Management of emergent bleeding in adult patients receiving direct oral anticoagulants (DOACs)

NOTE: for urgent reversal of dabigatran, utilize **Idarucizumab** orderable through pharmacy

- Currently approved DOACs for clinical use in Canada:
  - Direct thrombin inhibitor: Dabigatran
  - Direct FXa inhibitors: Rivaroxaban, Apixaban, Edoxaban
- Normal thrombin time (TT) rules out significant plasma level of dabigatran
- Normal anti-Xa (heparin) level rules out significant plasma level of direct FXa inhibitors
- Although elevated INR and/or PTT suggest therapeutic or higher plasma DOAC levels, normal results do NOT rule out significant levels
- Definitive interventions (e.g., compression, endoscopy) are the cornerstone of therapy in bleeding, including DOAC-related bleeding
- The use of PCC for the reversal of DOACs is mainly based on prospective observational data
  - Andexanet alfa (Andexxa®), a specific antidote for anti-Xa inhibitors, has been approved by US FDA. As of March 2021, it has not been approved by Health Canada, nor is it available in any BC hospital pharmacy.
  - There is insufficient published evidence available to allow a recommendation for use in pregnant women.

Flow chart for reversal of Anti-Xa DOACs

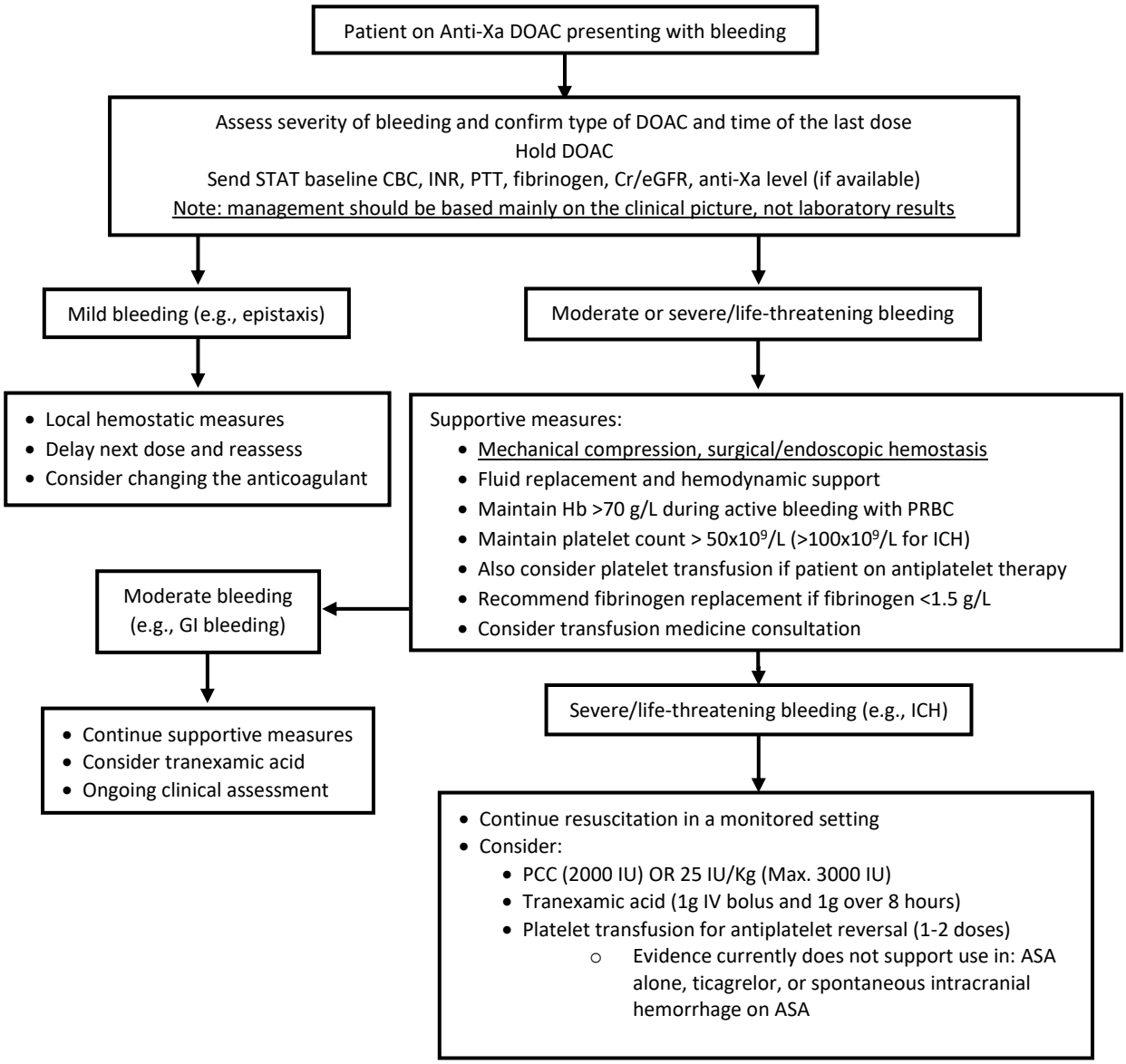

Table 1. Pharmacologic properties of direct oral anticoagulants

Agent	Mechanism of action	Time to peak onset (hours)	Renal clearance	Half-life (hours)			Antidote
				CrCl ≥50 ml/min	**CrCl 30-49 ml/min**	**CrCl <30 ml/hour**	
Dabigatran (Pradaxa®)	Direct FIIa (thrombin) inhibitor	1-3	80-85%	7-17	17-20	21-35	Idarucizumab (Praxbind®)
Rivaroxaban (Xarelto®)	Direct FXa inhibitors	2-4	36%	7-11	7-11	11-15	Andexanet alfa (Andexxa®)*
Apixaban (Eliquis®)		1-3	25%	8-12	8-12	12-17	
Edoxaban (Lixiana®)		1-2	36-45%	10-14	-	-	No (as of March 2021)†

*Andexanet alfa (Andexxa®), antidote for rivaroxaban and apixaban, has been approved by US FDA on May 2018. However, andexanet alfa has not been approved in Canada yet as of March 2021.
†Ciraparantag is small synthetic and cationic molecule that binds direct Xa inhibitors, direct thrombin inhibitors, and unfractionated and low molecular weight heparin (LMWH) which is currently being evaluated in phase 3 trial for its effect in the reversal of edoxaban.

Table 2. Summary of effects of DOACs on coagulation testing and available special testing

Agent	INR	PTT	Thrombin Time (TT)	Dilute TT	Anti-Xa (Heparin Level)
Dabigatran (Pradaxa®)	↑ / ↔	↑ (usually)	↑	↑	↔
Rivaroxaban (Xarelto®)	↑ / ↔	↑ / ↔	↔	↔	↑
Apixaban (Eliquis®)	↑ / ↔	↑ / ↔	↔	↔	↑
Edoxaban (Lixiana®)	↑ / ↔	↑ / ↔	↔	↔	↑

↑ Elevated, ↔ Normal

References:

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Revision Log:

Version	Date	Medical Acknowledgment/ Review
1.0	March 2011	K Chipperfield, K Roland, T Smith
2.0	October 2015	N Sunderland, T Smith
3.0	July 2018	M Al Moosawi, A Shih, T Smith A Lee (Hematology), Dr J Andrade (Cardiology)
3.1	November 2020	A Shih, J Trudeau, K Marcon, T Smith
VPP 1.0	March 2021	A Shih, J Trudeau, K Marcon, T Smith, T Winckler M Bahmanyar, C Brunk, H Nicolson, R Onell