



Nova Scotia Provincial Blood Coordinating Team

# Nova Scotia Guideline for the Management of Patients on Vitamin K Antagonists or Direct Oral Anticoagulants Utilizing Prothrombin Complex Concentrates

Version 4.0  
September 2020

**PROMOTING EXCELLENCE IN TRANSFUSION MEDICINE**  
<http://www.cdha.nshealth.ca/nova-scotia-provincial-blood-coordinating-team>

**Developed by the Prothrombin Complex Concentrate Working Group ([Appendix A](#))**  
with input from **New Anticoagulants and Bleeding Working Group ([Appendix B](#))**  
regarding Direct Oral Anticoagulants

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## 1. BACKGROUND

The Nova Scotia Provincial Blood Coordinating Team (NSPBCT) provides leadership in collaborating with health care providers across the province and Canadian Blood Services (CBS) to maximize the safe and appropriate management of blood and blood products for patients in Nova Scotia. The NSPBCT maintains a surveillance program for adverse events related to transfusion therapy while ensuring appropriate standards for blood-transfusion therapy are being implemented and maintained within Nova Scotia health-care facilities.

In 2009, the NSPBCT convened a physician working group for the development of the Utilization Guidelines for *Prothrombin Complex Concentrates (PCC)*. At the same time, the NSPBCT began collecting utilization data for PCCs within Nova Scotia. The guideline was revised in 2012 and 2013 when the National Advisory Committee on Blood and Blood Products (NAC) provided updated versions of their recommendations. In 2014, NAC revised their *Recommendations for Use of Prothrombin Complex Concentrates in Canada*. The PCC working group ([Appendix A](#)) was reconvened in 2015 and the guideline has been adapted from the 2014 NAC recommendations with the dosing recommendations based on data results from PCC utilization in Nova Scotia. With the introduction of reversal agents for some direct oral anticoagulants (DOACs), the NSPBCT has included recommendations from the New Anticoagulants and Bleeding Working Group (NAB WG) ([Appendix B](#)) for the care of patients receiving DOACs in the guideline ([Appendix C](#)).

The *Nova Scotia Guideline for the Management of Patients on Vitamin K Antagonists or Direct Oral Anticoagulants utilizing Prothrombin Complex Concentrates* is intended for provincial implementation.

## 2. INTRODUCTION

Oral vitamin K antagonists (VKAs) such as warfarin (Coumadin®) or acenocoumarol (Sintrom®) and Direct Oral Anti Coagulants (DOACs), such as apixaban (Eliquis®), dabigatran (Pradaxa®), edoxaban (Lixiana®) and rivaroxaban (Xarelto®) are administered for the prevention and treatment of thromboembolic disorders. VKAs reduce blood clotting by inhibiting the activation of vitamin K dependent clotting factors II, VII, IX and X. Unlike vitamin K antagonists, DOACs act by directly interfering with specific clotting factors in the coagulation cascade. Dabigatran is a direct thrombin (Factor II) inhibitor whereas apixaban, edoxaban and rivaroxaban are direct factor Xa inhibitors. The main adverse effect of all anticoagulants is bleeding. For patient on prolonged warfarin the average annual rate of major bleeding is in the range of 1- 3%, while minor bleeding events occur in 10-20%.<sup>3, 4</sup> DOACs are considered safer than VKAs and the risk of major bleeding is lower than that of warfarin, however serious bleeding does still occur.<sup>4, 5</sup> When bleeding is life threatening or when urgent surgery is required rapid reversal of VKAs or DOACs anticoagulant effects is critical in mitigating patient morbidity and mortality.

The objective of the *Nova Scotia Guideline for the Management of Patients on Vitamin K Antagonists or Direct Oral Anticoagulants Utilizing Prothrombin Complex Concentrates* is to provide evidence based recommendations for the clinical management of bleeding patients on anticoagulant therapy. This document provides healthcare professionals guidance in situations where the reversal of VKAs and DOACs has proven beneficial to patient outcome. The intent is to standardize patient care and to ensure the appropriate utilization of antithrombotic reversal agents.

Prothrombin complex concentrates (PCCs) (octaplex® and Beriplex®P/N), are coagulation factor concentrates derived from human plasma, that have been licensed for use by Health Canada. In Canada, PCCs contain 4 coagulation factors (Factors II, VII, IX, X) in addition to heparin and the coagulation inhibitors protein C and protein S.

PCC administration along with Vitamin K is the most effective method for the rapid reversal of the anticoagulation effect of VKAs. Currently, there are no Health Canada approved reversal agents for the direct factor Xa inhibitors, apixaban, edoxaban and rivaroxaban, however, evaluation for specific reversal agents is ongoing. Although PCCs do not interfere with the inhibitory effects of DOACs and are considered a nonspecific indirect reversal strategy, published evidence suggests that PCC may be effective in managing DOAC associated bleeding.<sup>3, 6</sup>

Due to the potential for thrombotic complications, treatment with PCCs should be initiated under the supervision of a clinician experienced in the treatment of coagulation disorders (e.g. emergency clinicians, hematologists, anesthesiologists). The use of PCCs requires careful risk benefit evaluation with awareness of contraindications and laboratory follow-up for dose adjustment.

In order to monitor adherence to the *Nova Scotia Guideline for the Management of Patients on Vitamin K Antagonists or Direct Oral Anticoagulants, Utilizing Prothrombin Complex Concentrates* PCC utilization is reported to the NSPBCT on a quarterly basis by NSHA Transfusion Services.

### 3. DEFINITIONS

**Coagulopathy** - a condition where the ability to form clots/coagulate is impaired causing a tendency to have prolonged or excessive bleeding either spontaneously or with invasive or surgical procedures.

**Direct Oral Anticoagulants (DOACs)** - anticoagulants inhibiting clot formation by inhibiting factor Xa or thrombin activity. Apixaban, edoxaban and rivaroxaban are direct inhibitors of factor Xa, whereas dabigatran is a direct thrombin inhibitor.

**INR (International Normalized Ratio)** - a standardized method of reporting prothrombin time (PT) normalized for the different types of PT reagents available in laboratories.

**Major Bleeding** - acute major bleeding that includes one of the following: potentially life threatening, hemorrhage with a drop in Hgb of greater than or equal to 20 g/L or requiring transfusion of 2 units of RBC or critical site bleeding (i.e. intracranial, retroperitoneal, intra-spinal, intra-ocular, intra-articular or pericardial, ruptured abdominal aortic aneurysm, acute dissection, intramuscular with compartment syndrome)

**Prothrombin Complex Concentrate (PCC)** - a lyophilized plasma protein product (PPP) derived from human plasma containing the vitamin K dependent coagulation factors.

**Vitamin K Antagonist (VKA)** - an anticoagulant inhibiting the synthesis of vitamin K dependent clotting factors (Factors II, VII, IX and X, and the anticoagulant proteins C and S). The vitamin K antagonists referred to in this guideline are the oral medications - warfarin (Coumadin®) or acenocoumarol (Sintrom®).

## 4. PCC USE FOR REVERSAL OF VITAMIN K ANTAGONISTS

### 4.1. INDICATIONS FOR USE

Rapid reversal of VKAs or vitamin K deficiency in patients with an INR greater than or equal to 1.7 **AND** who have major bleeding and/or require urgent surgical or other interventional procedures within 6 hours.

*The 6 hour recommendation reflects the half-life of the product and does not apply to the urgency of the surgery/procedure.<sup>8</sup>*

It is recommended the INR be available prior to administering PCCs, however, in emergent situations (i.e. major bleeding or intracranial hemorrhage) where the INR result is delayed or not available and it is known the patient is taking a VKA, the administration of PCCs is acceptable with the understanding the INR will be collected prior to PCC administration.

For management of VKA treatment with a supratherapeutic INR in the absence of bleeding, it is recommended clinicians refer to the American College of Chest Physicians (ACCP) 2012 recommendations (Table 1). In most instances, reduction of the VKA dose and/or administration of Vitamin K is usually sufficient for patient management.<sup>7</sup>

Table 1: CHEST Guidelines for the Management of Elevated INRs while on Vitamin K Antagonist Therapy<sup>7</sup>

Condition	Recommendation
INR 4.5 to 10 <i>No evidence of bleeding</i>	Do not administer vitamin K. Hold or lower the dose of VKA
INR greater than 10 <i>No evidence of bleeding</i>	Administer oral vitamin K. Hold or lower the dose of VKA
<i>Major bleeding</i>	Rapid reversal of VKA with PCC rather than plasma and slow administration of vitamin K 5-10 mg IV.

*“It is critical to recognize that the use of prothrombin complex concentrates may unmask thrombotic risk factors that were being managed through the use of Vitamin K antagonists”.<sup>8</sup>*

### 4.2. RECOMMENDED DOSING

The following dosing recommendations are based on utilization data results received from Nova Scotia hospitals from - April 2013 to March 2015

Table 3: PCC Dosing for Pediatrics for Vitamin K Antagonist Reversal<sup>15</sup>

Weight (Kg)	INR < 3	INR ≥ 3
< 10	10 mL	20 mL
10 - 25	20 mL	30 mL
25 - 50	30 mL	40 mL

**This pediatric dosing strategy does not replace the need for consultation and approval from a pediatric hematologist prior to administration.**

### 4.3. MONITORING

**Pre-dose monitoring:** A pre-dose INR is required. There may be situations where the clinician cannot wait for the INR result prior to administering the PCC dose, however the pre-PCC INR should be collected and determined.

**Post-dose monitoring:** Efficacy of dosing must be determined by testing the INR 10 - 30 minutes post PCC administration. The post PCC administration target INR is less than or equal to 1.7, however for intracranial hemorrhage, the target INR is less than 1.3. If the target INR is not obtained after initial or subsequent doses, consider administering an additional PCC dose of 20 mL (500 IU). It is recommended to recheck the INR 24 hours post PCC administration.

**NOTE: In emergency situations in the OR, PCC can be dispensed prior to receiving an INR. In all other situations, an INR is required prior to dispense.**

It is recommended that clinical outcomes (including thrombotic events) be assessed by clinicians at 24 hours and upon hospital discharge or 30 days post PCC administration, whichever comes first. Any adverse events that the PCC may have contributed to are to be reported to Transfusion Services.

## 5. PCC USE FOR REVERSAL OF DIRECT ORAL ANTICOAGULANTS

### 5.1. INDICATIONS FOR USE

PCCs may be considered as a reasonable option for the management of direct factor Xa inhibitors, apixaban (Eliquis®), edoxaban (Lixiana®) and rivaroxaban (Xarelto®) in the following circumstances:

<b>Life-threatening/critical site bleeding</b>	Hemorrhage resulting in airway compromise Hemorrhage with a drop in Hgb of greater than or equal to 20 g/L or transfused 2 or more RBC units Intracranial hemorrhage Major trauma Intra-articular Intra-ocular Intra-spinal Limb - compromising vascular supply and limb viability Retroperitoneal
<b>Emergency surgery</b>	Bowel obstruction Cardiac surgery (urgent) Cord compression Ischemic bowel Open fracture Ruptured AAA Ruptured spleen

Given the short half-life of DOAC and their quick off set of anticoagulants effects in patients with normal renal function, as well as the low but clinically relevant rate of thrombotic events after administration of PCC, this treatment option should be reserved

for the life-threatening bleeding/emergency surgeries stated above.<sup>4, 6, 9</sup> **Situations outside of this require approval of the Transfusion Medicine Physician or designate.**

## 5.2. RECOMMENDED DOSING

Due to the relatively short half-lives of these medications, discontinuation of anticoagulant therapy can be sufficient enough to manage non-life threatening bleeds. The appropriate assessment for the level of reversal in DOAC related bleeding requires evaluation of the patient's last dose, renal function and either the extent of bleeding or time to surgical intervention.<sup>6,9</sup>

For the management of apixaban, edoxaban or rivaroxaban in life-threatening/critical site bleeding or when emergency surgery is required, the PCC dose is a **fixed dose of 80 mL (2000 IU)**. If significant bleeding continues the Transfusion Medicine Physician should be consulted before an additional dose is given. If an additional dose is given, the maximum total should not exceed 120 mL (3000 IU).

PCC is not recommended for the reversal of dabigatran. Idarucizumab (Praxbind®) is a pharmacy-issued drug used for the specific reversal of dabigatran. This antidote is intended for patients with suspected or proven dabigatran related coagulopathy and experiencing life threatening bleeding or requiring emergency surgical intervention.

## 5.3. MONITORING

Unlike VKAs, the DOACs have a fast onset of action and are given as fixed dosing regimens without routine coagulation monitoring because of their more predictable pharmacokinetics and pharmacodynamics. There is currently no readily available, "routine laboratory" test that can accurately monitor the anticoagulant effect of dabigatran, apixaban, edoxaban, and rivaroxaban in a manner similar to how the INR is used to monitor VKA therapy.<sup>10</sup> For most indications, PT/INR & PTT monitoring will identify whether significant residual medication effect remains from a qualitative perspective only. Regardless of these limitations, coagulation testing and/or drug levels may be helpful in certain clinical scenarios such as in patients with life-threatening bleeding events.

With respect to DOAC treated patients and common coagulation tests, a highly elevated aPTT (i.e. greater than 80 sec) indicates an anticoagulant effect of dabigatran.<sup>6, 10</sup> A prolonged PT is more suggestive of anticoagulant effects from factor Xa inhibitors apixaban, edoxaban, or rivaroxaban. However, it is important to note that the usefulness of these common tests is limited due to the fact that a normal aPTT or PT does not exclude clinically relevant plasma levels of dabigatran and factor Xa inhibitors.

Specialized coagulation tests, such as thrombin time (TT) and drug specific anti-factor Xa assays can be used to measure the anticoagulant effects of DOACs. However, due to these tests not being widely available, delayed turnaround times may reduce their usefulness in emergency situations. The thrombin time is the most sensitive test for dabigatran, as even low levels of dabigatran will prolong the TT.<sup>6, 10</sup> Drug specific anti-factor Xa assays are recommended for quantifying the anticoagulant activity of apixaban, edoxaban, and rivaroxaban. Anti-Xa assays specific for low-molecular-weight heparins should not be used to monitor these drugs.



Table 4: Effect of Direct Oral Anticoagulants on Laboratory Coagulation Tests<sup>10</sup>

Laboratory Test	Dabigatran (thrombin inhibitor)	Apixaban, Edoxaban or Rivaroxaban (Xa inhibitor)
Prothrombin time (PT) and International Normalized Ratio (INR)	Variable effect (usually INR < 2.0 at peak blood levels)	Rivaroxaban and edoxaban can increase; apixaban has a minimal effect
Activated partial thromboplastin time (aPTT)	Non-linear increase	Rivaroxaban and edoxaban can increase; apixaban has a minimal effect
Thrombin Time (TT) (not widely available)	Increase; if normal no detectable anticoagulant effect	No effect
Anti-factor Xa level (not widely available)	No effect	Can be used to measure anticoagulant effect

## 6. CONTRAINDICATIONS

PCCs are not indicated for the following:

- In patients with a history of heparin induced thrombocytopenia (HIT) as the products contain heparin.
- Those who have shown hypersensitivity to any ingredient in the product
- In patients with immunoglobulin A (IgA) deficiency, with known antibodies against IgA (octaplex only)
- For the treatment of intracranial hemorrhage or other bleeding occurring as a complication of thrombolytic therapy

PCCs are generally not recommended\* for:

- Elective reversal of oral anticoagulant therapy pre - invasive procedure
- Treatment of elevated INRs without bleeding or need for surgery or other interventional
- For treatment (refer to the ACCP 2012 recommendations)
- Massive transfusion
- Coagulopathy associated with liver dysfunction
- Disseminated intravascular coagulopathy (DIC)
- Utmost caution should be used in patients with a recent (within three months) history of thrombosis (myocardial infarction, ischemic stroke or thromboembolism)

## 7. SPECIAL PATIENT POPULATIONS\*

- There is insufficient published evidence to recommend the use of PCCs in pregnant and lactating women. Caution should be exercised if used in pregnancy, particularly in the peripartum/early postpartum period because of the heightened tendency for thrombosis.

- Although there appears to be potential advantages for PCC use in pediatric patients the product manufacturer and Canadian Advisory Committee (NAC) reports that there is insufficient data to allow for any recommendation.
- The use and dosing of the product for congenital factor II or X deficient patients should be at the discretion of the bleeding disorder/hemophilia clinic.
- PCCs are not indicated for the reversal of dabigatran (Pradaxa®). Idarucizumab (Praxbind™) is a pharmacy-issued drug for the reversal of dabigatran in life-threatening bleeding situations. Call pharmacy for dosing and administration.
- There is insufficient published evidence to recommend PCCs for the reversal of the following direct thrombin inhibitors (Argatroban, bivalirudin) or factor Xa inhibitors (dalteparin, danaparoid, enoxaparin, tinzaparin, fondaparinux).

*\*There may be extenuating clinical circumstances necessitating the use of PCCs in these clinical situations where the benefit outweighs the risk. They should be evaluated on a case-by-case basis with a clinician experienced in the use of this product. If the decision is made to use the product off-label in liver dysfunction and DIC, consult the product monograph for further recommendations (e.g. the need for antithrombin levels or replacement).<sup>8</sup>*

## **Disclaimer**

This guideline establishes the preferred approach for PCC administration in the typical population of patients on anticoagulant therapy. Clinical guidelines support healthcare practitioners' decision making by providing them with evidence based research and current best practice models of care. They are not intended to provide a protocol that fits every patient's clinical needs or replace a clinician's judgment. No guideline can account for all clinical scenarios nor do they establish the only acceptable approach for addressing a patient's healthcare needs.

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## Appendix A – Prothrombin Complex Concentrates Working Group Members

The NSPBCT acknowledges the tremendous and diligent work of the provincial PCC WG for providing valuable expertise and contributions in the development of this guideline.

<b>Prothrombin Complex Concentrates Working Group</b>	
Dr. Frank Cragg	Medical Leader (Blood Transfusion and Hematology), Cape Breton Regional Hospital
Dr. Brian Jollymore	Medical Director, Blood Transfusion Services, Valley Regional Hospital
Dr. Eiad Kahwash	Medical Director, Canadian Blood Services, Nova Scotia and Prince Edward Island
Dr. Blaine Kent	Chief, Division of Cardiac Anesthesia; Surgical Director of Perioperative Blood Management Program, Queen Elizabeth II Health Sciences Centre
Dr. Jean F. Legare	Cardiac Surgeon, Queen Elizabeth II Health Sciences Centre
Dr. Stephen Phillips	Stroke Neurologist, Queen Elizabeth II Health Sciences Centre
Dr. Victoria Price	Pediatrician/Hematologist, IWK Health Centre
Dr. Irene Sadek	Medical Director, Pathology & Laboratory Medicine, Department of Pathology and Laboratory Medicine, Queen Elizabeth II Health Sciences Centre
<b>Nova Scotia Provincial Blood Coordinating Team (NSPBCT)</b>	
Dr. Sudeep Shivakumar	Clinical Advisor
Jennifer LeFrense	Nova Scotia Provincial Blood Coordinating Team Manager
Jill Wilson	Utilization Management Coordinator

## Appendix B – New Anticoagulants & Bleeding Working Group (NAB WG)

The NSPBCT acknowledges the tremendous and diligent work of the Atlantic NAB WG for providing valuable expertise and contributions in the development of this guideline.

<b>New Anticoagulants and Bleeding Working Group</b>	
Gail Samaan	Healthcare Consultant, Acute Care New Brunswick Health
Bruce Cameron	Hematological Pathologist Georges-L Dumont Hospital Moncton, New Brunswick
Nizar Abdel Samad	Hematologist - Medical Oncology, The Moncton Hospital Moncton, New Brunswick
Jennifer LeFrense	NSPBCT Program Manager Halifax, Nova Scotia
Sudeep Shivakumar	NSPBCT Clinical Advisor Hematologist QEII Health Sciences Centre Halifax, Nova Scotia
Patrick Bergin	Internal Medicine Queen Elizabeth Hospital Charlottetown, Prince Edward Island
Jennifer Fesser	Prince Edward Island Division Head Transfusion Services PEI and Lab Hematology Queen Elizabeth Hospital Charlottetown, Prince Edward Island
Daphne Osborne	NL Provincial Blood Coordinating Program Interim Program Manager Newfoundland and Labrador
Lucinda Whitman	Associate Professor of Laboratory Medicine, Memorial University NL PBCP Medical Consultant St. John's, Newfoundland and Labrador

## Appendix C - Recommendations for the Management of Vitamin K Antagonists Treatment in Bleeding Patients or With a Supratherapeutic INR

Clinical Scenario	Reversal Strategy	Recheck INR	Other Considerations
<b>INR 4.5 to 10 with no evidence of bleeding</b>	<ul style="list-style-type: none"> <li>Consider holding or lowering VKA dose</li> </ul>	24-48 hours	Do not administer vitamin K
<b>INR greater than 10 with no evidence of bleeding</b>	<ul style="list-style-type: none"> <li>Consider holding or lowering VKA dose</li> <li>Administer oral vitamin K</li> </ul>	24 Hours	
<b>INR 1.7 to 5.0 with major bleeding</b>	<ul style="list-style-type: none"> <li>Hold VKA until bleeding is controlled</li> <li>Vitamin K 5-10 mg IV</li> <li>PCC 40 mL (1000 IU)</li> </ul>	10-30 mins after PCC dose	If post PCC INR is > 1.7 or 1.3 for intracranial hemorrhage and major bleeding continues, consider an additional PCC dose of 20 mL (500 IU)
<b>INR ≥ 5.1 with major bleeding</b>	<ul style="list-style-type: none"> <li>Hold VKA until bleeding is controlled</li> <li>Vitamin K 5-10 mg IV</li> <li>PCC 80 mL (2000 IU)</li> </ul>	10-30 mins after PCC dose and again in 24 hours	
<b>Unknown INR with major bleeding</b>	<ul style="list-style-type: none"> <li>Hold VKA until bleeding is controlled</li> <li>Vitamin K 5-10 mg IV</li> <li>PCC 80 mL (2000 IU)</li> </ul>	10-30 mins after PCC dose and again in 24 hours	
<b>Any INR with need for reversal for planned procedure (&gt; 6 hours)</b>	<ul style="list-style-type: none"> <li>Consider holding or lowering VKA dose</li> <li>Consider vitamin K</li> </ul>	12-24 hours	
<b>INR 1.7 -5.0 with need for reversal for planned procedure (&lt; 6 hours)</b>	<ul style="list-style-type: none"> <li>Hold VKA until bleeding is controlled</li> <li>Vitamin K 5-10 mg IV</li> <li>PCC 40 mL (1000 IU)</li> </ul>	10-30 mins after PCC dose and again in 24 hours	
<b>INR ≥ 5.1 with need for reversal for planned procedure (&lt; 6 hours)</b>	<ul style="list-style-type: none"> <li>Hold VKA until bleeding is controlled</li> <li>Vitamin K 5-10 mg IV</li> <li>PCC 80 mL (2000 IU)</li> </ul>	10-30 mins after PCC dose and again in 24 hours	

## Appendix D - Recommendations for the Management of Bleeding Patient on Direct Oral Anticoagulants (DOACs)

	Minor Bleeding	Moderate Bleeding	Severe / Life Threatening Bleeding
	<ul style="list-style-type: none"> <li>Determine the drug, dose and time of the last dose</li> <li>Identify medications expected to increase bleeding risk or known to increase DOAC plasma levels:</li> </ul>		
<b>Laboratory Testing</b>	<ul style="list-style-type: none"> <li>Consider CBC, creatinine, INR, aPTT</li> </ul>	<ul style="list-style-type: none"> <li>CBC, creatinine, INR, aPTT, fibrinogen, Type &amp; Screen</li> </ul>	<ul style="list-style-type: none"> <li>CBC, creatinine, INR, aPTT, fibrinogen, Type &amp; Screen,</li> <li>Thrombin Time (<b>Dabigatran</b>)</li> <li>Anti Xa level (<b>Apixaban, edoxaban and rivaroxaban</b>)</li> </ul>
<b>Medication Dosing</b>	<ul style="list-style-type: none"> <li>Consider holding DOAC or delaying the next dose</li> </ul>	<ul style="list-style-type: none"> <li>Hold DOAC (document time of last dose)</li> <li>Consider holding or reducing other medications known to increase bleeding risk</li> </ul>	<ul style="list-style-type: none"> <li>Hold DOAC (document time of last dose)</li> <li>Hold other medications known to increase bleeding risk</li> </ul>
<b>Supportive Therapy</b>	<ul style="list-style-type: none"> <li>Local hemostatic management</li> </ul>	<ul style="list-style-type: none"> <li>Local hemostatic management</li> <li>Surgical intervention</li> <li>Maintain adequate hydration for drug clearance</li> <li>Transfuse blood and blood products as needed - Refer to the <i>Nova Scotia Guideline for Blood Component Utilization in Adults and Pediatrics Version 2.0</i></li> </ul>	<ul style="list-style-type: none"> <li>Initiate resuscitation and/or activate the Massive Transfusion Protocol</li> <li>Consult specialists as indicated (hematologist, internist, ER physician transfusion medicine physician)</li> </ul>
<b>Anticoagulant Reversal Strategy</b>	<ul style="list-style-type: none"> <li>None</li> </ul>	<ul style="list-style-type: none"> <li>Consider tranexamic acid (1g IV)</li> </ul>	<ul style="list-style-type: none"> <li><b>Dabigatran</b> - administer idarucizumab (Praxbind)</li> <li><b>Apixaban, edoxaban and rivaroxaban</b> consider PCC fixed dose 80 mL (2000 Units)</li> <li>Maximum total PCC dose 120 mL (3000 Units);</li> </ul>
Plasma or vitamin K will not reverse the anticoagulant effect in DOAC associated bleeding unless another concomitant coagulopathy is present.			

### Direct Oral Anticoagulant Pharmacologic Properties

Pharmacologic Properties	Apixaban (Eliquis®)	Dabigatran (Pradaxa®)	Edoxaban (Lixiana®)	Rivaroxaban (Xarelto®)
Peak level	3-4 hours	0.5-2 hours	1-2 hours	2-4 hours
Renal clearance	27%	80%	50%	33 %
Half-life	8-12 hours (longer in elderly and patients with renal dysfunction)	7-17 hours	10-14 hours	7-11 hours

### Medications expected to increase bleeding risk or increase DOAC plasma levels

#### Systemic treatment with strong inhibitors of CYP3A4 and P- glycoprotein

- Itraconazole, ketoconazole, ritonavir
- Dabigatran only - amiodarone, cyclosporine, quinidine, tacrolimus, verapamil

#### Antiplatelet agents

- Clopidogrel (Plavix®), Prasugrel (Effient®), Ticagrelor (Brilinta®), NSAIDs, ASA

#### Herbal medications

- Black cohosh, chamomile, feverfew, garlic, ginger, ginkgo biloba, ginseng, omega-3 fatty acids, saw palmetto, St. John's Wort