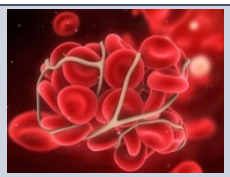


Iredell Memorial Hospital Pharmacy

Guidelines for Reversal of Oral Anticoagulants

OCTOBER 2016

Direct-Acting Oral Anticoagulants (DOACs)

Determining the time the last dose of anticoagulant was given is critical in forming a reversal plan. If the last anticoagulant dose was taken more than 24-48 hours previously, depending on agent and renal function, pharmacologic reversal is not likely to be beneficial. Other strategies are outlined in this document and summarized in the chart on the reverse side.

General strategies for managing bleeding events

Many bleeding events can be managed conservatively with local hemostatic measures, fluid replacement, hemodynamic support, and blood product transfusion without anticoagulant reversal. These measures may allow resolution of bleeding without requiring aggressive treatments that may expose the patient to the risks of potential thrombosis.

Aggressive treatment with reversal agents such as idarucizumab (Praxbind®) and prothrombin complex concentrates (PCCs) such as KCentra® should generally be reserved for the most serious/life-threatening cases such as ongoing bleeding that is likely to lead to death or permanent disability if not stopped immediately. PCCs have the potential to cause thrombosis, and their efficacy in treating DOAC-associated bleeding has not been validated in clinical trials. They should usually be reserved for extreme clinical circumstances. KCentra® contains factors II, VII, IX and X, along with proteins C and S. It also contains small amounts of heparin and is thus contraindicated in patients with known Heparin-Induced Thrombocytopenia (HIT).

Dabigatran (Pradaxa®) – Direct thrombin inhibitor

- **Activated charcoal** may decrease absorption if given within 2 hours of ingestion of dabigatran.
- **Adequate diuresis** aids excretion, since dabigatran is primarily renally eliminated.
- **Hemodialysis** is effective in removing up to 65% of dabigatran.
- **Use of FFP** for bleeding management with dabigratran has not been evaluated in clinical studies but may be considered if hemostasis is not achieved with the above strategies, or to correct a coexisting coagulopathy.
- **Idarucizumab (Praxbind®)** is an immediate and specific reversal agent for dabigatran. It is FDA approved when reversal is needed in adults with (1) life-threatening or uncontrolled bleeding or (2) the need for emergency surgery/urgent procedures. Praxbind® is not intended for use for (1) minor or nuisance bleeding/bruising in clinically stable patients; (2) patients for whom simple support, monitoring, or time prior to a surgical procedure is appropriate; (3) elective procedures or surgeries.
    - Praxbind® dose is 5grams IV x one dose.
    - The cost for one dose of Praxbind® is approximately $3500.

Apixaban (Eliquis®), edoxaban (Savaysa®), and rivaroxaban (Xarelto®) – Factor Xa inhibitors

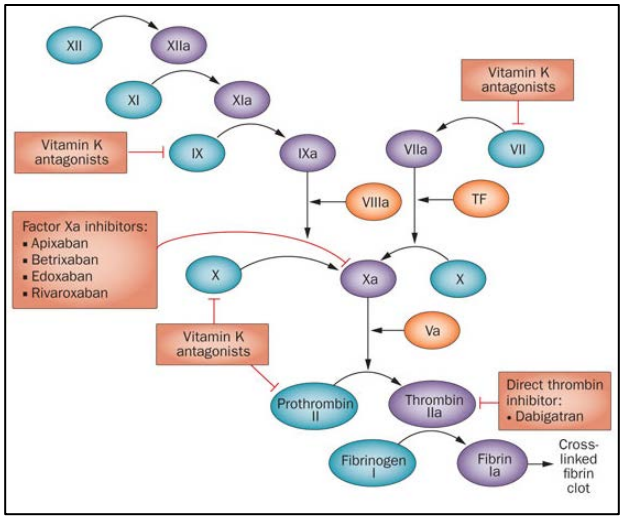
- **Activated charcoal** may decrease absorption if given within 2 hours of ingestion of these agents.
- As of October 2016, there are no specific reversal agents for these medications; management of hemorrhagic complications is thus primarily supportive. These agents are highly protein bound and are not dialyzable. While no agent currently available in the US has been shown to reverse the anticoagulant effects of Factor Xa inhibitor-related bleeding events, the following may be considered in the case of life-threatening bleeding, in addition to the general strategies outlined previously:
- **KCentra® (4-factor Prothrombin Complex Concentrate)** 50 units/kg IV x one dose, with a maximum dose of 5000 units.
    - The cost for a 5000-unit dose of KCentra® is approximately $7800.
- **Vitamin K** 10mg IV x one dose over 30 minutes, if PT is prolonged (as there may be vitamin K deficiency present).
- **Use of FFP** for bleeding management with these agents has not been evaluated in clinical studies but may be considered if hemostasis is not achieved with the above strategies, or to correct a coexisting coagulopathy.

Surgery and invasive procedures

Due to the relatively short half-lives of the DOACs, it is often possible to delay procedures long enough to allow most or all of the anticoagulant effect to dissipate in patients with normal renal function. However, if emergent surgery or procedures are required and there is insufficient time to allow the anticoagulant effect to dissipate, the reversal strategies outlined in this document may be appropriate. Decisions regarding the need for reversal must be individualized based on the urgency and bleeding risk of the procedure.

Summary of Guidelines for Reversal of Direct-Acting Oral Anticoagulants

Drug	Elimination Half-Life	Removed by dialysis	Summary of emergent reversal for life-threatening bleeding or emergent surgery / procedure
Dabigatran (Pradaxa®)	12-17 hours (up to 34 hours in severe renal impairment)	~65%	If ingested within 2 hours, may give activated charcoal. Consider idarucizumab (Praxbind®): 5g IV for one dose.
Apixaban (Eliquis®)	8-15 hours (longer in renal impairment)	No	If ingested within 2 hours, may give activated charcoal. Consider KCentra® (4-factor PCC): 50 units/kg for one dose (Maximum dose 5000 units). **Hematology should be consulted for use of Kcentra® with these Factor Xa inhibitors.*
Edoxaban (Savaysa®)	10-14 hours (longer in renal impairment)	No	
Rivaroxaban (Xarelto®)	Healthy: 5-9 hours Elderly: 11-13 hours (longer in renal impairment)	No	



http://www.nature.com/nrcardio/journal/v10/n7/fig_tab/nrcardio.2013.73_F1.html

2016 Costs

Idarucizumab (Praxbind®)	~ $3500 for 5 grams
4-factor prothrombin complex concentrate (Kcentra®)	~ $7800 for 5000 units
FFP	$48 for one unit

Vitamin K Tips:

High doses of vitamin K (>10mg), though effective, may lower the INR more than is necessary and may lead to warfarin resistance for a week or more. While larger doses inhibit the vitamin K cycle for a longer time, eventually lowering the INR more substantially, they do NOT decrease the INR more quickly. Thus, small doses, and if necessary, repeated small doses, can be better for decreasing INR while preventing warfarin resistance.

Doses of ≤ 5mg oral vitamin K will usually decrease the INR substantially in 24 hours, and doses > 5-10mg orally will usually decrease the INR substantially in 24-48 hours. Doses > 10mg may take much longer to achieve full INR lowering and may eliminate warfarin sensitivity.

The onset of action of oral vitamin K is 12-24 hours; onset for IV vitamin K is 4-12 hours.

CHEST guidelines recommend oral administration of vitamin K for patients with mild to moderate elevation of INRs without severe bleeding. IV administration has a faster onset and is recommended for significant, serious, or life-threatening bleeding or if an emergent procedure is needed.

Subcutaneous vitamin K does not produce reliable, rapid reductions in INR and is no longer recommended.

Guidelines for the Management of a Supratherapeutic INR or Acute Bleeding Episode Associated with Warfarin Use

Condition	Recommendation
INR above therapeutic range but <4.5 No evidence of bleeding	1. Lower or omit next warfarin dose(s)
INR between 4.5 and 10 No evidence of bleeding	1. Omit next warfarin dose(s). 2. Consider vitamin K **1.25-2.5mg orally** if patient at increased risk of bleeding. 3. May repeat vitamin K **1.25-2.5mg orally** if INR still high after 24 hours.
INR >10 No evidence of bleeding	1. Hold warfarin 2. Give vitamin K **2.5 orally** (expect substantial reduction in INR in 24-48 hours) 3. May repeat vitamin K in 24 hours if necessary.
Moderate to significant bleeding at any elevation of INR, unlikely to decompensate	1. Hold warfarin 2. Give vitamin K **5-10mg by slow IV infusion.** 3. May supplement with fresh frozen plasma, depending on the urgency of the situation. 4. Vitamin K may be repeated every 12 hours if necessary.
Serious bleeding at any elevation of INR, with risk for hemodynamic instability	1. Hold warfarin 2. Give vitamin K **5-10mg by slow IV infusion.** 3. Supplement with fresh frozen plasma. 4. Vitamin K may be repeated every 12 hours if necessary.
Major, life-threatening bleeding at any elevation of INR	1. Hold warfarin. 2. Give vitamin K **5-10mg by slow IV infusion.** 3. Supplement with prothrombin complex concentrate (KCentra®)ǂ or fresh frozen plasma. 4. Vitamin K may be repeated every 12 hours if necessary.

Guidelines for Reversal of Warfarin for Invasive Procedures

Reversal for urgent surgical or other invasive procedure	Vitamin K **2.5-5mg orally or IV.** May also consider fresh frozen plasma or prothrombin complex concentrate (KCentra®)ǂ in addition to vitamin K if more immediate reversal is needed.
Reversal in patients who require temporary interruption of warfarin before surgery or a procedure and whose INR is still above goal for procedure one day before procedure	Vitamin K **2.5mg orally**

ǂ If KCentra® is used to manage bleeding events with warfarin, vitamin K should be given concurrently to maintain factor levels once the effects of KCentra® have diminished. The safety and efficacy of repeat dosing of KCentra® have not been established, and repeat dosing is not recommended.

KCentra® Dosing for bleeding events with warfarin:
Pretreatment INR 2 to <4: Give 25 units/kg, with maximum dose of 2,500 units
Pretreatment INR 4 to 6: Give 35 units/kg, with maximum dose of 3,500 units
Pretreatment INR >6: Give 50 units/kg, with maximum dose of 5,000 units

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