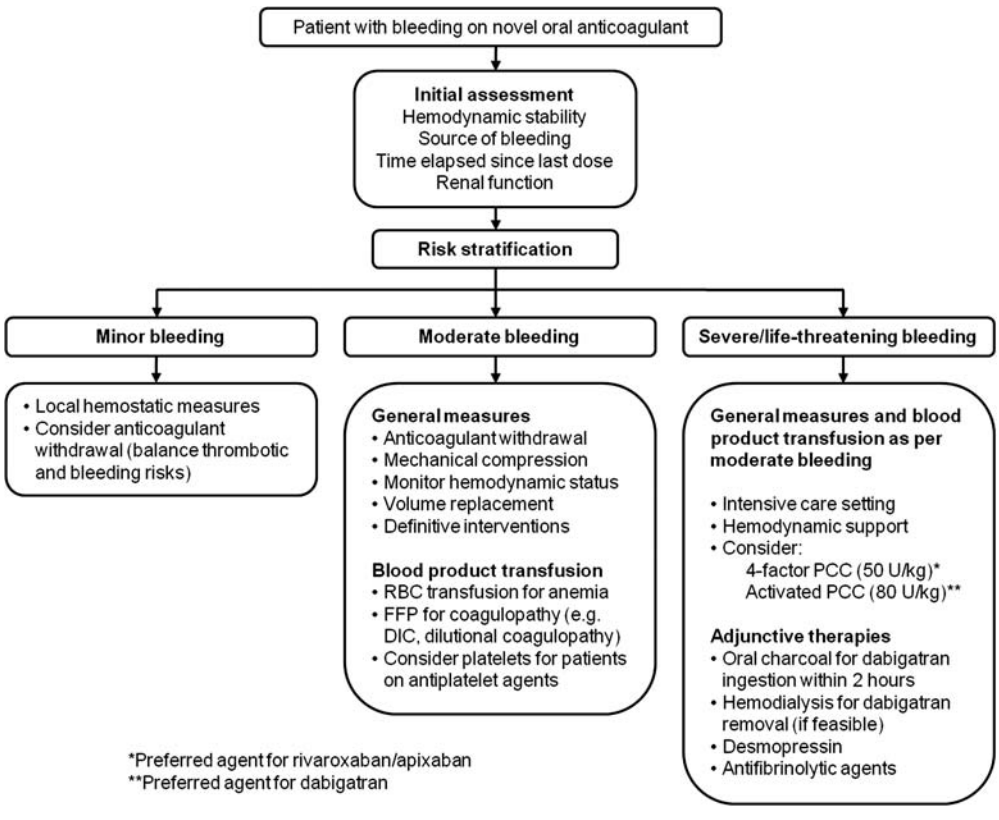

Figure 1 Suggested management of acute bleeding in patients taking novel oral anticoagulants

PCC has been shown to correct the anticoagulant effect of high-dose rivaroxaban in animal models.[73,74] In human plasma incubated with dabigatran, aPCC reduced clot initiation time *in vitro*.[75] Even at low doses (75–80 U/kg), aPCC corrected thrombin generation parameters *in vitro* in plasma from healthy volunteers receiving single doses of rivaroxaban or dabigatran and in blood from healthy volunteers following the addition of apixaban.[62,76]

Activated PCC safety data are limited to pharmacovigilance studies in haemophilia patients showing a low risk of thrombosis (4–8 per 10^5 infusions).[77,78] However, a majority of thrombotic events (81%) occurred in patients with risk factors for thrombosis raising concerns about applying these data to non-haemophiliac patients requiring anticoagulant therapy for thrombosis prevention or treatment.[77,79]

Oral activated charcoal

An *in vitro* model using dabigatran suspended in acidic water demonstrated absorption of >99.9% of drug after the addition of activated charcoal, suggesting it may be effective for reducing dabigatran absorption following recent ingestion.[38] To our knowledge, there are no data regarding the use of oral activated charcoal with rivaroxaban or apixaban.

Haemodialysis

Acute haemodialysis can be considered for removal of dabigatran in cases of severe bleeding, or in patients with renal impairment. In patients with end-stage renal disease up to 68% of active dabigatran was removed after 4 h of haemodialysis.[80] Rivaroxaban and apixaban may not be dialysable due to a high degree of protein binding.[7,11] Charcoal haemoperfusion removes highly protein-bound drugs; however, this intervention is not evidence-based, has limited availability and should only be considered in the context of a clinical trial.

Adjunctive therapies

There are no clinical data regarding the efficacy of desmopressin (DDAVP) and antifibrinolytic agents (tranexamic acid and ε-aminocaproic acid) for the reversal of bleeding with the novel oral anticoagulants. They may be considered as adjunctive therapies in the event of severe bleeding. Use of desmopressin requires close monitoring of serum electrolytes as it is associated with clinically significant hyponatraemia which may lead to seizures.

Suggested management of the actively bleeding patient

Figure 1 provides a suggested approach to the management of acute bleeding in patients receiving novel oral anticoagulants. Actively bleeding patients should undergo rapid assessment with attention to haemodynamic stability and identification of bleeding source followed by risk stratification. Time elapsed since last

dose and renal function (particularly for dabigatran) should be ascertained as they may influence the threshold for implementation of interventions described subsequently.

Minor bleeding (e.g. epistaxis, ecchymosis, menorrhagia) should be managed using local haemostatic measures. A short period of anticoagulant withdrawal may be considered, but should be balanced against individual thromboembolic risk and followed by re-initiation of drug.

In the event of moderate bleeding (e.g. upper or lower gastrointestinal bleeding), anticoagulants should be discontinued. An extended period of withdrawal may be required depending on the feasibility of local or mechanical haemostasis. Patients should be monitored for deterioration and referred for definitive haemostatic interventions. The addition of a low-dose parenteral anticoagulant may be considered for patients at high risk of thromboembolic events.

Severe/life-threatening bleeding requires transfer to an intensive care setting with provision of life-supporting therapies (e.g. volume replacement, vasopressors, mechanical ventilation) as required. Urgent referral should be made for procedural or surgical haemostasis. Anticoagulant medications should be withdrawn and haemostatic function and complete blood count assessed. Packed red blood cells (PRBC) should be transfused in response to actual or expected severe anaemia. Coagulation factor replacement with FFP should be administered to patients in whom coagulation factor levels are abnormally low (e.g. dilutional coagulopathy, disseminated intravascular coagulation). Platelet transfusions can be given to patients receiving concurrent antiplatelet therapies. A pro-haemostatic agent may be a reasonable addition to maximum supportive therapies for severe/life-threatening bleeding. Based on available and methodologically limited data, we recommend 4-PCC (50 IU/kg) over aPCC (80 U/kg) for rivaroxaban or apixaban. For dabigatran, aPCC (80 U/kg) is preferred over 4-PCC (50 IU/kg). We acknowledge a lack of clinical data to guide the use of these agents and recommend consideration of the increased thrombosis risk prior to administration. Adjunctive therapies such as desmopressin or antifibrinolytic agents may be added. Haemodialysis can be considered for dabigatran removal if practically feasible.

Summary

The novel oral anticoagulants which directly inhibit thrombin (dabigatran) or factor Xa (rivaroxaban and apixaban) have significant advantages over VKAs and LMWH for the prevention and treatment of thromboembolism. Use of novel oral anticoagulants may avoid bleeding complications in some patients such as those with atrial fibrillation in whom intracranial haemorrhage is significantly reduced with these agents. However, there are no specific antidotes to reverse their anticoagulant effect in the event of bleeding. Currently, there is a paucity of clinical evidence regarding the efficacy of therapies such as FFP, PCC, aPCC, and rVIIa. However, administration of a 4-factor PCC or aPCC may be a reasonable addition to maximum supportive measures in cases of severe/life-threatening bleeding associated with these agents. Further studies are needed to clarify the role of these treatments, and others, for the reversal of the novel oral anticoagulants and management of bleeding complications. In the interim, aggressive supportive management and prompt consideration of procedural/surgical haemostatic intervention remain the mainstays of treatment.

Conflicts of interest: D.M.S. has no conflict of interest to declare. M.A.C. has sat on advisory boards for Leo Pharma, Pfizer, Bayer, Boehringer Ingelheim, Alexion, CSL Behring, and Artisan Pharma. M.A.C. has prepared educational materials for Pfizer, Octapharm, and CSL Behring. M.A.C. has provided expert testimony for Bayer. M.A.C. holds a Career Investigator award from the Heart and Stroke Foundation of Canada, and the Leo Pharma Chair in Thromboembolism Research at McMaster University. M.A.C.'s institution has received funding for research projects from Boehringer Ingelheim, Octapharm, Pfizer, and Leo Pharma.

References

1. Gross PL, Weitz JI. New antithrombotic drugs. *Clin Pharmacol Ther* 2009;**86**:139–146.
2. Weitz JI. Factor Xa or thrombin: is thrombin a better target? *J Thromb Haemost* 2007(Suppl. 1);**5**:65–67.
3. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e44S–e88S.
4. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* 2007;**64**:292–303.
5. Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor—after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 2005;**61**:873–880.
6. Garcia D, Libby E, Crowther MA. The new oral anticoagulants. *Blood* 2010;**115**:15–20.
7. Bristol-Myers Squibb. Eliquis Product Monograph. 2011. http://www.bmscanada.ca/static/products/en/pm_pdf/Eliquis_EN_PM.pdf. (12 May 2012).
8. Raghavan N, Frost CE, Yu Z, He K, Zhang H, Humphreys WG, Pinto D, Chen S, Bonacorsi S, Wong PC, Zhang D. Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos* 2009;**37**:74–81.
9. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor xa inhibitors in development. *Clin Pharmacokinet* 2009;**48**:1–22.
10. Lexi-Comp Online™. Lexi-Interact™ Online. Lexi-Comp, Inc., Hudson, OH, USA, 2012 (10 June 2012).
11. Bayer PHarma AG. Xarelto Summary of Product Characteristics. 2011. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf (12 May 2012).
12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
13. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
14. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
15. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. *Am J Cardiol* 2012;**110**:453–460.
16. Eikelboom JW, Quinlan DJ, Connolly SJ, Hart RG, Yusuf S. Dabigatran efficacy-safety assessment for stroke prevention in patients with atrial fibrillation. *J Thromb Haemost* 2012;**10**:966–968.
17. EudraVigilance Database, European Medicines Agency. http://eudravigilance.ema.europa.eu/human/index.asp (12 May 2012).
18. FDA Drug Safety Communication: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate

mesylate), U.S. Food and Drug Administration. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm Accessed November 25, 2012.
19. Cano EL, Miyares MA. Clinical challenges in a patient with dabigatran-induced fatal hemorrhage. *Am J Geriatr Pharmacother* 2012;**10**:160–163.
20. Truumees E, Gaudu T, Dieterichs C, Geck M, Stokes J. Epidural hematoma & intra-operative hemorrhage in a spine trauma patient on Pradaxa(R) [Dabigatran]. *Spine (Phila Pa 1976)* 2012;**37**:E863–E865.
21. Cotton BA, McCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. *N Engl J Med* 2011;**365**:2039–2040.
22. Harper P, Young L, Merriman E. Bleeding risk with dabigatran in the frail elderly. *N Engl J Med* 2012;**366**:864–866.
23. Legrand M, Mateo J, Aribaud A, Ginisty S, Eftekhari P, Huy PT, Drouet L, Payen D. The use of dabigatran in elderly patients. *Arch Intern Med* 2012;**171**:1285–1286.
24. Kalina M, Tinkoff G, Gbadebo A, Veneri P, Fulda G. A protocol for the rapid normalization of INR in trauma patients with intracranial hemorrhage on prescribed warfarin therapy. *Am Surg* 2008;**74**:858–861.
25. Goldstein JN, Thomas SH, Frontiero V, Joseph A, Engel C, Snider R, Smith EE, Greenberg SM, Rosand J. Timing of fresh frozen plasma administration and rapid correction of coagulopathy in warfarin-related intracerebral hemorrhage. *Stroke* 2006;**37**:151–155.
26. Mountain D, Sistenich V, Jacobs IG. Characteristics, management and outcomes of adults with major trauma taking pre-injury warfarin in a Western Australian population from 2000 to 2005: a population-based cohort study. *Med J Aust* 2010;**193**:202–206.
27. Chapman SA, Irwin ED, Beal AL, Kulinski NM, Hutson KE, Thorson MA. Prothrombin complex concentrate versus standard therapies for INR reversal in trauma patients receiving warfarin. *Ann Pharmacother* 2011;**45**:869–875.
28. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn). *Chest* 2008;**133**:257S–298S.
29. Dahl OE, Kurth AA, Rosencher N, Noack H, Clemens A, Eriksson BI. Thromboprophylaxis with dabigatran etexilate in patients over seventy-five years of age with moderate renal impairment undergoing or knee replacement. *Int Orthop* 2012;**36**:741–748.
30. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HC, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;**123**:2363–2372.
31. Limdi NA, Limdi MA, Cavallari L, Anderson AM, Crowley MR, Baird MF, Allon M, Beasley TM. Warfarin dosing in patients with impaired kidney function. *Am J Kidney Dis* 2010;**56**:823–831.
32. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, Paolini JF, Hankey GJ, Mahaffey KW, Patel MR, Singer DE, Califf RM. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011;**32**:2387–2394.
33. Friedman RJ, Kurth A, Clemens A, Noack H, Eriksson BI, Caprini JA. Dabigatran etexilate and concomitant use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid in patients undergoing total hip and total knee arthroplasty: no increased risk of bleeding. *Thromb Haemost* 2012;**108**.
34. Hart RG, Diener HC, Yang S, Connolly SJ, Wallentin L, Reilly PA, Ezekowitz MD, Yusuf S. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY Trial. *Stroke* 2012;**43**:1511–1517.
35. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, Pedersen KE, Lionetti DA, Stangier J, Wallentin L. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol* 2007;**100**:1419–1426.
36. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**366**:9–19.
37. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, Huber K, Liaw D, Husted SE, Lopez-Sendon J, De Caterina R, Jansky P, Darius H, Vinereanu D, Cornel JH, Cools F, Atar D, Leiva-Pons JL, Keltai M, Ogawa H, Pais P, Parkhomenko A, Ruzyllo W, Diaz R, White H, Ruda M, Geraldes M, Lawrence J, Harrington RA, Wallentin L. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011;**365**:699–708.
38. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A. Dabigatran etexilate–a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010;**103**:1116–1127.
39. Lindahl TL, Baghaei F, Blixter IF, Gustafsson KM, Stigendal L, Sten-Linder M, Strandberg K, Hillarp A. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. *Thromb Haemost* 2011;**105**:371–378.
40. Freyburger G, Macouillard G, Labrouche S, Sztark F. Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: two observational studies in patients undergoing total hip or total knee replacement. *Thromb Res* 2011;**127**:457–465.
41. Samama MM, Guinet C. Laboratory assessment of new anticoagulants. *Clin Chem Lab Med* 2011;**49**:761–772.
42. Nowak G. The ecarin clotting time, a universal method to quantify direct thrombin inhibitors. *Pathophysiol Haemost Thromb* 2003;**33**:173–183.
43. Stangier J, Feuring M. Using the HEMOCLOT direct thrombin inhibitor assay to determine plasma concentrations of dabigatran. *Blood Coagul Fibrinolysis* 2012;**23**:138–143.
44. Aniara. Dabigatran (Pradaxa) Plasma Calibrator Package Insert, 2011. http://www.aniara.com/pdf/INS-A222801.pdf. (12 May 2012).
45. Hillarp A, Baghaei F, Fagerberg Blixter I, Gustafsson KM, Stigendal L, Sten-Linder M, Strandberg K, Lindahl TL. Effects of the oral, direct factor Xa inhibitor rivaroxaban on commonly used coagulation assays. *J Thromb Haemost* 2011;**9**:133–139.
46. Barrett YC, Wang Z, Frost C, Shenker A. Clinical laboratory measurement of direct factor Xa inhibitors: anti-Xa assay is preferable to prothrombin time assay. *Thromb Haemost* 2010;**104**:1263–1271.
47. Samama MM, Martinoli JL, LeFlem L, Guinet C, Plu-Bureau G, Depasse F, Perzborn E. Assessment of laboratory assays to measure rivaroxaban—an oral, direct factor Xa inhibitor. *Thromb Haemost* 2010;**103**:815–825.
48. Samama MM, Contant G, Spiro TE, Perzborn E, Guinet C, Gourmelin Y, Le Flem L, Rohde G, Martinoli JL. Evaluation of the anti-factor Xa chromogenic assay for the measurement of rivaroxaban plasma concentrations using calibrators and controls. *Thromb Haemost* 2012;**107**:379–387.
49. Wong PC, Crain EJ, Xin B, Wexler RR, Lam PY, Pinto DJ, Luettgen JM, Knabb RM. Apixaban, an oral, direct and highly selective factor Xa inhibitor: in vitro, antithrombotic and antihemostatic studies. *J Thromb Haemost* 2008;**6**:820–829.
50. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos* 2008;**36**:386–399.
51. Rohde G. Determination of rivaroxaban–a novel, oral, direct Factor Xa inhibitor–in human plasma by high-performance liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2008;**872**:43–50.
52. Schulman S, Crowther MA. How I anticoagulate in 2012, new and old anticoagulant agents, and when and how to switch. *Blood* 2012.
53. Boehringer Ingelheim International GmbH. Pradaxa Summary of Product Characteristics, 2011. http://spaf.pradaxa.com/content/dam/internet/chc/pradaxa/com_COPY/documents/SmPC%20English%20version%20anx_104049_en_04Aug2011.pdf (10 June 2012).
54. Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S, Themeles E, Heidbuchle H, Avezum A, Reilly P, Connolly SJ, Yusuf S, Ezekowitz M. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation* 2012;**126**:343–348.
55. Van Ryn J, Litzenburger T, Waterman A, Canada K, Hauel N, Kroe-Barrett R, Singh S, Park J. Dabigatran anticoagulant activity is neutralized by an antibody selective to dabigatran in in vitro and in vivo models. *J Am Coll Cardiol* 2011;**57**:E1130.
56. Lu G, DeGuzman FR, Lakhotia S, Hollenbach SJ, Phillips DR, Sinha U. Recombinant antidote for reversal of anticoagulation by factor Xa inhibitors. *ASH Annual Meeting Abstracts* 2008;**112**:983.
57. Lu GP, Peng L, Hollenbach SJ, Abe K, DeGuzman FR, Siu G, Hutchaleelaha A, Inagaki M, Conley PB, Phillips DR, Sinha U. Reconstructed recombinant factor Xa as an antidote to reverse anticoagulation by factor Xa inhibitors. *J Thromb Haemost* 2009;**7**:309.
58. Zhou W, Schwarting S, Illanes S, Liesz A, Middelhoff M, Zorn M, Bendszus M, Heiland S, van Ryn J, Veltkamp R. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. *Stroke* 2011;**42**:3594–3599.
59. Crowther MA, Warkentin TE. Managing bleeding in anticoagulated patients with a focus on novel therapeutic agents. *J Thromb Haemost* 2009;**7**(Suppl. 1):107–110.
60. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;**124**:1573–1579.
61. Godier A, Miclot A, Le Bonniec B, Durand M, Fischer AM, Emmerich J, Marchand-Leroux C, Lecompte T, Samama CM. Evaluation of prothrombin

complex concentrate and recombinant activated factor VII to reverse rivaroxaban in a rabbit model. *Anesthesiology* 2012;**116**:94–102.
62. Escolar G, Arellano-Rodrigo E, Reverter JC, Villalta J, Sanz V, Molina P, Diaz-Ricart M, Galan AM. Reversal of apixaban induced alterations of hemostasis by different coagulation factor concentrates: studies in vitro with circulating human blood. *Circulation* 2012;**126**:520–521.
63. Dentali F, Marchesi C, Pierfranceschi MG, Crowther M, Garcia D, Hylek E, Witt DM, Clark NP, Squizzato A, Imberti D, Ageno W. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost* 2011;**106**:429–438.
64. Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 2004;**104**:3858–3864.
65. MacLaren R, Weber LA, Brake H, Gardner MA, Tanzi M. A multicenter assessment of recombinant factor VIIa off-label usage: clinical experiences and associated outcomes. *Transfusion* 2005;**45**:1434–1442.
66. Fishman PE, Drumheller BC, Dubon ME, Slesinger TL. Recombinant activated factor VII use in the emergency department. *Emerg Med J* 2008;**25**:625–630.
67. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008;**358**:2127–2137.
68. Diringer MN, Skolnick BE, Mayer SA, Steiner T, Davis SM, Brun NC, Broderick JP. Risk of thromboembolic events in controlled trials of rFVIIa in spontaneous intracerebral hemorrhage. *Stroke* 2008;**39**:850–856.
69. Hsia CC, Chin-Yee IH, McAlister VC. Use of recombinant activated factor VII in patients without hemophilia: a meta-analysis of randomized control trials. *Ann Surg* 2008;**248**:61–68.
70. Novo Nordisk. NovoSeven RT Coagulation Factor VIIa (recombinant) Prescribing Information, 2010. http://www.novosevenrt.com/pdfs/PI_novosevenrt.pdf (12 May 2012).
71. Wolzt M, Levi M, Sarich TC, Bostrom SL, Eriksson UG, Eriksson-Lepkowska M, Svensson M, Weitz JI, Elg M, Wahlander K. Effect of recombinant factor VIIa on melagatran-induced inhibition of thrombin generation and platelet activation in healthy volunteers. *Thromb Haemost* 2004;**91**:1090–1096.
72. Key NS, Negrier C. Coagulation factor concentrates: past, present, and future. *Lancet* 2007;**370**:439–448.
73. Gruber A, Marzec UM, Buetehorn U, Hanson S, Perzborn E. Potential of activated prothrombin complex concentrate and activated factor VII to reverse the anticoagulant effects of rivaroxaban in primates. *ASH Annual Meeting Abstracts* 2008; **112**:3825.
74. Perzborn E, Tinel H. FEIBA reverses the effects of a high dose of rivaroxaban in rats. *Pathophysiol Haemost Thromb* 2008;**36**:A40.
75. Chan HHW, Atkinson HM, Goncharenko M, Berry LR, Chan AKC. Reversal of dabigatran using recombinant activated factor VII and activated prothrombin complex concentrates in thromboelastography assay. *J Thromb Haemost* 2011;**9**: 576–577.
76. Marlu R, Hodaj E, Paris A, Albaladejo P, Crackowski JL, Pernod G. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. A randomised crossover ex vivo study in healthy volunteers. *Thromb Haemost* 2012; **108**:217–224.
77. Ehrlich HJ, Henzl MJ, Gomperts ED. Safety of factor VIII inhibitor bypass activity (FEIBA): 10-year compilation of thrombotic adverse events. *Haemophilia* 2002;**8**: 83–90.
78. Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. *J Thromb Haemost* 2004;**2**: 1700–1708.
79. Baxter Corporation. FEIBA Product Monograph, 2010. http://www.baxter.ca/en/downloads/product_information/feiba_pm_cust_2010oct07_en.pdf (10 June 2012).
80. Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010;**49**:259–268.
81. Wolowacz SE, Roskell NS, Plumb JM, Caprini JA, Eriksson BI. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. *Thromb Haemost* 2009;**101**:77–85.
82. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;**361**:2342–2352.
83. Turpie AG, Lassen MR, Eriksson BI, Gent M, Berkowitz SD, Misselwitz F, Bandel TJ, Homering M, Westermeier T, Kakkar AK. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb Haemost* 2011;**105**:444–453.
84. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;**363**:2499–2510.
85. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;**366**:1287–1297.
86. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, Kakkar AK, Misselwitz F, Schellong S. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59–7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients with Acute Symptomatic Deep-Vein Thrombosis) study. *Circulation* 2007;**116**:180–187.
87. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009; **361**:594–604.
88. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010;**375**:807–815.
89. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010; **363**:2487–2498.
90. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–817.
91. Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, Weitz JI. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011;**365**:2167–2177.
92. Levine MN, Gu C, Liebman HA, Escalante CP, Solymoss S, Deitchman D, Ramirez L, Julian J. A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. *J Thromb Haemost* 2012;**10**:807–814.
93. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**:692–694.
94. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P, Markis JE, Mueller H, Passamani ER, Powers ER, Rao AK, Robertson T, Ross A, Ryan TJ, Sobel BE, Willerson J, Williams DO, Zaret BL, Braunwald E. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987;**76**:142–154.
95. Buchan I. Relative risk and risk difference confidence intervals calculator, public health informatics, University of Manchester http://www.phsim.man.ac.uk/risk/ (29 July 2012).
96. Gart JJ, Nam J. Approximate interval estimation of the ratio of binomial parameters: a review and corrections for skewness. *Biometrics* 1988;**44**:323–338.