INESSS
LE SAVOIR PREND FORME

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DRUG

DIRECT ORAL ANTICOAGULANTS AND WARFARIN

DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM IN ADULTS

RECURRENCE RISK FACTORS

- Currently, there is no consensus regarding the predictive value of any of the models that have been developed to assess the risk of venous thromboembolism (VTE) recurrence.
- The VTE recurrence risk can nonetheless be generalized, as shown in the table below. For further details, consult Thrombosis Canada's website (guide entitled "Venous Thromboembolism: Duration of Treatment").

Type of VTE	Recurrence risk
Provoked by surgery	3% recurrence at 5 years
Provoked by a nonsurgical transient risk factor*	15% recurrence at 5 years
Associated with cancer	15% annualized risk
Idiopathic	30% recurrence at 5 years (10% the first year and 5% each year thereafter)

* Examples: estrogen therapy, pregnancy, a leg injury and an airplane flight > 8 hours.

TREATMENT PRINCIPLES

- Any patient with proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) should receive anticoagulation therapy.
- Preference should be given to a direct oral anticoagulant (DOAC) over a vitamin K antagonist (VKA)[1] in patients newly starting oral anticoagulation therapy and who have no particular medical condition. However, it is not possible, with the current state of knowledge, to make a recommendation favouring one DOAC over another[2].
- Switching a VKA-treated patient with a stable international normalized ratio (INR) to a DOAC may be considered after an informed discussion of the risks and benefits of oral anticoagulants and in accordance with his/her values and preferences.
- Because of the short half-life of DOACs, all patients treated with these drugs should be made aware of the importance of good therapeutic compliance, this before the start of treatment and during the follow-ups.
- For further details on the characteristics of DOACs and warfarin, consult the table of pharmacokinetic parameters.

1. In this guide, "VKA" refers to synthetic coumarin derivatives, such as warfarin or acenocoumarol.
2. No study has directly compared the efficacy and safety of the different DOACs with each other, and there are significant differences between the definitions of bleeding used and between the patient populations recruited in the large studies of DOACs.

Québec

ANTICOAGULATION THERAPY

		Apixaban	Edoxaban	Rivaroxaban	Dabigatran	Warfarin
Dosage		**10 mg PO BID for 7 days, then 5 mg PO BID**	**60 mg PO daily** Start after an initial treatment of at least 5 days' duration with a parenteral anticoagulant	**15 mg PO BID for 21 days then 20 mg PO daily**	**150 mg PO BID** Start after an initial treatment of 5 to 10 days' duration with a parenteral anticoagulant	**PO daily** Adjust dosage according to INR Start concomitantly with parenteral anticoagulation therapy, which will be stopped after obtaining an INR ≥ 2.0 on two consecutive days.
		If long-term therapy is being considered, reduce the dose to 2.5 mg PO BID after an initial treatment of 6 months' duration.	Reduce the dose to 30 mg PO daily if: • CrCl between 30 and 50 ml/min[1] **or** • Weight ≤ 60 kg **or** • Concomitant therapy with a potent P-glycoprotein inhibitor	If long-term therapy is being considered, consider reducing the dose to 10 mg PO daily after an initial treatment of 6 months' duration.	Reduce the dose to 110 mg PO BID if: • Age ≥ 80 years **or** • High bleeding risk	
Specific populations in whom certain DOACs may be considered						
CrCl (ml/min)[1]	**15 to 30**	⚠	?	⚠	?	✓
	< 15	?	?	?	?	✓
Active cancer[2]		⚠[3]	⚠[3]	⚠[3]	?	Opt preferably for a LMWH
Antiphospholipid syndrome		?	?	?	?	✓
Weight > 120 kg		⚠[4]	⚠[4]	⚠[4]	⚠[4]	✓
Parietal gastrectomy		⚠	?	✗[5]	✗	✓
PE and hemodynamic instability[6]		?	?	?	?	After heparin therapy
Mild (Child-Pugh A) or moderate (Child-Pugh B) liver failure		⚠[7]	⚠[7]	⚠[7]	⚠[7]	⚠[7]
Populations in whom DOACs should not be used						
Pregnant women		✗	✗	✗	✗	✗[8]
Nursing women		✗	✗	✗	✗	✓
Mechanical valve prosthesis		✗	✗	✗	✗	✓
Atrial fibrillation accompanied by rheumatic heart disease or moderate to severe mitral stenosis		✗	✗	✗	✗	✓
Severe liver failure (Child-Pugh C) or liver failure accompanied by a coagulopathy		✗	✗	✗	✗	⚠[7]
Gastric bypass		✗	✗	✗	✗	✓

Legend: ✓ Recommended ⚠ May be considered with caution, taking into account the risks and benefits ✗ Not recommended ? Insufficient data

1. The creatinine clearance should be calculated using the Cockcroft-Gault formula.
2. During the first 6 months of treatment or if the cancer remains active (extensive, metastatic or treated with chemotherapy).
3. Caution, especially if gastrointestinal or urogenital cancer.
4. Little data is available on the efficacy and safety of DOACs in patients weighing more than 120 kg. Before prescribing a DOAC, it is important to clearly inform the patient of this and of the potential risk of underdosing.
5. Rivaroxaban is not recommended in patients who have undergone a parietal gastrectomy. It may, however, be considered for patients at a dose of 10 mg PO daily for the long-term prevention of VTE recurrences, if the benefits outweigh the risks.
6. Patients whose blood pressure is less than 90 mm Hg for more than 15 minutes and for whom systemic fibrinolysis therapy might be considered.
7. When deemed safe following a specialist consultation.
8. Warfarin should not be administered to pregnant women during the first trimester or during the 2 to 4 weeks before delivery. It may, however, be considered during the rest of the pregnancy if the benefits outweigh the risks.

	Apixaban	Edoxaban	Rivaroxaban	Dabigatran	Warfarin
Duration of treatment	• VTE should be treated for **at least 3 months.** • Prolonged anticoagulation therapy for a period of more than 3 months should be considered: - In cases of unprovoked proximal DVT (excluding the calf veins) or PE; - If the patient has active cancer; - In patients with antiphospholipid syndrome. • The oral anticoagulant used during the short-term treatment may be continued when prolonged treatment is required. It should be noted that acetylsalicylic acid is not as effective as oral anticoagulants for secondary VTE prevention.				
Exception code (and RAMQ coverage criteria)	**CV169 (treatment)** Standard dosage (6-month authorization) **CV170 (prevention of recurrences of idiopathic VTE)** Dosage: 2.5 mg BID (12-month authorization - renewable)	**CV239** Standard dosage (12-month authorization)	**CV157 (PVT)** Standard dosage (6-month authorization) **CV165 (PE)** Standard dosage (long-term authorization)	Is not on the lists of medications for this indication	—
Antidote available	No	No	No	**Yes**	**Yes**
Important Precautions					
Prior to initiating treatment	Assess **renal function (CrCl)** and order a **complete blood count.**				
Drug interactions	**DOACs:** Consult the table of drug interactions with DOACs **Warfarin:** Consult the appendix to INESSS's medical protocol on warfarin adjustment The information on drug interactions should be used primarily to minimize the bleeding risk. A dose reduction should be considered only when indicated in the tool.				
Specific instructions	Take with or without food.	Take with or without food.	Take the 15-mg and 20-mg doses **with food.**	Take with or without food. If dyspepsia occurs, take with food.	Take with or without food.
	The tablets can be crushed.	The tablets can be crushed.	The tablets can be crushed.	The capsule **must not** be crushed, chewed or opened.	The tablets can be crushed.
	Can be administered via a nasogastric tube.	Can be administered via a nasogastric tube.	Can be administered via a nasogastric tube.	**Do not** administer via a nasogastric tube.	Can be administered via a nasogastric tube.
	—	—	—	Sensitive to moisture: keep in the original packaging or a pill organizer[1].	Store away from light and moisture.
Missed dose	Take a missed dose as soon as possible. **Do not** take a double dose to make up for a missed dose.	Take a missed dose as soon as possible. **Do not** take a double dose to make up for a missed dose.	**15 mg PO BID:** Take a missed dose at once (the total daily dose should be 30 mg). In this case, two 15-mg tablets can be taken at the same time. **10-20 mg PO daily:** Take a missed dose as soon as possible. **Do not** take a double dose to make up for a missed dose.	Take a missed dose as soon as possible, up to 6 hours before the next scheduled dose. Otherwise, **do not** take the missed dose.	Take a missed dose as soon as possible, on the same day. **Do not** take a double dose to make up for a missed dose.

1. Dabigatran is stable for 3 months in a pill organizer.

RISK ASSESSMENT FOR BLEEDING COMPLICATIONS

- Currently, no clinical tool validated in a VTE context is available for guiding clinicians in assessing the risk of bleeding complications in a patient on anticoagulant therapy.
- The risk assessment for bleeding complications is therefore based on the clinician's judgement. The following main factors may be taken into account when assessing the risk:
  - Age
  - History of bleeding
  - Renal failure
  - Thrombocytopenia

FOLLOW-UP

- The relevance of prolonged anticoagulation therapy should be reassessed periodically.

	DOACs	VKAs
Measurement of anticoagulant activity	None for the standard follow-up	Periodic monitoring of the INR
Other measurements	Renal function (CrCl) and a complete blood count at least once a year*. (Also monitor body weight.)	

* Adjust according to changes in the patient's medication profile or health status.

VKA THERAPY SELF-MONITORING AND SELF-MANAGEMENT

- The current scientific data show that self-monitoring and self-management are at least as effective and safe as a standard follow-up (management done entirely by a health professional). These results concern, among others, patients with a mechanical valve prosthesis.
- Self-monitoring and self-management should therefore be proposed to any patient who:
  - Is on long-term VKA therapy;
  - Wishes to monitor his/her INR him/herself;
  - Is physically and mentally able to do such a follow-up appropriately[1];
  - Has access to a health professional qualified to monitor oral VKA anticoagulation therapy.
- Patients who opt to monitor or manage their VKA therapy themselves should receive adequate, specific training.
- A medical follow-up, at least once a year, should be set up for patients who monitor or manage their VKA anticoagulation therapy themselves. The follow-up includes external quality control of their coagulometer in accordance with the manufacturer's recommendations.
- Consult the clinical tool "Dialogue with your patient" to facilitate the shared decision-making.

1. Or can call on a family member with the necessary skills.

RECURRENT VTE

- It is unusual for VTE to recur during effective anticoagulation therapy. If it does, consider:
  - Reevaluating the diagnosis of recurrent VTE;
  - Reassessing the patient's therapeutic compliance;
  - Determining if there is an underlying neoplasm or another acquired thrombophilia;
  - A specialist consultation.

PERIOPERATIVE MANAGEMENT

- Here is a simple, general procedure for managing patients treated with DOACs. Certain **local tools** with information supplementing that in this guide may be available, depending on the region. Thrombosis Canada's website (guide entitled "NOACs/DOACs: Perioperative Management") can be consulted as well for further details.
- Consult the local protocols or Thrombosis Canada's website (guide entitled "Warfarin: Peri-Operative Management") for the appropriate procedure for managing patients treated with VKAs.
- During the first 3 months after a diagnosis of proximal DVT or PE, consider postponing any elective surgery or any procedure where anticoagulation therapy would have to be stopped. All cases of emergency or semi-emergency surgery should be referred to a specialist.

	Moderate bleeding risk surgery or procedure	Major surgery or procedure (high bleeding risk)
Preoperatively		
Apixaban **Edoxaban** **Rivaroxaban**	**CrCl ≥ 30 ml/min:** Stop anticoagulation therapy **at least 24 hours** before the procedure	**CrCl ≥ 30 ml/min:** Stop anticoagulation therapy **at least 48 hours** before the procedure
Dabigatran	**CrCl ≥ 80 ml/min:** Stop anticoagulation therapy **at least 24 hours** before the procedure **CrCl 50 to 79 ml/min:** Stop anticoagulation therapy **24 to 48 hours** before the procedure **CrCl 30 to 49 ml/min:** Stop anticoagulation therapy **48 to 72 hours** before the procedure	**CrCl ≥ 80 ml/min:** Stop anticoagulation therapy **at least 48 hours** before the procedure **CrCl 50 to 79 ml/min:** Stop anticoagulation therapy **48 to 72 hours** before the procedure **CrCl 30 to 49 ml/min:** Stop anticoagulation therapy **96 hours** before the procedure
Postoperatively		
Apixaban **Edoxaban** **Rivaroxaban** **Dabigatran**	Resume anticoagulation therapy **approximately 24 hours after** the procedure.	Resume anticoagulation therapy **approximately 48 to 72 hours after** the procedure. A prophylactic dose of anticoagulant may be considered in the interim.

PROCEDURES FOR SWITCHING BETWEEN ANTICOAGULANTS

SWITCHING FROM AN ANTICOAGULANT TO A DOAC

Initial treatment	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
Heparin	Start treatment with apixaban as soon as the heparin infusion is stopped.	Start treatment with edoxaban **4 hours after stopping** the heparin infusion.	Start treatment with the DOAC as soon as the heparin infusion is stopped.	
Low-molecular-weight heparin (LMWH)	Start treatment with apixaban or edoxaban when the next dose of LMWH is due.		Start treatment with dabigatran or rivaroxaban within 2 hours before the next dose of LMWH is due.	
VKA	Stop the VKA and start treatment with a DOAC when:			
	INR < 2.0	INR ≤ 2.5	INR ≤ 2.5	INR < 2.0

SWITCHING FROM A DOAC TO ANOTHER ANTICOAGULANT

Initial treatment	Heparin or LMWH	VKA
Apixaban	Stop the DOAC and start treatment with heparin or a LMWH when the next dose of DOAC is due.	Start treatment with a VKA but continue treatment with the DOAC[1]. Stop the DOAC when the INR is ≥ 2.0 (measure the INR just before the DOAC dose is taken)[2].
Edoxaban		
Rivaroxaban		
Dabigatran	Start treatment with heparin or a LMWH 12 hours after the last dabigatran dose.	**CrCl ≥ 50 ml/min:** start treatment with the VKA 3 days before stopping dabigatran. **CrCl 30 to 49 ml/min:** start treatment with the VKA 2 days before stopping dabigatran.

1. During concomitant therapy, reduce the edoxaban dose by half.
2. DOACs may increase laboratory- or coagulometer-measured INR values. Therefore, an INR measurement should generally be performed the day after a DOAC is stopped, to confirm the value obtained.

BLEEDING MANAGEMENT

Type of bleeding	DOAC-treated patient	VKA-treated patient
Minor	Delay the administration of the DOAC by 1 dose or 1 day.	Delay the administration of the VKA until the INR is < 2. If the INR is supratherapeutic, consider administering vitamin K (2.5 to 5 mg PO).
Moderate to severe	Add a symptomatic treatment: • Fluid replacement; • Blood transfusion; • Treating the cause of the bleeding. Consider administering charcoal orally if a DOAC was taken recently.	Add a symptomatic treatment: • Fluid replacement; • Blood transfusion; • Treating the cause of the bleeding. Consider administering vitamin K (10 mg IV).
Severe or potentially fatal	Consider administering: • A specific antidote (dabigatran) **or** • A prothrombin complex concentrate[3] (50 U/kg; max.: 5000 U) if no antidote is available (apixaban, edoxaban or rivaroxaban). Consider platelet replacement if thrombopenia or antiplatelet therapy.	Administer vitamin K (10 mg IV). Consider administering a prothrombin complex concentrate (as per protocol, based on the patient's weight and INR) or fresh frozen plasma. Consider platelet replacement if thrombopenia or antiplatelet therapy.

3. Health Canada has not approved any prothrombin complexes for the treatment of bleeding in cases of DOAC-induced acquired clotting factor deficiencies. However, the experts are of the opinion that this treatment is a valid option in cases of severe or potentially fatal bleeding.

MAIN REFERENCES

Farge D, Bounameaux H, Brenner B, Cajfinger F, Debourdeau P, Khorana AA, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol 2016;17(10):e452-e66.

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Thrombosis Canada. Deep Vein Thrombosis (DVT): Treatment. Thrombosis Canada 2018. June 18 2018. Available at: http://thrombosiscanada.ca/clinicalguides/.

Thrombosis Canada. Venous Thromboembolism: Duration of Treatment. Thrombosis Canada 2018. October 9 2018. Available at: http://thrombosiscanada.ca/clinicalguides/.

To consult all the references:
See the report in support of the OUG and the systematic review report.

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Pharmacokinetic parameters of DOACs and warfarin:

	Apixaban	Edoxaban	Rivaroxaban	Dabigatran	Warfarin
Mechanism of action	Direct, specific factor Xa inhibitor			Direct, specific factor IIa (thrombin) inhibitor	Inhibitor of vitamin K-dependent clotting factors and anticoagulant proteins C and S
Peak anticoagulant effect	3 to 4 hours	1 to 2 hours	2 to 4 hours	0.5 to 2 hours	3 to 4 days
Half-life	8 to 13 hours	10 to 14 hours	5 to 13 hours	11 to 17 hours	20 to 60 hours
Renal elimination of the active form	27%	50%	33%	85%	—

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