

## INVITED REVIEW

# Managing bleeding in anticoagulated patients with a focus on novel therapeutic agents

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**Summary.** Heparin, low molecular weight heparin (LMWH) and coumarins are familiar to most clinicians, inexpensive, highly effective when correctly used and widely available. However, coumarin has a delayed onset of action, interacts with many medications, has a narrow therapeutic window, and can cause thrombosis in some settings (e.g. hereditary protein C deficiency, heparin induced thrombocytopenia, warfarin loading). Additionally, warfarin and heparin require monitoring of their therapeutic effect. These real and perceived limitations have led to the development of ‘novel’ anticoagulants. However, these new agents have one general limitation – a lack of a widely available antidote. We focus on the management of bleeding in anticoagulated patients, with particular regard to novel anticoagulants.

**Keywords:** clinical trials, hemorrhage, management, review.

## Introduction

Novel anticoagulant drugs that have been approved or which are undergoing clinical studies are predominantly direct inhibitors of coagulation which do not require an intermediate such as antithrombin [1]. Agents licensed in Europe and Canada include rivaroxaban and dabigatran (neither is approved in the United States); older agents include bivalirudin, hirudin and argatroban. Additional direct inhibitors of thrombin and factor Xa are under development [1].

To facilitate rapid reversal of anticoagulant effect of novel agents a specific antidote would be valuable. However, none exists [2,3]. Anticoagulation with novel agents is further complicated by a lack of validated and widely accessible laboratory tests which quantitatively and specifically measure their effect; thus unanticipated accumulation of these anticoagulants can occur, with bleeding potential. Traditional anticoagulant tests may be used to judge whether these drugs are present, for example prothrombin time (PT), activated

partial thromboplastin time (APTT), thrombin clotting time or anti-Xa heparin activity assay (Table 1). However, none has been validated as a quantitative measure of the amount of these anticoagulants present in an individual patient.

Both rivaroxaban and dabigatran have relatively long half-lives (~ 9 h and ~ 17 h, respectively). Thus, bleeding due to these agents may be prolonged as they are slowly cleared. Both agents are also partially dependent on renal function and thus in the setting of known or unanticipated renal insufficiency, bioaccumulation and prolonged elimination half-lives could worsen bleeding complications.

Development of guidelines for the management of bleeding is complicated by a lack of consensus on the definition of ‘major bleeding’. Thus, and for example, in orthopedic surgery studies (which form the basis for approval of novel antithrombotic agents) surgical site bleeding may or may not be defined as major bleeding. Transfusion of red blood cells generally indicates major bleeding, although in some studies, the pre- and post-transfusion hemoglobin is also factored into the assessment of bleeding. The number of units constituting major bleeding varies from as few as 2 U to 5 or more units. Bleeding that is fatal, into an enclosed space, or requiring a major therapeutic intervention is generally regarded as major. A lack of consensus has led to confusion around the rate of bleeding with various agents, and has hampered design of studies of therapies for bleeding.

## Methods

We intended a systematic evaluation of the literature available to guide management of anticoagulant-associated bleeding. A MEDLINE search using the terms ‘rivaroxaban AND bleeding AND treatment’ limited to clinical trials yielded 13 references, none relevant to the subject of treatment of bleeding complications. Similarly, a MEDLINE search using the terms ‘dabigatran AND bleeding AND treatment’ limited to clinical trials yielded eight results, also none relevant. A search of the OVID database using the terms (Dabigatran OR rivaroxaban) AND (factor VIIa OR plasma OR prothrombin complex concentrate) produced one irrelevant result (all searches performed January 28, 2009). Similar searches for

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**Table 1** Impact of rivaroxaban and dabigatran on commonly used coagulation tests. The real effect of an agent on an individual laboratory in any particular patient is variable. In particular, dose and time since dosing will markedly impact the degree of prolongation of the laboratory test [19,20]

	Prothrombin time (INR)	Activated partial thromboplastin time	Fibrinogen	Thrombin clotting time	Ecarin clotting time
Dabigatran	↑	↑	No change*	↑↑↑	↑↑↑
Rivaroxaban	↑↑	↑↑	No change	No change	No change

\*Certain thrombin-based fibrinogen assays can yield falsely low fibrinogen levels in the presence of high concentrations of direct thrombin inhibitors.

desmopressin acetate (DDAVP), antifibrinolytic agents and hemodialysis, hemofiltration, and plasmapheresis yielded no references. Therefore, we present a narrative review providing general advice for the management of bleeding.

### Bleeding risks with novel anticoagulants

#### *Risk of bleeding with rivaroxaban*

In a large randomized trial that evaluated four different rivaroxaban doses for the treatment of acute deep vein thrombosis (DVT), major bleeding was observed in 1.7%–3.3% of patients [4]. The combination of major and clinically relevant non-major bleeding occurred in 2.2%–6.6% of patients in a second study evaluating different rivaroxaban doses for DVT treatment [5]. Major bleeding rates < 1% were seen in thromboprophylaxis studies of short-duration rivaroxaban [6]. In earlier studies, a dose-dependent increase in bleeding was observed when rivaroxaban was used at doses exceeding those approved for thromboprophylaxis [7]. In summary, using 'standard' prophylactic doses (10–20 mg once daily), major bleeding will be seen in < 1% of patients receiving rivaroxaban. Rates increase somewhat as the duration of therapy is increased (for example, for treatment of DVT).

#### *Risk of bleeding with dabigatran*

In a stroke prevention study, major bleeding was only observed in patients treated with a large dose (400 mg BID)

**Table 2** Principals of management of anticoagulant associated bleeding

Assess and monitor vital signs – intervene as required with life-saving therapies
Consider transfer to intensive care setting
Alert other health care professionals including radiology, endoscopy, surgery, as required
Measure the coagulation cascade and complete blood count – reassess periodically if bleeding continues
Withdraw the anticoagulant
Address mechanical causes of bleeding using interventional procedures
Consider administration of non-specific prohemostatic agents
Antifibrinolytics
DDAVP
rFVIIa
Activated prothrombin complex concentrates
Consider modalities that may remove the anticoagulant
Hemodialysis
Hemoperfusion
Plasmapheresis

of dabigatran in combination with aspirin [8]. In a study of patients, undergoing total hip replacement, major bleeding occurred in 2.0% and 1.3% of patients treated with a short-course 220 and 150 mg twice daily dabigatran dose, respectively [9].

### Management of bleeding in patients receiving novel antithrombotic agents

Given the emergent, unpredictable, and heterogeneous nature of bleeding, randomized trials or even large cohort studies will be difficult or impossible to perform. More likely, 'weak' recommendations will be based on case series and anecdotal experience. For rivaroxaban and dabigatran, even case series are lacking; our recommendations are based on theoretical rationale and anecdote.

#### *Blood product transfusion*

Transfusion of blood products, usually plasma, is often used to manage anticoagulant-associated bleeding. However, except in the presence of a dilutional coagulopathy, there is neither evidence nor rationale to support use of either plasma or PCC as adjunct to treatment of patients who are actively bleeding as a result of novel anticoagulant use. Clinicians may be tempted to transfuse plasma as rivaroxaban and dabigatran prolong the PT and APTT. However, prolongation is due to inhibition of coagulation rather than coagulation factor depletion. Coagulation factor inhibition is not effectively treated by plasma. Administration of activated PCCs reduces bleeding in dabigatran treated animals [10,11]. Whether it ameliorates bleeding in patients remains unknown.

### Other agents for anticoagulant reversal

Recombinant factor VIIa (rFVIIa) rFVIIa is a potent procoagulant that can generate thrombin even in the absence of tissue factor [12]. As a result, this agent has been proposed to reverse a variety of anticoagulants. Although normal volunteer and *ex vivo* data suggest that rFVIIa antagonizes the anticoagulant effect of a variety of agents [2], particularly dabigatran [10,11], there are no data demonstrating utility in actively bleeding patients. Thrombosis may complicate its use [13]. A Medline search using the terms VIIa AND (dabigatran OR rivaroxaban) yielded four references, none relevant to the topic at hand.

### *Desmopressin*

Desmopressin acetate (DDAVP) stimulates release of factor VIII and vWF from endothelial stores. DDAVP is widely used for the treatment or prevention of bleeding in patients with mild hemophilia A, type I von Willebrand disease, and congenital platelet dysfunction. Although DDAVP has been studied as an agent to reduce the anticoagulant effect of a variety of novel agents, there are no data in actively bleeding patients treated with rivaroxaban or dabigatran. DDAVP is an analog of vasopressin and retains associated side effects such as headaches, palpitations and facial flushing. It also produces clinically significant hyponatremia due to water retention, with potential to induce seizures. Its safety over > 30 years of use has been recently reviewed [14].

### *Antifibrinolytic therapy*

Tranexamic acid and  $\epsilon$ -aminocaproic acid block the proteolytic site of plasmin and inhibit plasminogen activator incorporation into the fibrin clot. These agents have been studied in patients undergoing orthopedic, urological, and cardiac surgery [15,16]. These agents have not been studied as an adjunct to other therapies for patients with anticoagulant associated bleeding.

### *Hemodialysis, hemofiltration, and plasmapheresis*

Mechanical strategies to remove anticoagulants might be considered in patients with life-threatening bleeding or those with large overdoses. Selected high-flux hemodialyzer membranes remove hirudin [17]. Plasmapheresis and hemoperfusion have both been used in cases of anticoagulant overdose, although neither intervention is supported by good-quality evidence.

### **Management strategies in the event of a major bleed**

Recommendations for treatment of actively bleeding patients receiving anticoagulants are based on anecdotal experience and 'common sense' (Table 2). The fundamentals of bleeding management include a rapid and focused patient evaluation aimed at determining the patient's hemodynamic stability and the source, cause, and severity of bleeding. If the bleeding is minor, simple packing and/or dressing may be all that is required; in some cases, anticoagulants may even be continued, perhaps at a lower dose.

In the presence of major bleeding, more rapid and oftentimes invasive approaches are required. Care may require a team of experienced clinicians particularly if hypovolemic shock or end-organ dysfunction is present. Life saving interventions, such as mechanical ventilation and hemodynamic support should be provided. Identifying the cause of the bleeding may require endoscopy, surgery, or interventional radiology. Although proceduralists may hesitate to intervene in an anticoagulated patient, the risks associated with unmanaged bleeding far outweigh the risks of procedure-associated hemorrhage.

It is important to maintain body temperature, blood pH, and electrolyte balance. Frequent monitoring of coagulation tests and the complete blood count is required; massively transfused patients may require replacement of plasma and/or platelets in addition to red blood cells. Plasma and cryoprecipitate should not be given unless there is evidence of hemostatic factor deficiency. Inappropriate transfusion therapy may also delay other needed therapies, and can produce an 'unreasonable expectation of efficacy'.

As there are no specific reversal agents for rivaroxaban or dabigatran, use of DDAVP or antifibrinolytic agents might be considered. Activated PCC or rFVIIa should be considered as a 'last resort' in instances of life-threatening bleeding when conventional treatment methods have failed. The development of specific antidotes for the anticoagulant effect of novel agents would be useful. However, of products in development, only biotinylated idraparinux has an effective antidote; this product is currently in late phase clinical trials for selected indications [18].

Although wide-bore intravenous access is essential in the management of the critically ill, indwelling capped central venous catheters should not be used for fluid resuscitation until the indwelling fluid has been withdrawn along with an adequate blood discard (minimum of 10 mL). If this is not done, the anticoagulant dwelling in the line will be flushed into the patient. Anticoagulant-containing intravenous (IV) solutions should be removed from the patient's bedside to avoid inadvertent administration. A supply of protamine, DDAVP, and antifibrinolytic agents should be easily accessible in at least one location in the hospital to avoid the need to contact employees to obtain medication should bleeding occur after usual pharmacy hours. Finally, guidelines for the treatment of major or life-threatening bleeding should be developed and be easily accessible at each hospital.

### **Conclusions**

Although novel anticoagulants offer great promise, they will cause bleeding, and lack effective antidotes. Managing bleeding is therefore challenging. Fundamentals of care include rapid clinical assessment of the source, cause, and severity of bleeding, and prompt appropriate action, both mechanical and systemic, to control the bleeding.

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## References

- Weitz JI, Hirsh J, Samama MM. New antithrombotic drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn.). *Chest* 2008; **133**(6 Suppl): 234S–56S.
- Kessler CM. Current and future challenges of antithrombotic agents and anticoagulants: strategies for reversal of hemorrhagic complications. *Semin Hematol* 2004; **41**(1 Suppl 1): 44–50.
- Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. *Blood* 2008; **111**: 4871–4879.
- Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, Kakkar AK, Misselwitz F, Schellong S, ODI-XA-DVT study Investigators. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODI-Xa-DVT (oral direct factor Xa inhibitor BAY 59-7939 in patients with acute symptomatic deep-vein thrombosis) study. *Circulation* 2007; **116**: 180–7.
- Buller HR, Lensing AW, Prins MH, Agnelli G, Cohen A, Gallus AS, *et al.* A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT dose-ranging study. *Blood* 2008; **112**: 2242–7.
- Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, *et al.* Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; **358**: 2765–75.
- Fisher WD, Eriksson BI, Bauer KA, Borris L, Dahl OE, Gent M, *et al.* Rivaroxaban for thromboprophylaxis after orthopaedic surgery: pooled analysis of two studies. *Thromb Haemost* 2007; **97**: 931–7.
- Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, *et al.* Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol* 2007; **100**: 1419–26.
- Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, *et al.* Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007; **370**: 949–56.
- van Ryn D, Ruehl H, Priepe N, Huel W, Wienen W. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran by recombinant factor VIIa or activated prothrombin concentrate complex. *Haematologia* 2008; **93**(Suppl. 1): 148.
- Wienen W, Ruehl D, Stassen JM, Priepe H, Ries UJ, Huel N. Effect of recombinant factor VIIa or activated prothrombin complex concentrate on the bleeding time in anaesthetized rats during anticoagulant treatment with the direct thrombin inhibitor dabigatran. *J Thromb Haemost* 2008; **3**(Suppl. 1): P1703.
- Ovanesov MV, Pantelev MA, Sinauridze EI, Kireev DA, Plyushch OP, Kopylov KG, *et al.* Mechanisms of action of recombinant activated factor VII in the context of tissue factor concentration and distribution. *Blood Coagul Fibrinolysis* 2008; **19**: 743–55.
- 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**: 61–8.
- Vande WJ, Stockner M, Raes A, Norgaard JP. Desmopressin 30 years in clinical use: a safety review. *Curr Drug Saf* 2007; **2**: 232–8.
- Mahdy AM, Webster NR. Perioperative systemic haemostatic agents. *Br J Anaesth* 2004; **93**: 842–58.
- Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. *Thromb Res* 2009; **123**: 687–96.
- Benz K, Nauck MA, Bohler J, Fischer KG. Hemofiltration of recombinant hirudin by different hemodialyzer membranes: implications for clinical use. *Clin J Am Soc Nephrol* 2007; **2**: 470–6.
- Savi P, Herault JP, Duchaussoy P, Millet L, Schaeffer P, Petitou M, *et al.* Reversible biotinylated oligosaccharides: a new approach for a better management of anticoagulant therapy. *J Thromb Haemost* 2008; **6**: 1697–706.
- 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.
- 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**: 873–80.