CRITICAL CARE

REVIEW

Clinical review: Clinical management of new oral anticoagulants: a structured review with emphasis on the reversal of bleeding complications

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Abstract

New oral anticoagulants, including dabigatran, rivaroxaban, and apixaban, have been recently approved for primary and secondary prophylaxis of thromboembolic conditions. However, there is no clear strategy for managing and reversing their anticoagulant effects. We aimed to summarize the available evidence for clinical management and reversal of bleeding associated with new oral anticoagulants. Using a systematic review approach, we aimed to identify studies describing reversal strategies for dabigatran, rivaroxaban, and apixaban. The search was conducted using Medline, EMBASE, HealthSTAR, and grey literature. We included laboratory and human studies. We included 23 studies reported in 37 out of 106 potentially relevant references. Four studies were conducted in humans and the rest were *in vitro* and *in vivo* studies. The majority of the studies evaluated the use of prothrombinase complex concentrate (PCC), either activated or inactivated, and recombinant activated factor VII (rFVIIa). Other interventions were also identified. Laboratory studies suggest that hemostatic parameters and bleeding might be partially or completely corrected by PCC for rivaroxaban better than dabigatran. Studies in humans suggest that PCC might reverse the effects of rivaroxaban better than dabigatran assessed by hemostatic tests. We were not able to locate studies evaluating the clinical efficacy of these agents. The best available evidence suggests that PCC (activated or inactivated) might be the best option for reversing new anticoagulants. Evidence for rFVIIa is less compelling. There might be differences in the efficacy of reversing agents for different anticoagulants. Studies assessing the clinical efficacy of these reversal agents are urgently needed.

Background

Dabigatran etexilate (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) are new oral anticoagulants (NOACs) that are approved in North America for reducing the risk of venous thromboembolism after hip or knee replacement and for stroke prevention in non-valvular atrial fibrillation. In addition, rivaroxaban is approved for the treatment deep vein thrombosis without pulmonary embolism in Canada or deep vein thrombosis with or without pulmonary embolism in the US [1]. The key properties of these drugs are summarized in Table 1. Dabigatran directly inhibits both free and clot-bound thrombin, which impedes the conversion of fibrinogen to fibrin, thus preventing thrombus development [2] (Figure 1). Rivaroxaban and apixaban are selective direct inhibitors of activated factor X (FXa) and result in decreased activation of prothrombin to thrombin [3].

Until the approval of the NOACs, warfarin was the only orally administered anticoagulant available for use in all of the aforementioned indications. However, warfarin use is associated with several drawbacks, including its narrow therapeutic range, extensive drug and food interactions, and need for laboratory monitoring. Nevertheless, there is extensive experience regarding the clinical management of warfarin and its associated complications (in particular, bleeding), but this is not the case for NOACs. In the case of warfarin, the management of bleeding is well known; however, experience in the management of bleeding complications associated with NOACs is very limited and there are no available antidotes (whereas antidotes are available for warfarin). Therefore, in the case of NOAC-associated hemorrhage, treatment options are unclear and there is a need to provide evidence-based guidance on the management of these potentially life-threatening complications. This is

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Table 1. Characteristics of new oral anticoagulants

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)
Clinical indications and dosing[a]			
Atrial fibrillation	Normal renal function: 150 mg bid >75 years: 110 mg bid	CrCl >50 mL/min: 20 mg od CrCl 30-49 mL/min: 15 mg od	CrCl ≥25 mL/min: 5 mg bid If 2 or more of the following: age ≥80, weight ≤60 kg or creatinine ≥1.5 mg/dL: 2.5 mg bid
Deep vein thrombosis without symptomatic pulmonary embolism (Canada) Deep vein thrombosis and pulmonary embolism (US)	Not approved	CrCl > 50 mL/min: 15 mg bid × 21 days then 20 mg od for at least 3-6 months CrCl 30-49 mL/min: 15 mg bid × 21 days then 15 mg od for at least 3-6 months	Not approved
Venous thromboembolism prophylaxis after total hip replacement surgery (14-35 days)	Normal renal function: 220 mg od × 10 days >75 years or CrCl 30-50 mL/min: 150 mg od × 10 days	10 mg od × 35 days	2.5 mg bid × 32-38 days
Venous thromboembolism prophylaxis after total knee replacement surgery (14-35 days)	Normal renal function: 220 mg od × 28-35 days >75 years or CrCl 30-50 mL/min: 150 mg od × 28-35 days	10 mg od × 14 days	2.5 mg bid × 10-14 days
Pharmacologic characteristics			
Mechanism of action	Direct thrombin (FIIa) inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Clearance	Renal ~85% Biliary/Fecal ~20%	Renal ~66% (active and unchanged drug and inactive metabolites) Biliary/Fecal ~33% (active drug)	Renal ~27% Biliary/Fecal ~75% (active drug)
Half-life			
Normal renal function (CrCl >80 mL/min)	~13 hours	5-9 hours	~12 hours
Mild renal impairment (CrCl 50-80 mL/min)	~15 hours	5-9 hours	~12 hours
Moderate renal impairment (CrCl 30-49 mL/min)	~18 hours	11-13 hours	10-14 hours
Severe renal impairment (CrCl <30 mL/min)	Contraindicated	Contraindicated	Contraindicated[b]
Onset of action (after oral intake)	1-3 hours	1-4 hours	3-4 hours
Food or alcohol interactions	None	None	None
Drug interactions	P-glycoprotein inhibitors[c] (increase systemic exposure) P-glycoprotein inducers[d] (decrease systemic exposure)	P-glycoprotein inhibitors[c] (increase systemic exposure) P-glycoprotein inducers[d] (decrease systemic exposure) Strong *CYP 3A4* inhibitors and inducers[e]	P-glycoprotein inhibitors[c] (increase systemic exposure) P-glycoprotein inducers[d] (decrease systemic exposure) Strong *CYP 3A4* inhibitors and inducers[e]

[a]Indications and dosing are based on Canadian information unless otherwise stated. For indications and dosing in other jurisdictions, please consult local authorities. [b]Apixaban is contraindicated in patients with a creatinine clearance (CrCL) of less than 15 mL/min or on dialysis, and there is very limited experience in patients with a CrCl of 15-24 mL/min, in whom no dosing recommendations exist. [c]P-glycoprotein inhibitors include verapamil, dronedarone, quinidine, amiodarone, clarithromycin, ritonavir, saquinavir, cyclosporine, tacrolimus, ketoconazole, and other azole antifungals. [d]P-glycoprotein inducers include rifampicin, carbamazepine, Saint John's Wort, and tenofovir. [e]Strong *CYP 3A4* inhibitors include ketoconazole, voriconazole, posaconazole, and ritonavir. Fluconazole is a moderate *CYP 3A4* inhibitor and may be used with caution. Strong *CYP 3A4* inducers include rifampicin, phenytoin, carbamazepine, and phenobarbitone. bid, twice daily; *CYP 3A4*, cytochrome P450 *3A4* enzyme; od, once daily. Adapted from [1-3,17-19,57-61].

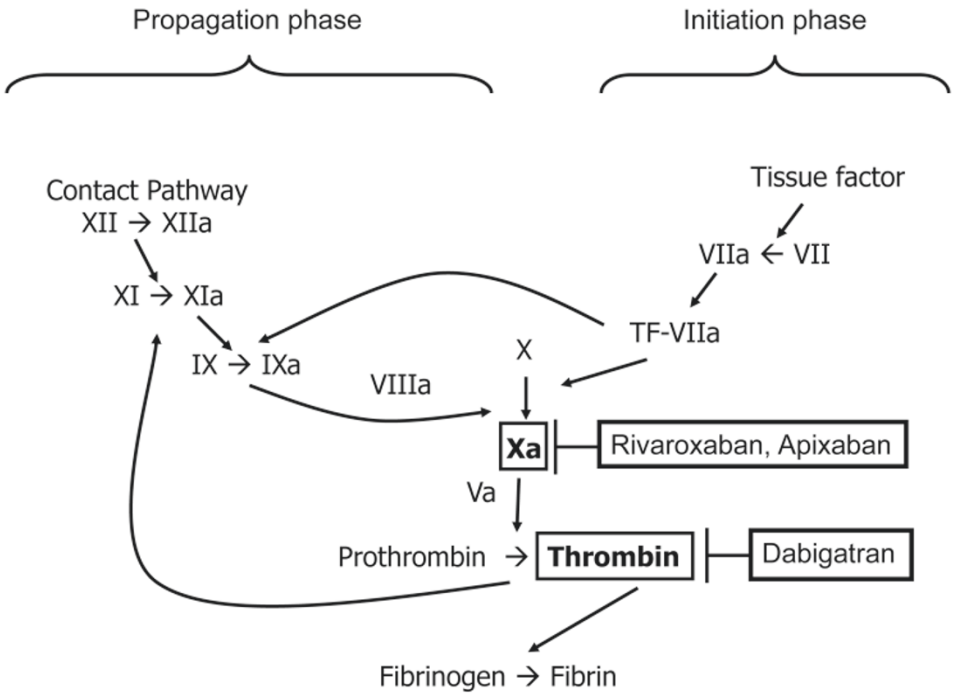

Figure 1. Schematic representation of the coagulation system and sites of action of new oral anticoagulants. The coagulation response is triggered by tissue damage and exposure of components of the extracellular matrix, including collagen and tissue factor, which will activate factor VII and form a complex that triggers the activation of factors X and IX. This initiation phase will be rapidly inactivated by the tissue factor pathway inhibitor. The generation of small amounts of thrombin from prothrombin by the initial activation of factor X will in turn activate factor XI and the non-enzymatic factors VIII and V, resulting in a rapid amplification of the coagulation response with the subsequent generation of large quantities of thrombin and the subsequent conversion of fibrinogen to fibrin. The steps of the coagulation system that are affected by the new anticoagulant drugs are shown in boxes. Roman numerals indicate coagulation factors; a subindex 'a' indicates an activated coagulation factor. TF, tissue factor.

an urgent need because of the rapid uptake of NOACs in clinical practice, which will undoubtedly carry an increment in NOAC-associated bleeding. Therefore, because of the aforementioned reasons and the uncertainty about best practices, we conducted – in concert with clinical guide development for the Thrombosis Interest Group of Canada [4] – a review of the literature focusing on the management of bleeding associated with NOACs, the results of which are included herein.

Clinical considerations in the management of new oral anticoagulants

Hemostasis is a cautiously balanced process that teeters between thrombus formation and degradation and that consists of a series of enzyme-mediated reactions in which thrombin plays a central role (Figure 1). A basic understanding of the physiology of the hemostatic system might help when considering the selection of a reversal agent. It is theoretically possible that an agent such as activated prothrombinase complex concentrate (aPCC) is a better option when treating bleeding in patients who are receiving dabigatran, because it might provide a more efficient activation of the coagulation cascade, although it is also possible that if dabigatran is still present in plasma, it could neutralize the newly generated thrombin. In the case of rivaroxaban, it is also conceivable that PCC or aPCC might be effective since they would bypass the effect of FXa inhibition. However, it should be underscored that these considerations remain theoretical and are clinically unproven. It is also possible that pro-hemostatic agents lessen NOAC-related bleeding by overcoming the inhibitory effect of these drugs by means of providing massive amounts of factors II and X, either active or inactive.

In general, it should be recognized that pro-hemostatic agents are not antidotes to NOACs and do not affect the ongoing inhibitory effect of these drugs on factors IIa and Xa. Furthermore, it should be noted that previous studies in patients with intracerebral hemorrhage have suggested that, although pro-hemostatic agents can limit the extent of bleeding, their effect on mortality and disability appears minimal [5]. It should also be recognized that there is a small but clinically important risk when administering these agents as their use has been associated with an increased risk for venous and arterial thrombosis [6-10].

Blood products such as cryoprecipitate and fresh frozen plasma are unlikely to result in a clinically significant reversal. We were unable to find evidence supporting the use of anti-fibrinolytic agents such as aminocaproic and tranexamic acid. A number of new agents are currently in different phases of development. They include monoclonal antibodies and small molecules with specific affinity for the NOACs [11-13]. Clinical studies are eagerly awaited.

A number of practical considerations must be made when managing bleeding in patients on anticoagulants. It is necessary to understand the two different types of bleeding events often reported in the literature evaluating anticoagulants for different indications. A major bleed is usually defined as a fatal or symptomatic event that involves a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome) or causes a hemoglobin level decrease of 20 g/L or more within 24 hours or results in transfusion of more than two units of packed red blood cells. The most common sites of major bleeding are gastrointestinal (approximately 80% of all bleeds), genitourinary, intracranial (including subdural, intracerebral (worst prognosis: 45% to 50% case fatality) [14,15], and subarachnoid), and soft tissue and intra-articular, which are typically traumatic. In contrast, minor bleedings are those that may require medical attention but, in general, do not require transfusion or hospitalization, are usually self-limiting, and do not require interruption of anticoagulant medication, although this could be necessary in cases of non-self-limiting events.

In the case of patients requiring an invasive procedure, temporary interruption of NOACs might be considered, but this should be individualized according to the type of procedure required. It should be remembered that NOACs have much shorter half-lives than warfarin (38 to 42 hours): dabigatran (11 to 17 hours), rivaroxaban (5 to 9 hours), and apixaban (9 to 12 hours). Thus, their anticoagulant effects may be reduced by over 75% within 24 to 36 hours of the last NOAC dose, after two half-lives have elapsed. Thus, even if coagulation tests are normal, elective procedures should not be performed until at least 24 to 36 hours (or longer in renal dysfunction) after discontinuation. Paradoxically, however, their short half-lives might put the patients at a higher risk of thrombosis in the case of interruptions, as was suggested by the slight increase in thrombotic events in patients enrolled in the ROCKET AF trial when transitioning from rivaroxaban to warfarin at the end of the study, although this remains largely a theoretical concern [16].

In the case of patients with kidney disease, dose reductions are required in patients with a creatinine clearance (CrCl) of 30 to 50 mL/min because renal impairment prolongs the half-lives of NOACs, especially dabigatran. The use of NOACs is contraindicated in patients with a CrCl of less than 30 mL/min in the case of dabigatran or a CrCl of less than 15 mL/min for rivaroxaban and apixaban [2,17,18]. For patients with a CrCl of between 15 and 30 mL/min, no clear dosing recommendations exist. In bleeding patients receiving dabigatran, hemodialysis may be considered in cases of acute renal failure and laboratory evidence of an excessive anticoagulant effect since 80% of dabigatran is not plasma-bound. There is no available information for rivaroxaban or apixaban in this regard, although owing to their high protein binding, dialysis is unlikely to be very effective. One study showed that hemodialysis removes 62% to 68% of drug after a single 50 mg dabigatran dose in patients with end-stage renal disease [19]. Another study suggests that dabigatran could be removed with the use of dialysis and charcoal hemoperfusion columns [20]. However, it is not known whether the removal of dabigatran by dialysis results in better bleeding control clinically. Finally, NOACs should be avoided in patients with moderate-to-severe liver dysfunction because of the lack of data in such patients.

Concomitant use of P-glycoprotein and *CYP3A4* inhibitors (for example, azole antifungals such as ketoconazole) or inducers (for example, rifampicin and antiepileptics) may increase or decrease both drugs' anticoagulant effect, and their concurrent use is contraindicated (Table 1).

Finally, caution should be exerted when interpreting coagulation tests since all NOACs may alter common coagulation laboratory tests (Table 2). Although routine coagulation tests generally are not useful in evaluating the degree of anticoagulation in patients receiving NOACs, there is some evidence that, in a bleeding patient, the activated partial thromboplastin time (aPTT) may be useful in determining anticoagulant activity. Lindahl and colleagues [21] demonstrated that a prolonged aPTT of greater than 90 seconds and a prolonged quick prothrombin time (PT) may indicate overdosing or accumulation of dabigatran. However, it is very important to note that a normal aPTT or international normalized ratio result may not exclude the presence of clinically relevant levels of dabigatran and other NOACs. In addition, fibrinogen concentration can be falsely low in patients receiving dabigatran and this may lead to the unnecessary use of blood products such as cryoprecipitate [21]. Finally, although it has been noted that a normal thrombin time may indicate a lack of dabigatran activity, this test is extremely sensitive to very small amounts of the drug, rendering it unsuitable for clinical use. Owing to their predictable pharmacokinetic and pharmacodynamic profiles, NOACs do not require routine laboratory monitoring, but this does not preclude the need to monitor specific coagulation-related conditions

Table 2. Effects of new anticoagulants on common coagulation tests

Test	Dabigatran etexilate	Rivaroxaban or apixaban
Activated partial thromboplastin time	Prolongation, variation among reagents	Prolongation, variation among reagents
Prothrombin time (Quick method)[a]	Prolongation	Prolongation
Prothrombin time (Owren method) [a]	Prolongation	Prolongation
Fibrinogen (Clauss method)	Moderate to marked underestimation	Minimal effect
Thrombin time	Marked prolongation	Minimal effect
Hemoclot thrombin inhibitor assay	Prolongation	Not applicable
International normalized ratio (point-of-care)	Elevation	Elevation?[b]
Activated factor X (FXa) activity	Minimal effect	Marked overestimation
HepTest assay for monitoring heparin in plasma and whole blood	Not applicable	Marked, dose-dependent overestimation

[a]There is significant variability in prothrombin time and international normalized ratio (INR) prolongation, depending on the reagents used and the time of administration of the drug. INR results might be elevated, ranging from 1.2 to more than 3.0. [b]No available information. Adapted from [2,17,21,56,62-69].

related to bleeding complications or changes in bleeding risk factors such as renal function.

Management of bleeding associated with new oral anticoagulants

To evaluate the interventions so far tested for managing bleeding in patients taking NOACs, we used a structured approach. We aimed to retrieve randomized controlled trials, cohort studies, case control studies, case series-case reports (including self-poisoning), or studies conducted in animal models or *in vitro*. To be considered for inclusion, a study had to propose an intervention to reverse the anticoagulant effect of the drugs of interest and measure either clinical or laboratory indices of bleeding.

The search was conducted in November 2012 by using the exploded terms rivaroxaban, dabigatran, and apixaban and the textwords 'reverse' or 'reversal'. The search was conducted by using the OVID interface in the following electronic databases: MEDLINE, EMBASE, and Healthstar. The search was restricted to articles written in English or French. The retrieved references were assessed for possible inclusion on the basis of the evaluation of the title and the abstract (or the full text if no abstract was available). Letters to the editor, review articles, editorials, and commentaries were excluded. Grey literature was considered, and we included the electronic versions of the abstracts of the following major international meetings: the International Society on Thrombosis and Haemostasis (1999 to 2011) and the American Society of Hematology (1999 to 2012). In addition, the reference lists of the retrieved journal articles were reviewed to locate additional studies of potential interest. The search was limited to articles published after 1996 since no information on these drugs was available prior to this date.

Potentially relevant studies were selected by one author and checked for accuracy by a second author. Owing to the heterogeneous nature of the studies included and to the lack of validated scales to assess the quality of the study designs included, we did not perform a quality assessment. Reports were divided into the following categories: (a) *in vitro* or *in vivo* studies (or both) in animal models and (b) studies in humans. Outcome was the effectiveness or potential effectiveness of the proposed interventions to revert NOACs. Owing to the heterogeneity among the studies, a formal meta-analysis was not conducted.

The search identified 106 potentially relevant references, of which 35 were included in the final review. Two additional references were identified through the review of reference lists. Excluded references included two mechanistic studies and one letter, whereas the rest were reviews. One additional study was excluded because it did not provide sufficient information [22]. We identified 23 studies reported in 37 references [11-13,20,23-55]. Nine studies were reported in more than one reference, and only five studies have been published in full, whereas the rest have been reported only in conference abstracts. Reversal of apixaban, dabigatran, and rivaroxaban has been evaluated in two, nine, and eight studies, respectively. Four studies have evaluated reversal of both rivaroxaban and dabigatran administered to human subjects, and only one has evaluated the administration of the proposed reversal agent to healthy volunteers. Nine studies included the evaluation of an *in vivo* model of bleeding in animals, whereas all studies evaluated different hemostatic parameters. The interventions evaluated included recombinant human activated factor VII (rFVIIa) (NovoSeven), four-factor prothrombinase complex (PCC) (Beriplex, Octaplex, Kaskadil, Cofact, and Kanokad), activated prothrombinase complex (aPCC) (FEIBA), fibrinogen concentrate, fIX/fX concentrate and fresh frozen plasma (FFP), high-purity FX concentrate, activated charcoal hemoperfusion, hemodialysis, an anti-dabigatran antibody/Fab fragment, and a recombinant

reconstructed mutant factor Xa (r-Antidote, PRT064445). The 23 included studies are summarized in Table 3.

General principles should be observed for managing bleeding, including resuscitation, bleeding source control, drug cessation, and appropriate use of blood products. Activated charcoal can be considered if the offending drug was taken within two hours [56]. In the case of life-threatening or intracranial bleeding, the use of pro-hemostatic agents should be considered. Table 4 summarizes the currently available information regarding the reversal of NOACs, all of which is based on limited studies and should be considered low-quality. The best evidence so far comes from four studies in healthy volunteers who were receiving NOACs. The first study included healthy volunteers to whom rivaroxaban (20 mg twice a day) or dabigatran (150 mg twice a day) was administered for 2.5 days, after which they received a single dose of 50 IU/kg of four-factor (II, VII, IX, X) PCC, and its effects on PT, aPTT, thrombin time (TT), ecarin clotting time (ECT), and endogenous thrombin potential (ETP) were evaluated [26]. The study used Cofact, an agent available in Europe, but other similar four-factor PCCs (such as Octaplex or Beriplex) are available. The study showed that in subjects receiving rivaroxaban, both the PT and the ETP corrected to normal levels after administration of the PCC. In contrast, in patients receiving dabigatran, there were no corrections in the aPTT, ECT, ETP, or TT. In three other studies including healthy volunteers, participants received one or two doses of rivaroxaban (20 mg) or dabigatran (150 mg), and samples were obtained at different times after administration [33]. To test the *ex vivo* effect of pro-hemostatic agents, patients' samples were incubated with different concentrations of recombinant activated factor VII (rFVIIa, Novoseven), four-factor PCC (Kanokad, available in Europe; Beriplex; and Cofact), and activated four-factor PCC (aPCC) (FEIBA; similar to four-factor PCC but with a more rapid effect because of the presence of 'activated' clotting factors). Coagulation was evaluated by measuring thrombin generation and other tests. The results of the studies showed that overall aPCC achieved the best correction of the coagulation parameters after rivaroxaban and dabigatran administration. Less efficient corrections were achieved with PCC and rFVIIa. Interestingly, one study suggested that lower doses of FEIBA might also be effective [33].

Bleeding has been assessed in some studies in animal models. A study evaluating the effects of rFVIIa and PCC in a rabbit bleeding model failed to show reversal of rivaroxaban-induced bleeding in spite of improvement in laboratory parameters [29]. However, other studies have reported reduced bleeding time in animal models of rivaroxaban-induced bleeding after administration of FEIBA [31,39]. In the case of dabigatran, animal models suggest that PCC, FEIBA, and rFVIIa could reduce bleeding [41,43,46]. There are other agents, such as three-factor (II, IX, X) PCC (currently used in the US), but evidence supporting their use in bleeding patients receiving NOACs is lacking and their use cannot be supported on the basis of currently available evidence. Perhaps the most significant *in vivo* animal study was published by Zhou and colleagues [46], who evaluated the effect of rFVIIA and PCC in an animal model of intracerebral bleeding in mice receiving dabigatran. The authors found that PCC at a dose of 100 IU/kg decreased the size and deterred the progression of the intraparenchymal hematoma and resulted in a lower mortality in the treated animals. Finally, only one study has described the experience with bleeding events in trials evaluating dabigatran for different indications [22]. The study reviewed 1,121 reports of major bleeding events and found that patients receiving dabigatran who developed major bleeding were older, had a lower creatinine clearance, and had more concurrent use of antiplatelet agents than those receiving warfarin. However, only nine patients received PCCs and two received rFVIIA, but no details were available at the time of review, and nothing can be extrapolated to the clinical scenario on the basis of the available information.

Finally, it should be re-emphasized that all information on clinical management should be considered low-quality on the basis of currently available data. When considering the use of these reversal agents, clinicians should very carefully consider the trade-off between benefits and potential risk.

Conclusions

In spite of the emerging information, there is still a considerable lack of evidence to inform clinical practice, and most of the recommendations are based on expert opinion and interpretation of available evidence. Whereas experience today suggests that in the case of a catastrophic event such as an intracerebral bleeding the use of reversal agents is unlikely to result in major clinical benefit, such agents still have a role in the case of patients requiring urgent surgical interventions which are potentially life-saving. The overall evaluation of the limited available studies suggests that the agents most likely resulting in benefit are PCC and aPCC but evidence for rFVIIa is less consistent. However, it is essential to note that no clinical experience is available to date and that all studies have used surrogate measures such as coagulation-based assays of hemostatic function or animal models. The actual effect of these agents in patients with bleeding events remains to be determined. In addition, the existing literature suggests that correction in hemostatic parameters does not necessarily correlate with an improvement in actual bleeding, and the currently available evidence is still confusing because of

Table 3. Published studies evaluating interventions for the reversal of new oral anticoagulants

Study (Reference)	Anticoagulant(s) evaluated	Reversal agent(s)	Study design/ Hemostatic assessment	Outcome
In vitro studies and *in vivo* studies in animal models				
Escolar *et al*. [50]	Apixaban	rFVIIa (270 μg/kg) aPCC (75 IU/kg) PCC (50 IU/kg)	*In vitro* study in health donor samples spiked with apixaban at a concentration of 200 ng/mL assessing TG and TE. Additional studies assessed hemostasis under flow conditions.	TG parameters were variably improved in order of efficacy by PCC, aPCC, and rFVIIa. TE parameters were corrected in order of efficacy by rFVIIa, aPCC, and PCC. Flow studies (resembling more closely a bleeding situation) showed improvements in order of efficacy by rFVIIa, PCC, and aPCC.
Martin *et al*. [34-36]	Apixaban	rFVIIA, PCC, fibrinogen concentrate. Doses not reported.	Rabbit *in vivo* bleeding model (hepatosplenic section) assessing BT, PT, TE, TG, and blood loss. Apixaban dose was not reported.	All agents improved laboratory parameters but did not reduce blood loss.
Chan *et al*. [23]	Dabigatran	rFVIIa (150 μg/kg) aPCC (FEIBA VH, 100 IU/kg)	*In vitro* study using healthy donor samples spiked with dabigatran 150 ng/mL assessing TE	Both agents improved TE clot initiation time. aPCC achieved a more potent correction than rFVIIa.
Hoffman *et al*. [55]	Dabigatran	PCC (Beriplex) 0.25-2.0 IU/mL)	*In vitro* studies in human plasma spiked with dabigatran 189-944 ng/mL assessing TG	PCC corrected some parameters in the TG assay.
Lange *et al*. [51]	Dabigatran	Activated charcoal perfusion and hemodialysis	*In vitro* and *in vivo* (pig model) assessment of Absorba 300C activated charcoal filter or Polyflux 140H hemodialysis filter. Dabigatran tested in porcine whole blood at a concentration of 1,000 ng/mL.	Activated charcoal perfusion resulted in near-complete removal of dabigatran but showed saturation (maximum binding capacity ~30 mg). Hemodialysis with flows achieved similar results.
Pragst *et al*. [40]	Dabigatran	PCC (Beriplex P/N) 20, 35, or 50 IU/kg	Rabbit *in vivo* bleeding model (renal incision) assessing blood loss and time to hemostasis after dabigatran 0.4 mg/kg	Dose-dependent reduction of blood loss and time to hemostasis. Blood loss normalized at a dose of 50 IU/kg.
Toth *et al*. [48]	Dabigatran	Anti-dabigatran humanized Fab (30, 90, 175 mg/kg)	*In vivo* model in Rhesus monkeys receiving 12 mg/kg per day × 4 days. Coagulation activity was assessed by dilute TT.	Complete correction of TT at all 3 doses.
Van Ryn *et al*. (a) [41,43,44]	Dabigatran	PCC (Beriplex 35 IU/kg) PCC (Octaplex 40 IU/kg) Activated PCC (FEIBA 100 IU/kg) rFVIIa (Novoseven 0.5 μg/kg)	Rat *in vivo* bleeding model (tail cut) assessing time to hemostasis, aPTT, TT, PT, ECT, diluted TT, and Hemoclot. Dabigatran was administered at 30 mg/kg.	All agents tested completely corrected prolongation of BT up to 2 hours. TT, aPTT, and ECT remained prolonged after all four agents. PT was reversed to baseline with all agents.
Van Ryn *et al*. (b) [13,45,54]	Dabigatran	Anti-dabigatran antibody and Fab fragment	*In vitro* study in human plasma and rats *ex vivo* using diluted TT. *In vivo* rat tail bleeding model. Dabigatran was administered at 30 mg/kg.	*In vitro* studies showed rapid inhibition of dabigatran. BT in rat tail bleeding model was fully corrected.
Van Ryn *et al*. (c) [20,42]	Dabigatran	Activated charcoal hemoperfusion	*In vitro* assessment of Adsorba cartridge. Dabigatran tested in bovine whole blood at a concentration of 1,000 ng/mL.	Activated charcoal hemoperfusion resulted in near-complete removal of dabigatran.
Zhou *et al*. [46]	Dabigatran	PCC (Beriplex P/N; 50 and 100 IU/kg) rFVIIa (NovoSeven; 8.0 mg/kg) FFP (murine, 200 μL/kg)	*In vivo* and *ex vivo* study in mice receiving dabigatran at 2.25, 4.5, and 9.0 mg/kg assessing tail vein bleeding time and intracerebral hemorrhage volume and expansion (intrastriatal collagenase injection model)	At 9.0 mg/kg of dabigatran PCC (50 and 100 IU/kg) but not rFVIIa reduced intracerebral hematoma growth and mice mortality. FFP had an inconsistent beneficial effect on hematoma size reduction but not on mortality at lower dabigatran doses. PCC reduced tail vein BT more effectively at a dose of 100 IU/kg.

Continued overleaf

Table 3. Continued

Study (Reference)	Anticoagulant(s) evaluated	Reversal agent(s)	Study design/ Hemostatic assessment	Outcome
Godier *et al*. [27-29]	Rivaroxaban	rFVIIa (150 μg/kg) PCC (Kaskadil 40 IU/kg)	Rabbit *in vivo* bleeding model (hepatosplenic section) assessing BT, TE, TG, and blood loss. Rivaroxaban was administered at 5 mg/kg.	rFVIIa corrected BT but not blood loss. PCC did not correct BT or blood loss. PCC and rFVIIa decreased aPTT and TE clotting time.
Gruber *et al*. [30,31]	Rivaroxaban	rFVIIa (NovoSeven; 210 μg/kg) aPCC (FEIBA; 50 IU/kg)	*In vivo* study in baboons receiving rivaroxaban (IV bolus 0.6 mg/kg followed by continued infusion 0.6 mg/kg per hour) assessing PT, TE, and BT	aPCC reduced PT and normalized BT. fVIIa reduced but not fully corrected BT and PT.
Hollenbach *et al*. [53]	Rivaroxaban	r-Antidote (PRT064445) (76 mg/rabbit) rFVIIa (150 μg/kg)	*In vivo* rabbit liver laceration model assessing blood loss, anti-fXa activity, PT, and aPTT. Rivaroxaban was given at 1 mg/kg.	r-Antidote (PRT064445) reduced blood loss anti-fXa activity, PT, and aPTT. rFVIIa improved PT and aPTT but did not decrease blood loss.
Keller *et al*. [32]	Rivaroxaban	rFVIIa 90 and 180 μg/kg	*In vitro* study using healthy donor samples spiked with rivaroxaban 800, 2,000, or 5,000 ng/mL assessing TE	Both dosages improved TE parameters at all levels of rivaroxaban.
Lloyd *et al*. [47]	Rivaroxaban	High-purity factor X concentrate (1, 2.5, and 5 IU/mL)	*In vitro* study using commercial rivaroxaban calibration plasmas spiked with fX assessing PT	fX reduced but not completely corrected PT. No dose-response was observed.
Lu *et al*. [11,12]	Rivaroxaban	r-Antidote (PRT064445) (0.96 mg/mouse)	*In vitro* and *ex vivo* studies in mouse, rat, and human plasma assessing anti-fXa activity and TG. Blood loss assessed in a mouse tail transection model. Rivaroxaban was administered at 50 mg/kg.	r-Antidote (PRT064445) decreased blood loss, anti-fXa activity and whole blood INR.
Olesen *et al*. [37]	Rivaroxaban	rFVIIa (1.0 and 2.0 μg/mL) PCC (0.29 and 0.58 IU/mL) fIX/fX concentrate (0.29 and 0.58 IU/mL)	*In vitro* study in health donor samples spiked with rivaroxaban at a concentration of 1.33 μg/mL assessing TE	rFVIIa, PCC, and fIX/fX concentrate improved TE parameters but no complete reversal was obtained.
Perzborn *et al*. [38,39]	Rivaroxaban	PCC (Beriplex) 25 or 50 IU/kg	Rat *in vivo* bleeding model (mesenteric) assessing bleeding time, PT, and TAT after rivaroxaban 2 mg/kg	PCC at 50 IU/kg nearly normalized BT, improved PT, and decreased TAT levels. PCC at 25 IU/kg had no effect.
Studies in humans receiving new oral anticoagulants				
Eerenberg *et al*. [24-26]	Rivaroxaban Dabigatran	PCC (Cofact; 50 IU/kg)	Randomized controlled trial in healthy volunteers receiving either dabigatran (150 mg bid po) or rivaroxaban (20 mg bid po) × 2.5 days after which PCC (or placebo) was given by IV infusion. Rivaroxaban was assessed by PT and ETP. Dabigatran was assessed by aPTT, ETP, TT, and ECT.	For rivaroxaban, PCC infusion normalized PT and ETP. For dabigatran, PCC did not correct aPTT, ETP lag time, TT, or ECT.
Galan *et al*. [49]	Dabigatran Rivaroxaban	rFVIIa (270 μg/kg) aPCC (75 IU/kg) PCC (50 IU/kg)	*Ex vivo* studies using samples from healthy individuals receiving dabigatran (150 mg po bid) or rivaroxaban (20 mg po). Samples spiked with reversal agents were tested for TG, TE, PT, INR, and aPTT. Additional studies assessed hemostasis under flow conditions.	rFVIIa and aPCC corrected the effect of rivaroxaban on PT, INR and aPTT. aPCC corrected rivaroxaban induced abnormalities in TG whereas PCC and rFVIIa had modest or no effects, respectively. aPCC corrected the effect of dabigatran on aPTT. Flow studies (resembling more closely a bleeding situation) showed that alteration induced by rivaroxaban were variably reversed by all three agents whereas only aPCCs reversed the effects of dabigatran.

Continued overleaf

Table 3. Continued

Study (Reference)	Anticoagulant(s) evaluated	Reversal agent(s)	Study design/ Hemostatic assessment	Outcome
Marlu *et al*. [33]	Dabigatran Rivaroxaban	rFVIIa (NovoSeven; 20, 60, and 120 μg/kg) aPCC (FEIBA; 20, 40, and 80 IU/kg) PCC (Kanokad; 12.5, 25, and 50 IU/kg)	Crossover randomized *ex vivo* study in healthy donors receiving either dabigatran (150 mg po) or rivaroxaban (20 mg po) × 1 dose assessing TG, aPTT, and PT	For rivaroxaban PCC strongly corrected ETP-AUC and modestly corrected ETP-Peak. No correction of lag time. rFVIIa corrected only kinetic parameters. aPCC corrected all parameters. For dabigatran, PCC improved ETP-AUC but had no effect on kinetic parameters. rFVIIa and aPCC corrected lag time.
Pilliteri *et al*. [52]	Dabigatran Rivaroxaban	PCC (Beriplex; 12.5, 25, 50, and 100 IU/kg PCC (Cofact; 12.5, 25, 50, and 100 IU/kg) aPCC (FEIBA; 20, 40, 80, and 160 IU/kg) rFVIIa (NovoSeven; ~75, 125 250 and 500 μg/kg)	Crossover randomized *ex vivo* study in health donors receiving either dabigatran (150 mg po) or rivaroxaban (20 mg po) × 1 dose assessing TG, aPTT, and PT, TT, rivaroxaban, and dabigatran levels and ECT.	aPCC and rFVIIa showed reversal of both anticoagulants assessed by TG. Cofact showed improvement on TG but Beriplex did not.

anti-fXa, anti-activated factor X activity; aPCC, activated prothrombinase complex concentrate; aPTT, activated partial thromboplastin time; AUC, area under the curve; bid, twice daily; BT, bleeding time; ECT, ecarin clotting time; ETP, endogenous thrombin potential; FFP, fresh frozen plasma; fIX, coagulation factor IX; fX, coagulation factor X; INR, international normalized ratio; IV, intravenous; PCC, prothrombin complex concentrate; po, by mouth; PT prothrombin time; rFVIIA, recombinant activated factor VII; TAT, thrombin-antithrombin complex; TE, thromboelastography; TG, thrombin generation assay; TT, thrombin time.

Table 4. Pro-hemostatic agents and their potential role on the reversal of new oral anticoagulants

Agent	Doses tested in human studies	Dabigatran etexilate	Rivaroxaban or Apixaban[a]
Four-factor prothrombinase complex concentrate (Beriplex, Octaplex)	12.5 to 100 IU/kg 50 IU/kg is the only dose tested *in vivo* in humans	Possibly beneficial	Probably beneficial
Activated four-factor prothrombinase complex concentrate (FEIBA)	20 to 160 IU/kg	Probably beneficial	Probably beneficial
Recombinant activated factor VII (Novoseven, Niastase)	20 to 500 μg/kg)	Possibly beneficial	Possibly beneficial
Fresh frozen plasma	Not applicable	Probably ineffective	Probably ineffective
Cryoprecipitate	Not applicable	Probably ineffective	Probably ineffective
Three-factor prothrombinase complex concentrate	No data available	No available evidence	No available evidence
Antifibrinolytic agents (Aminocaproic acid-Amicar; Tranexamic acid-Cyklokapron)[b]	No data available	No available evidence	No available evidence

No study has assessed the clinical effect of these agents in patients with active bleeding events. The possible role of these agents is based on animal studies and human studies evaluating surrogate coagulation markers. All evidence should be considered low quality and the use of these agents should follow a careful consideration of risks and benefits. [a]No study has assessed the clinical effect of these agents in patients receiving apixaban. The possible role of these agents is theoretical and is based on extrapolation of evidence available for patients receiving rivaroxaban. [b]There is no available evidence regarding efficacy or safety. Adapted from [23,26,29,30,33,39,41,43,46].

the diversity of experimental models and assessments used and because of the lack of conclusive evidence relating the correction of laboratory parameters evaluating the hemostatic system with the effect on actual bleeding events.

Given the lack of effective reversal agents, several new agents are currently being evaluated, the most promising of which are the monoclonal humanized anti-dabigatran antibody and Fab fragment and the r-Antidote (PRT064445) for direct Xa inhibitors. To the best of our knowledge, the latter drug is the only one that has achieved clinical development and is currently being evaluated in a phase II study, the results of which could be expected in late 2014. Further studies are urgently needed to elucidate the clinical effect of the currently available and prospective agents on patients with actual bleeding events and in particular on vital and functional outcomes.

Abbreviations
aPCC, activated prothrombinase complex concentrate; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; ECT, ecarin clotting time; ETP, endogenous thrombin potential; FXa, activated factor X; NOAC, new oral anticoagulant; PCC, prothrombinase complex concentrate; PT, prothrombin time; rFVIIa, recombinant activated factor VII; TT, thrombin time.

Competing interests
AL-L has received honoraria from Pfizer Inc (New York, NY, USA), Leo Pharma (Ballerup, Denmark), Sanofi-Aventis (Paris, France), and Boehringer Ingelheim (Ingelheim, Germany). ESL has received speaking honoraria from Bayer (Leverkusen, Germany) and Boehringer Ingelheim. JD has been a consultant, in the past 10 years, for AGEN Biomedical (Melbourne, Australia), AstraZeneca (London, UK), Bayer, Boehringer Ingelheim, Bristol-Myers Squibb Company (Princeton, NJ, USA), Ortho-McNeil Pharmaceutical (Raritan, NJ, USA), Pfizer Inc, and Sanofi-Aventis.

Authors' contributions
AL-L abstracted data and contributed to searching the literature and selecting studies for inclusion, checking data for accuracy, and writing the manuscript. ESL and JD contributed to searching the literature and selecting studies for inclusion, checking data for accuracy, and writing the manuscript.

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Published: 17 June 2013

References

1. U.S. Food and Drug Administration: **FDA News release. FDA expands use of Xarelto to treat, reduce recurrence of blood clots** [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm326654.htm].
2. 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.
3. Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G: **Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor.** *Clin Pharmacol Ther* 2005, **78:**412-421.
4. **The Thrombosis Interest Group of Canada homepage** [http://www.tigc.org/].
5. 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.
6. Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, Sundaram V, McMahon D, Olkin I, McDonald KM, Owens DK, Stafford RS: **Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications.** *Ann Intern Med* 2011, **154:**529-540.
7. Dutton RP, Parr M, Tortella BJ, Champion HR, Bernard GR, Boffard K, Bouillon B, Croce MA, Dimsits J, Holcomb JB, Leppaniemi A, Vincent JL, Hauser CJ; CONTROL Study Group: **Recombinant activated factor VII safety in trauma patients: results from the CONTROL trial.** *J Trauma* 2011, **71:**12-19.
8. Majeed A, Eelde A, Agren A, Schulman S, Holmstrom M: **Thromboembolic safety and efficacy of prothrombin complex concentrates in the emergency reversal of warfarin coagulopathy.** *Thromb Res* 2012, **129:**146-151.
9. 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.
10. 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.
11. Lu G, Luan P, 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:** Abstract OC-TH-107.
12. Lu G, Deguzman FR, Karbarz MJ, Hollenbach SJ, Conley PB, Hutchaleelaha A, Sinha U: **Reversal of rivaroxaban mediated anticoagulation in animal models by a recombinant antidote protein (r-Antidote, PRT064445).** *Eur Heart J* 2011, **32:** Abstract 3715.
13. Van Ryn J, Litzenburger T, Waterman A, Canada K, Hauel N, Sarko C, Kroe-Barrett R, Singh S, Park J: **An antibody selective to dabigatran safely neutralizes both dabigatran-induced anticoagulant and bleeding activity in *in vitro* and *in vivo* models.** *J Thromb Haemost* 2011, **9:**110. Abstract P-MO-166.
14. Carrier M, Le Gal Gg, Wells PS, Rodger MA: **Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism.** *Ann Intern Med* 2010, **152:**578-589.
15. Linkins LA, Choi PT, Douketis JD: **Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis.** *Ann Intern Med* 2003, **139:**893-900.
16. 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; ROCKET AF Investigators: **Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.** *N Engl J Med* 2011, **365:**883-891.
17. 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.
18. Kubitza D, Becka M, Mueck W, Halabi A, Maatouk H, Klause N, Lufft V, Wand DD, Philipp T, Bruck H: **Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor.** *Br J Clin Pharmacol* 2010, **70:**703-712.
19. Stangier J, Rathgen K, Stähle 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.
20. Van Ryn J, Neubauer M, Flieg R, Krause B, Storr M, Hauel N, Priepke H, Clemens A: **Successful removal of dabigatran in flowing blood with an activated charcoal hemoperfusion column in an *in vitro* test system.** *Pathophysiol Haemost Thromb* 2010, **37:** Abstract P 485.
21. Lindahl TL, Baghaei F, Blixter IF, Gustafsson KM, Stigendal L, Sten-Linder M, Strandberg K, Hillarp A; Expert Group on Coagulation of the External Quality Assurance in Laboratory Medicine in Sweden: **Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays.** *Thromb Haemost* 2011, **105:**371-378.
22. Majeed A, Hwang H, Bruggink ED, Connolly S, Eikelboom JW, Ezekowitz M, Wallentin L, Yusuf S, Schulman S: **Management and outcomes of major bleeding on dabigatran or warfarin.** *Blood* 2012, **120:** Abstract 19.
23. 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. Abstract P-WE-180.
24. Eerenberg ES, Sijpkens MK, Kamphuisen PW, Meijers JCM, Levi M: **Prothrombin complex concentrate reverses the anticoagulant effect of rivaroxaban in healthy volunteers.** *Blood* 2010, **116:** Abstract 1094.
25. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JCM, Buller HR, Levi M: **Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, cross-over study in healthy subjects.** *J Thromb Haemost* 2011, **9:**657. Abstract P-WE-435.
26. 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.
27. Godier A, Miclot A, Le BB, Durand M, Lecompte T, Samama CM: **Evaluation of prothrombin complex concentrate, recombinant activated factor VII and fibrinogen concentrate to reverse rivaroxaban in a rabbit model of bleeding and thrombosis.** *Eur J Anaesthesiol* 2011, **28:**87. Abstract 6AP3-8.
28. Godier A, Miclot A, Le BB, Durand M, Emmerich J, Fischer AM, Lecompte T, Samama CM: **Evaluation of prothrombin complex concentrate, recombinant activated factor VII and fibrinogen concentrate to reverse**

rivaroxaban in a rabbit model. *J Thromb Haemost* 2011, **9:**388. Abstract P-TU-253.
29. Godier A, Miclot A, Le BB, Durand M, Fischer A-M, Emmerich J, Marchand-Leroux C, Lecompte T, Samama C-M: **Evaluation of prothrombin complex concentrate and recombinant activated factor VII to reverse rivaroxaban in a rabbit model.** *Anesthesiology* 2012, **116:**94-102.
30. Gruber A, Marzec UM, Buetehorn U, Hanson SR, Perzborn E: **Activated factor VII and activated prothrombin complex for reversal of the antihaemostatic effects of rivaroxaban in primates.** *Br J Haematol* 2009, **145:** Abstract 80.
31. Gruber A, Marzec UM, Buetehorn U, Hanson S, Perzborn E: **Reversal of the antihaemostatic effects of rivaroxaban by activated factor VII and activated prothrombin complex in primates.** *Haematologica* 2009, **94:**June. Abstract 0449.
32. Keller MK, Langer E, Ziemer S, Von HC: **RIVACAPT (RIVAroxaban Coagulation Antagonisation Pilot Trial).** *Hamostaseologie* 2012, **32:**A13. Abstract ED10-7.
33. 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.
34. Martin A-C, Le BB, Lecompte T, Dizier B, Emmerich J, Fischer A-M, Samama C-M, Godier A: **Evaluation of prothrombin complex concentrate, recombinant activated factor VII and fibrinogen concentrate to reverse apixaban in a rabbit model.** *Cardiovasc Res* 2012, **93:**S73. Abstract P364.
35. Martin A-C, Le-Bonniec B, Lecompte T, Fischer A-M, Emmerich J, Samama C-M, Godier A, Val De GH: **Evaluation of recombinant activated factor VII, prothrombin complex concentrate and fibrinogen concentrate to reverse apixaban in a rabbit model.** *J Am Coll Cardiol* 2012, **59:**E573.
36. Martin A-C, Le-Bonniec B, Lecompte T, Fischer A-M, Emmerich J, Samama C-M, Godier A: **Evaluation of recombinant activated factor VII, prothrombin complex concentrate and fibrinogen concentrate to reverse apixaban in a rabbit model.** *Eur Heart J* 2012, **33:**496. Abstract 2963.
37. Olesen JB, Christiansen K, Ingerslev J, Sorensen B, Hvas A: **Haemostatic response to *in vitro* addition of recombinant factor VIIa, prothrombin complex concentrate, or concentrate of Factor IX/X in blood spiked with a direct Xa inhibitor.** *J Thromb Haemost* 2009, **7:** Abstract PP-MO-386.
38. Perzborn E, Trabandt A, Selbach K, Tinel H: **Prothrombin complex concentrate reverses the effects of high-dose rivaroxaban in rats.** *Hamostaseologie* 2010, **30:**A103. Abstract P16-01.
39. Perzborn E, Trabandt A, Selbach K, Tinel H: **Prothrombin complex concentrate reverses the effects of high-dose rivaroxaban in rats.** *Pathophysiol Haemost Thromb* 2010, **37:** Abstract OC 251.
40. Pragst I, Zeitler SH, Doerr B, Kaspereit FJ, Herzog E, Dickneite G, van Ryn J: **Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model.** *J Thromb Haemost* 2012, **10:**1841-1848.
41. Van Ryn J, Ruehl D, Priepke H, Hauel N, Wienen W: **Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran, by recombinant factor VIIa or activated prothrombin complex concentrate.** *Haematologica* 2008, **93:** Abstract 0370.
42. Van Ryn J, Neubauer M, Flieg R, Krause B, Storr M, Hauel N, Priepke H, Clemens A: **Successful removal of dabigatran in flowing blood with an activated charcoal hemoperfusion column in an *in vitro* test system.** *Haematologica* 2010, **95:**293. Abstract 0700.
43. Van Ryn J, Dorr B, Kaspereit F, Krege W, Zeitler S, Pragst I: **Beriplex P/N reverses bleeding in an acute renal injury model after dabigatran overdose in rabbits.** *Pathophysiol Haemost Thromb* 2010, **37:** Abstract P 486.
44. Van Ryn J, Schurer J, Kink-Eiband M, Clemens A: **The successful reversal of dabigatran-induced bleeding by coagulation factor concentrates in a rat tail bleeding model do not correlate with *ex vivo* markers of anticoagulation.** *Blood* 2011, **118:** Abstract 2316.
45. Van Ryn J, Litzenburger T, Waterman A, Canada K, Hauel N, Sarko C, 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.
46. 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.
47. Lloyd J, Feldman P, Ryan L: ***In vitro* reversal of the direct Xa inhibitor rivaroxaban using high-purity factor X concentrate (factor X).** *Haemophilia* 2012, **18:**33. Abstract PO-TU-033.
48. Toth J, Gandolfi R, Van Ryn J, Dursema H, Isler J, Coble K, Burke J, Lalovic B, Olson S: **Reversal of dabigatran's anticoagulant activity in the monkey by a specific antidote and pharmacokinetic and pharmacodynamic modeling.** *Blood* 2012, **120:**Abstract 22.
49. Galan A, Arellano-Rodrigo E, Sanz V, Molina P, Reverter JC, Carne X, Villalta J, Tassies D, Diaz-Ricart M, Escolar G: **Reversal of the antithrombotic action of rivaroxaban and dabigatran: a clinical study in healthy volunteers.** *Blood* 2012, **120:**Abstract 2261.
50. Escolar G, Arellano-Rodrigo E, Reverter JC, Villalta J, Sanz V, Molina P, Diaz-Ricart M, Galan A: **Coagulation factor concentrates restore alterations in hemostasis induced by a high dose of apixaban: studies *in vitro* with circulating human blood.** *Blood* 2012, **120:**Abstract 2263.
51. Lange J, Thiel C, Thiel K, Klingert W, Klingert K, Konigsrainer A, Formella S, Clemens A, Van Ryn J, Schenk M: **Acceleration of dabigatran elimination by activated charcoal perfusion and hemodialysis in a pig model.** *Blood* 2012, **120:**Abstract 2272.
52. Pillitteri D, Pilgrimm-Thorp A, Krause M, Scholz T, Schwerdtfeger R, Behrendt T, Kirchmaier C: **Antidotal effects of non-specific reversal agents on anticoagulant-induced inhibition of thrombin generation.** *Blood* 2012, **120:**Abstract 2273.
53. Hollenbach SJ, Lu G, Tan S, Lee G, Hutchaleelaha A, Inagaki M, Sinha U: **PRT064445 but not recombinant Fviia reverses rivaroxaban induced anticoagulation as measured by reduction in blood loss in a rabbit liver laceration model.** *Blood* 2012, **120:**Abstract 3414.
54. Van Ryn J, Litzenburger T, Gan G, Coble K, Schurer J: ***In vitro* characterization, pharmacokinetics and reversal of supratherapeutic doses of dabigatran-induced bleeding in rats by a specific antibody fragment antidote to dabigatran.** *Blood* 2012, **120:**Abstract 3418.
55. Hoffman M, Volovyk Z, Monroe D: **Partial reversal of dabigatran effect by a prothrombin complex concentrate in a model of thrombin generation.** *Blood* 2012, **120:**Abstract 3420.
56. 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.
57. Bayer Inc.: **Xarelto (Rivaroxaban) Product Monograph.** Toronto, Ontario: 2012.
58. Boehringer Ingelheim: **Pradaxa (Dabigatran Etexilate) Product Monograph.** Burlington, Ontario: 2012.
59. Pfizer Inc., Bristol-Myers Squibb: **Eliquis (apixaban) Product Monograph.** Kirkland, Quebec; Montreal, Quebec: 2011.
60. Frost C, Wang J, Nepal S, Schuster A, Barrett YC, Mosqueda-Garcia R, Reeves RA, Lacreta F: **Apixaban, an oral, direct factor Xa inhibitor: single-dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects.** *Br J Clin Pharmacol* 2013, 75:476-487.
61. 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.
62. 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.
63. Douxfils J, Mullier F, Robert S, Chatelain C, Chatelain B, Dogne JM: **Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate.** *Thromb Haemost* 2012, **107:**985-997.
64. Stangier J, Feuring M: **Using the HEMOCLOT direct thrombin inhibitor assay to determine plasma concentrations of dabigatran.** *Blood Coagul Fibrinolysis* 2012, **23:**138-143.65. DeRemer CE, Gujral JS, Thornton JW, Sorrentino RA: **Dabigatran falsely elevates point of care international normalized ratio results.** *Am J Med* 2011, **124:**e5-e6.
66. Baruch L, Sherman O: **Potential inaccuracy of point-of-care INR in dabigatran-treated patients.** *Ann Pharmacother* 2011, **45:**e40.
67. 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.
68. Samama MM, Martinoli JL, LeFlem L, Guinet C, Plu-Bureau, Depasse F, Perzborn E: **Assessment of laboratory assays to measure rivaroxaban – an oral, direct factor Xa inhibitor.** *Thromb Haemost* 2010, **103:**815-825.

69. Wong PC, Crain EJ, Watson CA, Xin B: **Favorable therapeutic index of the direct factor Xa inhibitors, apixaban and rivaroxaban, compared with the thrombin inhibitor dabigatran in rabbits.** *J Thromb Haemost* 2009, **7:**1313-1320.

doi:10.1186/cc12592
Cite this article as: Lazo-Langner A, *et al.*: Clinical review: Clinical management of new oral anticoagulants: a structured review with emphasis on the reversal of bleeding complications. *Critical Care* 2013, **17:**230.