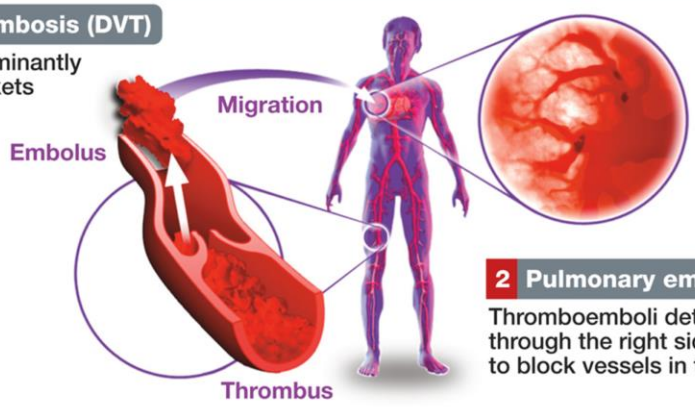
Venous Thromboembolism (VTE): Clot Formation Within the Venous Circulation

1 Deep vein thrombosis (DVT)

Thrombi form predominantly in venous valve pockets and other sites of presumed stasis



2 Pulmonary embolism (PE)

Thromboemboli detach and travel through the right side of the heart to block vessels in the lungs

Tapson VF. N Engl J Med 2008; 358(10):1037-52.
Image adapted from Tapson VF.

VTE in Canada

Incidence

- ~45,000 patients affected by DVT annually; ~1-2 cases per 1,000 persons annually[1]
- Among those who develop DVT[2]:
  - 1/3 will have long-term complications (chronic lower leg edema, post-phlebitic syndrome, pain, pigment changes)
  - 1/3 will develop a recurrent event within 10 years (as will **1/2** of those with **idiopathic VTE**)
- Despite adequate therapy, 1-8% of patients with PE will die[2]

Risks factors

- Clinical-setting-related or patient-related (clinical, inherited, acquired)[3]

1. Thrombosis Canada, 2015. Available at: *www.thrombosiscanada.ca/wp-content/uploads/2015/11/2_Deep-Vein-Thrombosis-Diagnosis_2015Nov02-FINAL1.pdf*.
2. Scarvelis D, et al. CMAJ 2006; 175(9):1087-92.
3. Arcelus JI, et al. Orthopedics 2006; 29(6):506-16.

Clinical Presentation: Signs and Symptoms[1-4]

DVT

- Pain
- Swelling
- Tenderness
- Discoloration
- Pitting edema

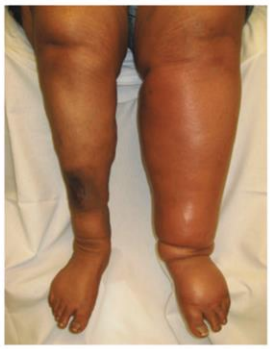


Image from National Blood Clot Alliance.

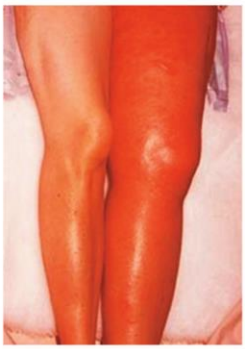


Image from University of Maryland Medical Center.

1. Moll S. Arterioscler Thromb Vasc Biol 2008; 28(3):373-9.
2. Pai M, et al. Available at: *www.uptodate.com/contents/deep-vein-thrombosis-dvt-beyond-the-basics*.
3. Thompson BT, et al. Available at: *www.uptodate.com/contents/pulmonary-embolism-beyond-the-basics*.
4. Goldhaber SZ. In: Bonow RO, et al (eds). *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 9th ed. Elsevier, Philadelphia, 2012.

Clinical Presentation: Signs and Symptoms[1-4]

PE

- Shortness of breath
- Cough
- Chest pain
- Tachycardia
- Hypotension
- Low-grade fever

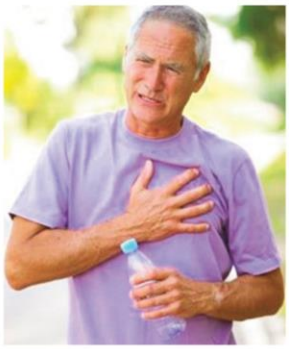


Image from Medic Scientist.

1. Moll S. Arterioscler Thromb Vasc Biol 2008; 28(3):373-9.
2. Pai M, et al. Available at: *www.uptodate.com/contents/deep-vein-thrombosis-dvt-beyond-the-basics*.
3. Thompson BT, et al. Available at: *www.uptodate.com/contents/pulmonary-embolism-beyond-the-basics*.
4. Goldhaber SZ. In: Bonow RO, et al (eds). *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 9th ed. Elsevier, Philadelphia, 2012.

Diagnosis

DVT[1]

- D-dimer measurements
- Venous ultrasonography
- Contrast venography

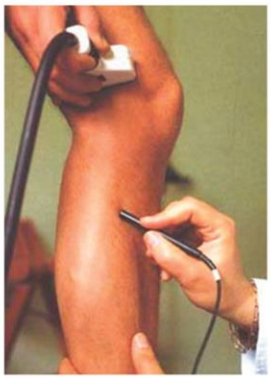
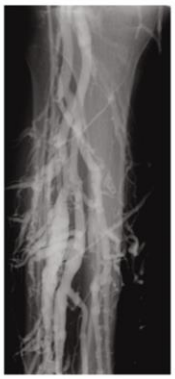


Image from Phlebologia.



Upper calf. Image from Sidhu PS et al, 2007.

1. Bates SM, et al. Chest 2012; 141(2 Suppl):e351S-e418S.

Diagnosis

PE[1]

- ECG
- Chest radiograph
- CT angiogram

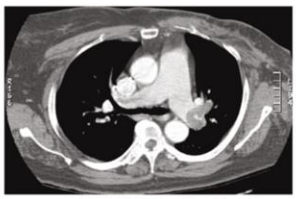


Image courtesy of RF Schneider, Pfizer.

- Ventilation/perfusion (V/Q) scan[2]

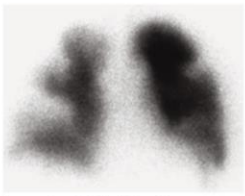


Image from Schümichen C.

- Pulmonary angiogram

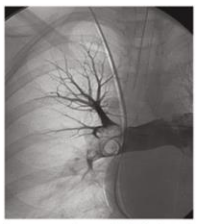
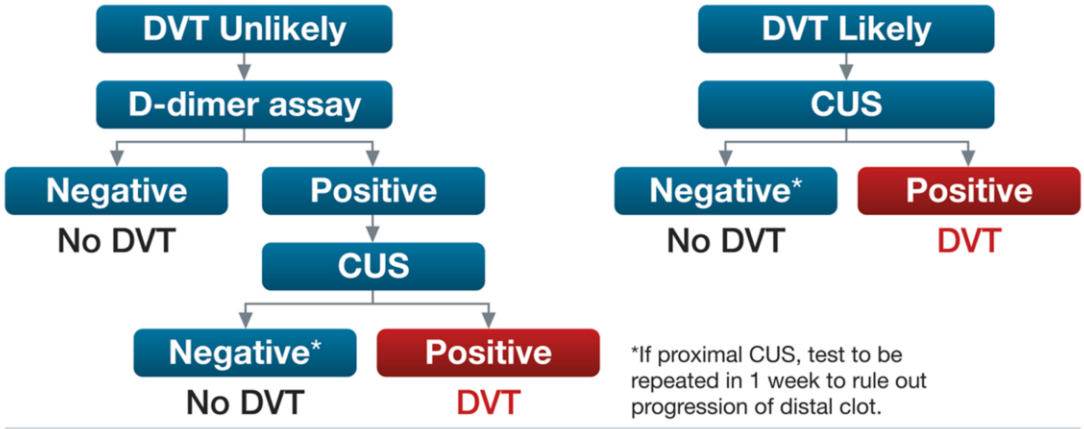


Image courtesy of RF Schneider, Pfizer.

1. Tapson VF. N Engl J Med 2008; 358(10):1037-52.
2. Schümichen C. Respiration 2003; 70(4):329-42.

Clinical Probability
Wells' Score for DVT Outpatients



Wells PS, et al. N Engl J Med 2003; 349(13):1227-35.
CUS = compression ultrasound.

Current Clinical Challenges in VTE Treatment

Conventional Anticoagulants

Parenterals

- **Advantages**
  - LMWH rarely requires monitoring
- **Disadvantages**
  - Must be injected
  - Dose adjustments for severe renal impairment and extreme obesity not standardized for LMWH
  - No antidote for LMWH
  - HIT is a complication of UFH more than LMWH

VKA therapy

- **Advantages**
  - Mainstay of long-term therapy since 1960
- **Disadvantages**
  - Slow onset/offset requires bridging
  - Interactions with other drugs and food
  - Narrow therapeutic window
  - Inter-individual variability in dose response

Direct Oral Anticoagulants (DOACs)

- **Advantages**
  - Predictable pharmacological profiles
  - Absence of major interactions with food or other drugs
  - Do not require routine monitoring
- **Disadvantages**
  - No available antidote
  - No readily available monitoring for special circumstances (*e.g.*, major bleeding, urgent procedure)

Van Es J, et al. J Thromb Haemost 2011; 9(Suppl 1):265-74.
LMWH = low-molecular-weight heparin; HIT = heparin-induced thrombocytopenia; UFH = unfractionated heparin.

Secondary Complications of VTE

Post-thrombotic syndrome (PTS)[1]

- Can occur within 1-2 years after DVT in 20-50% of all patients
- Severe PTS occurs in 25-33% of patients with PTS
  - Can lead to deep vein insufficiency and leg ulcers

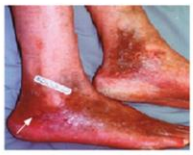


Image from UpToDate.

Chronic thromboembolic pulmonary hypertension (CTPH)

- Can occur after PE and is associated with significant morbidity and mortality[2]
- Frequency[3]
  - 1.0% at 6 months
  - 3.1% at 1 year
  - 3.8% at 2 years

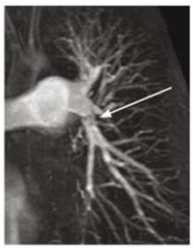


Image from McNeil K, Dunning J, 2007.

1. Kahn SR, Ginsberg JS. Arch Intern Med 2004; 164(1):17-26.
2. McNeil K, Dunning J. Heart 2007; 93(9):1152-8.
3. Pengo V, et al. N Engl J Med 2004; 350(22):2257-64.

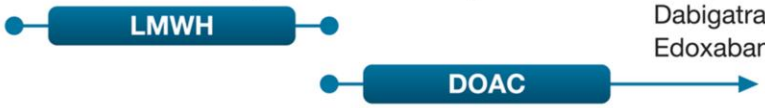
Current Treatment Options

Bridge

Single agent (rivaroxaban/apixaban)

Rivaroxaban **(EINSTEIN-DVT)**[1]
Rivaroxaban **(EINSTEIN-PE)**[2]
Apixaban **(AMPLIFY)**[3]

Switch (LMWH/dabigatran/edoxaban*)



Dabigatran **(RE-COVER)**[4]
Dabigatran **(RE-COVER II)**[5]
Edoxaban* **(HOKUSAI)**[6]

*Edoxaban is not approved in Canada.

1. EINSTEIN Investigators. N Engl J Med 2010; 363(26):2499-510. 2. EINSTEIN–PE Investigators. N Engl J Med 2012; 366(14):1287-97. 3. Agnelli G, et al. N Engl J Med 2013; 369(9):799-808. 4. Schulman S, et al. N Engl J Med 2009; 361(24):2342-52. 5. Schulman S, et al. Circulation 2014; 129(7):764-72. 6. Hokusai-VTE Investigators. N Engl J Med 2013; 369(15):1406-15.

Overview of VTE Treatment Trials with NOACs

Acute (≤ 1 week)	Long-term (3-6 months)	Extended (≥ 3 to 6 months)
	Dabigatran (RE-COVER)	Dabigatran (RE-SONATE)
(Parenterals)	Dabigatran (RE-COVER II)	Dabigatran (RE-MEDY)
	Edoxaban* (HOKUSAI)	
	Rivaroxaban (EINSTEIN-DVT)	Rivaroxaban (EINSTEIN-Extension)
	Rivaroxaban (EINSTEIN-PE)	
	Apixaban (AMPLIFY)	Apixaban (AMPLIFY-Extension)

*Edoxaban is not approved in Canada.
Becattini C, et al. Thromb Res 2012; 129(3):392-400.

Overview: DOAC Trials for Acute VTE Treatment

	Apixaban[1]	Rivaroxaban[2,3,4]	Dabigatran[5,6]
Trial design: double-blind	Yes	No	Yes
No LMWH and/or UFH lead-in (*i.e.*, single agent)	Yes	Yes	No
Duration of treatment	6 months	3, 6 or 12 months	6 months
Non-inferior efficacy vs. comparator* (recurrent or fatal VTE)	Yes	Yes	Yes
Major bleeding vs. comparator*	↓	↓	NS
Major or CRNM bleeding vs. comparator*	↓	NS	↓
Dosing	bid	bid then qd	bid

↓ Significant reduction

Head-to-head studies have not been conducted; therefore, comparative safety and efficacy have not been established.
*Comparator was LMWH or UFH followed by either a VKA (warfarin or acenocoumarol) in the rivaroxaban trials or warfarin in the other DOAC trials.
CRNM = clinically relevant non-major.

1. Agnelli G, et al. N Engl J Med 2013; 369:799-808. 2. The EINSTEIN Investigators. N Engl J Med 2010; 363:2499-510. 3. The EINSTEIN-PE Investigators. N Engl J Med 2012; 366:1287-97. 4. Prins M, et al. Thromb J 2013; 11(1):21. 5. Schulman S, et al. N Engl J Med 2009; 361:2342-52. 6. Schulman S, et al. Blood (ASH Annual Meeting Abstracts) 2011; 118:Abstract 205.

Trial Designs for Extended VTE Treatment

Trial	Treatment before randomization	Design	Study drug	Comparator	Length of treatment
AMPLIFY EXT[1]	6-12 months of AC	Double-blind	Apixaban 2.5 mg bid or 5 mg bid	Placebo	12 months
EINSTEIN Extension[2]	6-12 months of VKA or rivaroxaban	Double-blind	Rivaroxaban 20 mg od	Placebo	6-12 months
RE-SONATE[3]	6-18 months of VKA	Double-blind	Dabigatran 150 mg bid	Placebo	6 months
RE-MEDY[3]	3-12 months of AC	Double-blind	Dabigatran 150 mg bid	Warfarin	6-36 months

Head-to-head studies have not been conducted; therefore, comparative safety and efficacy have not been established.

1. Agnelli G, et al. N Engl J Med 2013; 368: 699-708.
2. The EINSTEIN Investigators. N Engl J Med 2010; 363:2499-510.
3. Schulman S, et al. N Engl J Med 2013; 368: 709-18.

Results of DOAC Trials for Extended VTE Treatment

			Recurrent VTE + VTE Death	Major Bleeding	Major + CRNM Bleeding
Drug	**Trial**	**Dose**	**DOAC vs. comparator (%), *p* value**		
Apixaban**	AMPLIFY-EXT[1] (placebo comparator) N = 2,482	2.5 mg bid	**Superiority** **81% RRR** 1.7 vs. 8.8 $p < 0.001$	**Not significant** 0.2 vs. 0.5 NR*	**Not significant** 3.2 vs. 2.7 NR*
		5 mg bid	**Superiority** **80% RRR** 1.7 vs. 8.8 $p < 0.001$	**Not significant** 0.1 vs. 0.5 NR*	**Not significant** 4.3 vs. 2.7 NR*
Dabigatran	RE-SONATE[3] (placebo comparator) N = 2,856	150 mg bid	**Superiority** **92% RRR** 0.4 vs. 5.6 $p < 0.001$	**Not significant** 0.3 vs. 0 $p = 1.0$	**Significant increase** 5.3 vs. 1.8 $p = 0.001$
	RE-MEDY[3] (warfarin comparator) N = 2,856	150 mg bid	**Non-inferiority** 1.8 vs. 1.3 $p = 0.01$ (NI)	**Not significant** 0.9 vs. 1.8 $p = 0.06$	**Significant reduction** **46% RRR** 5.6 vs. 10.2 $p < 0.001$
Rivaroxaban	EINSTEIN-Extension[2] (placebo comparator) N = 3,449	20 mg od	**Superiority** **82% RRR** 1.3 vs. 7.1 $p < 0.001$	**Not significant** 0.7 vs. 0 $p = 0.11$	**Significant increase** 6.0 vs. 1.2 $p < 0.001$

Head-to-head studies have not been conducted, therefore comparative safety and efficacy have not been established. The duration of follow-up differed between trials therefore event rates should not be compared or interpreted as an indicator of the risk of the population.

*Not significant based on 95% CI for relative risk. NR = not reported. **> 6 months of treatment, reduce the dose of apixaban to 2.5 mg bid.

1. Agnelli G, et al. N Engl J Med 2013; 368:699-708. 2. Bauersachs R, et al. N Engl J Med 2010; 363:2499-2510. 3. Schulman S, et al. N Engl J Med 2013; 368:709-18.

Overview: DOAC Trials for Extended VTE Treatment ≥ 6 months

	Apixaban[1]	Rivaroxaban[2]	Dabigatran[3]
Trial design: double-blind	Yes	Yes	Yes
Comparator	Placebo	Placebo	Placebo
Duration of treatment	12 months	6 or 12 months	6 months
Dosing	bid	od	bid
Dose/s of DOAC approved	2.5 mg	20 mg	150 mg or 110 mg*
Superior efficacy (recurrent or fatal VTE) vs. comparator	Yes	Yes	Yes
Major bleeding vs. comparator	NS	NS	NS
Major or clinically-relevant non-major bleeding vs. comparator	NS	↑	↑

↑ Significant increase *not studied

1. Agnelli G, et al. N Engl J Med 2013; 368:699-708.
2. Bauersachs R, et al. N Engl J Med 2010; 363:2499-2510.
3. Schulman S, et al. N Engl J Med 2013; 368:709-18.

Duration of Anticoagulant Therapy for VTE

Categories of VTE	Duration of Treatment
Provoked by a transient risk factor*	3 months
First unprovoked VTE†	Minimum of 3 months and then re-assess
Proximal DVT or PE with no or only minor risk factors for bleeding	Indefinite therapy with annual review
Isolated distal DVT	3 months, depending on patient preference
Second unprovoked VTE	Minimum of 3 months, then re-assess. For patients with no or only minor risk factors for bleeding, indefinite therapy with annual review‡
Cancer-associated VTE	Minimum 3 months, then re-assess and continue if active cancer (overt evidence of cancer) or continuing to receive anticancer therapy

*e.g., surgery, hospitalization, or plaster cast immobilization, all within 3 months; estrogen therapy; pregnancy; prolonged travel.
†Absence of a transient risk factor or active cancer.
‡Indefinite therapy is suggested if there is a moderate risk of bleeding, and 3 months is suggested if there is a high risk of bleeding.
Thrombosis Canada. Available at: *www.thrombosiscanada.ca/wp-content/uploads/2015/11/6_VTE-Duration-of-Treatment_2015Oct31-FINAL1.pdf*.

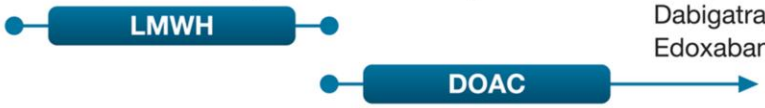
Current Treatment Options

Bridge

Single agent (rivaroxaban/apixaban)

Rivaroxaban **(EINSTEIN-DVT)**[1]
Rivaroxaban **(EINSTEIN-PE)**[2]
Apixaban **(AMPLIFY)**[3]

Switch (LMWH/dabigatran/edoxaban*)



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Bleeding Risk Mitigation

	Apixaban	Rivaroxaban	Dabigatran
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor IIa (thrombin) inhibitor
Renal clearance	27%[1]	33% (active drug)	80%
Half-life:			
Normal renal function (CrCl > 80 mL/min)	9 hours	9 hours	11 hours
Mild renal impairment (CrCl 50-80 mL/min)	9 hours	9 hours	14 hours
Moderate renal impairment (CrCl 30-49 mL/min)	10-14 hours	10-15 hours	15-17 hours
Onset of action (after oral intake)	1-3 hours	1-3 hours	1-3 hours

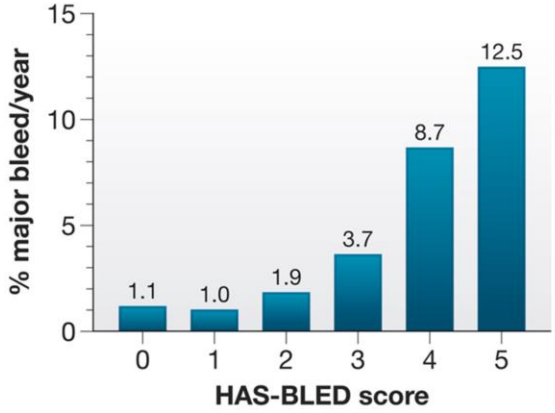
Adapted from: Thrombosis Canada. Available at: *www.thrombosiscanada.ca/guides/pdfs/NOACs_Comparison_and_FAQs.pdf*.
1. ELIQUIS Product Monograph. August 2015.

HAS-BLED Scoring System

Calculate bleeding risk

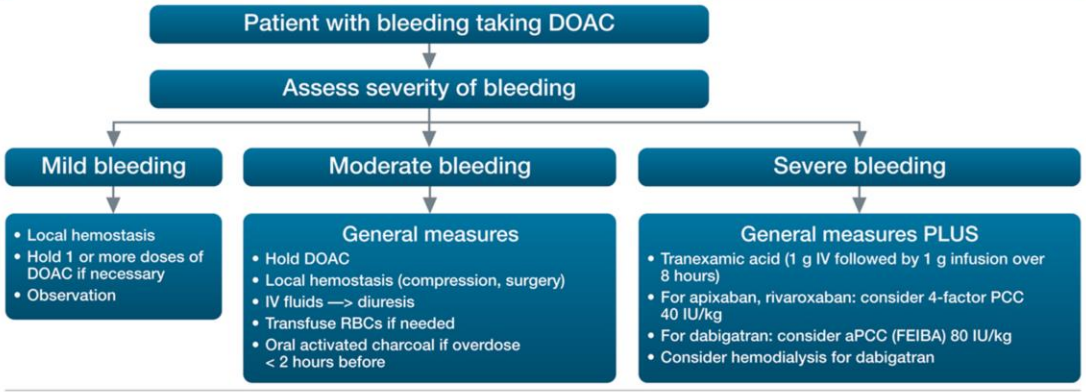
Feature	Score
H = hypertension	1
A = abnormal kidney or liver function	1 or 2
S = prior stroke	1
B = prior bleed	1
L = labile INRs (TTR < 60%)	1
E = elderly (> 65 yrs)	1
D = drugs or ETOH	1 or 2
Total score	9

Annual rate of major bleeding



Adapted from: Cairns JA, et al. Can J Cardiol 2011; 27:74–90.
INR = international normalized ratio; TTR = therapeutic time in range; ETOH = ethyl alcohol.

Strategies for Managing Minor, Moderate, and Major Bleeding Due to DOACs



Thrombosis Canada. Available at: *www.thrombosiscanada.ca/wp-content/uploads/2015/01/NOACs-Management-Bleeding-2015Jan22-FINAL.pdf*.
Adapted from: Siegal DM, et al. Blood 2014; 123(8):1152-1158.
RBC = red blood cell; PCC = prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; FEIBA = factor eight inhibitor bypassing activity.

Thrombosis Canada Suggested Guide for PRE-OPERATIVE Management of Patients Receiving a DOAC

Drug (Dose regimen)	Renal function	Procedures with low bleeding risk* 12-25% residual anticoagulant effect at time of surgery acceptable	Procedures with high or very high bleeding risk* < 10% residual anticoagulant effect at time of surgery acceptable
Apixaban (twice daily)	Normal renal function, mild or moderate impairment (CrCl > 30 mL/min)	Give last dose 2 days before surgery/procedure* (*i.e.*, skip 2 doses)	Give last dose 3 days before surgery/procedure* (*i.e.*, skip 4 doses)
Dabigatran (twice daily)	Normal renal function or mild impairment (CrCl > 50 mL/min)	Give last dose 2 days before surgery/procedure* (*i.e.*, skip 2 doses)	Give last dose 3-4 days before surgery/procedure* (*i.e.*, skip 4-6 doses)
	Moderate renal impairment (CrCl 30-50 mL/min)	Give last dose 3 days before surgery/procedure* (*i.e.*, skip 4 doses)	Give last dose 5-7 days before surgery/procedure* (*i.e.*, skip 8-12 doses)
Rivaroxaban (once daily)	Normal renal function, mild or moderate impairment (CrCl > 30 mL/min)	Give last dose 2 days before surgery/procedure* (*i.e.*, skip 1 dose)	Give last dose 3 days before surgery/procedure* (*i.e.*, skip 2 doses)

*No anticoagulant taken on the day of surgery/procedure

†Neuraxial procedures include spinal anesthesia, epidural catheter insertion and epidural catheter removal.

NOTE: Information on this slide is based on Thrombosis Canada guidelines and might not reflect the product monographs.

Adapted from: *www.thrombosiscanada.ca*.

Thrombosis Canada Suggested Guide for POST-OPERTATIVE Management of Patients Receiving a DOAC

Drug	Minor surgery/procedure (low bleeding risk)	Major surgery/procedure (high bleeding risk)
Apixaban	Resume on day after surgery (~24 hours post-operative)	Resume 2 days after surgery (~48 hours post-operative)
Dabigatran	Resume on day after surgery (~24 hours post-operative)	Resume 2 days after surgery (~48 hours post-operative)
Rivaroxaban	Resume on day after surgery (~24 hours post-operative)	Resume 2 days after surgery (~48 hours post-operative)

NOTE: Information on this slide is based on Thrombosis Canada guidelines and might not reflect the product monographs.

Adapted from: *www.thrombosiscanada.ca*.

Suggested Risk Stratification for Perioperative Thromboembolism

Risk stratum	VTE
High*	• Recent (within 3 months) VTE • Severe thrombophilia (*e.g.,* deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate	• VTE within the past 3-12 months • Non-severe thrombophilia (*e.g.,* heterozygous factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within 6 months or palliative)
Low	• VTE > 12 months previous and no other risk factors

*High-risk patients may also include those with a prior stroke or transient ischemic attack ocuring > 3 months before the planned surgery and a $CHADS_2$ score < 5; those with prior thromboembolism during temporary interruption of VKAs; or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (*e.g.,* cardiac valve replacement, carotid endarterectomy, temporary interruption of VKAs, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (*e.g.,* cardiac valve replacement, carotid endarterectomy, major vascular surgery).

Douketis JD, et al. Chest 2012; 141(2 Suppl):e326S-50S.