Management of Bleeding in Patients who are Receiving a New Oral Anticoagulant (dabigatran, rivaroxaban, apixaban)

Thrombosis Canada

Thrombose Canada

Target Audience: All Canadian health care professionals.

Objective:

To assist clinicians in the management of minor, major, and/or life-threatening bleeding in patients receiving new oral anticoagulants (NOACs).

Abbreviations:

aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
BID	twice daily
ECT	ecarin clotting time
ETP	endogenous thrombin potential
FEIBA	factor eight inhibitor bypass activity
FFP	fresh frozen plasma
NOAC	new oral anticoagulant
PCC	prothrombin complex concentrate
pRBC	packed red blood cell
PT	prothrombin time
rFVIIa	activated recombinant factor VII
TCT	thrombin clotting time

Background:

Three NOACs (dabigatran, rivaroxaban, apixaban) are approved for clinical use in Canada based on findings from large, well-designed, randomized trials.

Types of Clinical Bleeding:

- **Major bleeding:** a bleed that requires medical attention and, possibly, blood transfusion with or without administration of pro-hemostatic agents. These bleeds are usually symptomatic and involve a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome) or they cause a fall in hemoglobin ≥ 20 g/L. Major bleeding sites include: gastrointestinal (~80%), genitourinary, intracranial (subdural [most common], intracerebral [worst prognosis: 45-50% case-fatality], subarachnoid), soft tissue and intra-articular (typically traumatic).

- **Minor bleeding:** a bleed that may require medical attention but usually does not require transfusion or hospitalization, is usually self-limiting and does not require interruption of anticoagulant medication, and does not involve a critical site. Minor bleeds include: epistaxis; hemorrhoids; ecchymosis; subconjunctival; and bleeding related to minor trauma. Interruption of anticoagulation and medical intervention may become necessary if the bleed is not self-limited (e.g. epistaxis associated with a posterior bleeding source or ongoing hemorrhoid bleed).

MANAGEMENT:

General principles for NOAC-associated major bleeding:

This applies to any anticoagulant-associated bleeding and comprises:

- resuscitation (fluids, oxygen)
- bleeding source identification and control (packing, cauterization)
- drug cessation
- appropriate blood product use: packed red blood cells (pRBCs) if low hemoglobin and/or hemodynamic compromise; plasma and/or cryoprecipitate in cases of massive (> 8-10 pRBCs) transfusion

Activated charcoal can be considered if the offending NOAC was taken within 2 hours.

Current evidence for NOAC-associated life-threatening/intracranial bleeding:

Use of prohemostatic agents should be considered, although supportive clinical data are lacking (current knowledge summarized in **Table 1**). Two studies in healthy volunteers assessed the use of prohemostatic agents to neutralize the anticoagulant effect of NOACs:

- In one study, subjects received rivaroxaban (20 mg twice daily (BID)) or dabigatran (150 mg BID) for 2½ days after which they received 50 IU/kg of 4-factor prothrombin complex concentrate (PCC). With rivaroxaban, the prothrombin time (PT) and the endogenous thrombin potential (ETP) corrected to normal after PCC administration whereas in patients receiving dabigatran there were no corrections in the activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), ETP or thrombin clotting time (TCT). See NOAC: Monitoring guide.
- In another study, subjects received one dose of rivaroxaban (20 mg) or dabigatran (150 mg) and blood samples were obtained 2 hours afterwards and tested *ex vivo* after adding PCC, FEIBA or rFVIIa. With rivaroxaban, correction of coagulation parameters was best achieved with FEIBA, with less efficient corrections achieved with PCC and rFVIIa. With dabigatran, rFVIIa and FEIBA had better correction of coagulation parameters than PCC.

Use of Prohemostatic Agents in NOAC-associated Bleeding

It should be recognized that there is a small but clinically-important prothrombotic risk when administering these agents, as their use has been associated with an increased risk for venous and mainly arterial thrombosis.

Antifibrinloytics agents

The use of antifibrinolytic agents such as aminocaproic acid (Amicar™) and tranexamic acid (Cyclokapron™) has no supporting evidence of benefit.

PCCs (Octaplex™, Beriplex™), aPCCs (FEIBA™), rFVIIa (NovoSeven™, Niastase™):

It should be recognized that these prohemostastic agents are not NOAC antidotes and do not affect the ongoing inhibitory effect of these drugs on coagulation factors IIa (thrombin) and Xa. It is possible, however, that prohemostatic agents may lessen NOAC-related bleeding by bypassing the inhibitory effect of these drugs by providing massive amounts of factors II and X. Previous studies in patients with intracerebral bleeding suggest that although prohemostatic agents can limit the extent of bleeding, their effect on mortality and disability might be minimal.

Cryoprecipate and FFP:

Cryoprecipate, which contains mainly fibrinogen and factor VIII, and fresh frozen plasma (FFP), are unlikely to have a clinically-significant effect of reversing the anticoagulant effect of NOACs.

SPECIAL CONSIDERATIONS:

Patients with renal impairment:

Hemodialysis may be considered for patients receiving dabigatran with acute renal failure who are bleeding and have laboratory evidence of an excessive anticoagulant effect (i.e. elevated aPTT). However, clinical experience in such circumstances is limited. One study showed that hemodialysis removes 62-68% of drug after a single 50 mg dabigatran dose in patients with end-stage renal disease. Another study suggests that dabigatran could be removed with the use of dialysis and activated charcoal hemoperfusion columns.

Development of antidotes:

A number of antidotes to NOACs are currently in different phases of development. They include monoclonal antibodies and small molecules with specific affinity for NOACs.

PEDIATRICS:

There are no studies evaluating the management of bleeding in children receiving NOACs.

REFERENCES:

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Table 1. Prohemostatic Agents and their Potential Role in NOAC-associated Bleeding[a]

Agent	Dabigatran	Rivaroxaban or Apixaban[b]
4-Factor Prothrombinase Complex Concentrate (PCC; Beriplex, Octaplex)	Possibly beneficial	Probably beneficial
Activated 4-Factor Prothrombinase Complex Concentrate (FEIBA)	Probably beneficial	Probably beneficial
Recombinant activated Factor VII (Novoseven, Niastase)	Possibly beneficial	Possibly beneficial
Fresh frozen plasma	Probably ineffective	Probably ineffective
Cryoprecipitate	Probably ineffective	Probably ineffective
3-Factor Prothrombinase Complex Concentrate	No available evidence	No available evidence
Antifibrinolytic agents (Aminocaproic acid – Amicar; Tranexamic acid – Cyklokapron)	No available evidence	No available evidence

[a] 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.

[b] Only one study has assessed the effect of these agents on apixaban. The possible clinical role of these agents is theoretical and is based on extrapolation of evidence available for rivaroxaban

Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.