INESSS
LE SAVOIR PREND FORME

APRIL 2019

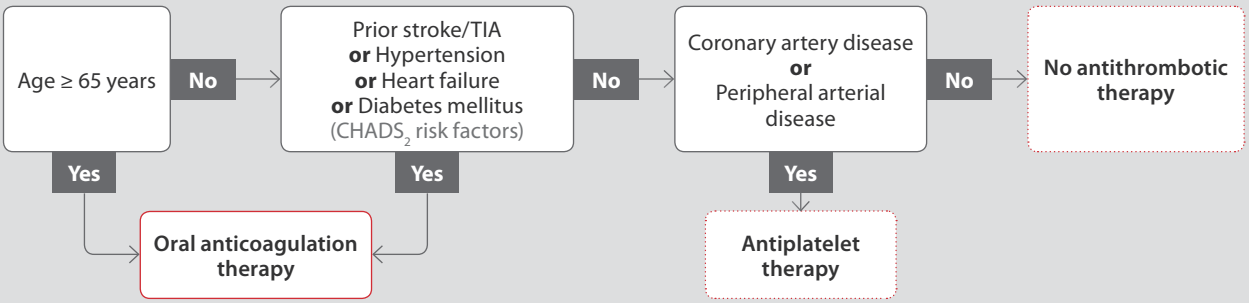
DRUG
DIRECT ORAL ANTICOAGULANTS AND WARFARIN

ATRIAL FIBRILLATION IN ADULTS

THROMBOEMBOLIC RISK

- Atrial fibrillation increases the risk of ischemic stroke 5-fold.

CHADS-65 Decision Algorithm (Canadian Cardiovascular Society)



Embolic risk assessment
(CHA_2-DS_2-VASc score)

Congestive heart failure	**+1**
Hypertension	**+1**
Age ≥ 75 years	**+2**
Diabetes mellitus	**+1**
History of stroke, transient ischemic attack (TIA) or peripheral embolism	**+2**
Vascular disease	**+1**
Age 65-74 years	**+1**
Sex (female)	**+1**

CHA_2DS_2-VASc score									
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Annual risk of stroke (%)									
0.7	1.5	3.0	4.4	6.7	10.4	12.9	13.9	14.1	16.1

Risk assessment for bleeding complications

- Clinical tools are currently available for guiding the clinician in assessing the risk of bleeding complications in patients receiving anticoagulation therapy, each with its limitations.
- To minimize the bleeding risk, pay close attention to the following risk factors:

Modifiable risk factors
Hypertension
Unstable INR
Use of drugs that promote bleeding
Excess alcohol consumption
Potentially modifiable risk factors
Anemia
Kidney failure
Liver failure
Thrombocytopenia or platelet dysfunction

TREATMENT PRINCIPLES

- 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.

Québec

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.

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.

		Apixaban	Edoxaban	Rivaroxaban	Dabigatran	Warfarin
Dosage		**5 mg PO BID**	**60 mg PO daily**	**20 mg PO daily**	**150 mg PO BID**	**PO daily** Adjust dosage according to INR
Reduced dose ! Use only if the detailed criteria are met		2.5 mg PO BID **At least 2** of the following criteria: • Age ≥ 80 years • Weight ≤ 60 kg • Serum creatinine ≥ 133 µmol/l	30 mg PO daily • CrCl between 30 and 50 ml/min[3] **or** • Weight ≤ 60 kg **or** • Use of potent P-glycoprotein inhibitors	15 mg PO daily • CrCl between 15 and 49 ml/min[3]	110 mg PO BID • Age ≥ 80 years **or** • High bleeding risk	
Exception code		**CV155**	**CV155**	**CV155**	**CV155**	—
Antidote available		No	No	No	**Yes**	**Yes**
Specific populations in whom certain DOACs may be considered						
CrCl (ml/min³)	**15 to 30**	⚠	?	⚠	?	✓
	< 15	?	?	?	?	✓
Weight > 120 kg		⚠[4]	⚠[4]	⚠[4]	⚠[4]	✓
Parietal gastrectomy		⚠	?	✗	✗	✓
Mild (Child-Pugh A) or moderate (Child-Pugh B) liver failure		⚠[5]	⚠[5]	⚠[5]	⚠[5]	⚠[5]
Recent AF-induced ischemic stroke		Consider starting a DOAC or a VKA within the 2 weeks following an ischemic stroke, when this treatment is deemed safe following a specialist consultation.				
Populations in whom DOACs should not be used						
Pregnant women		✗	✗	✗	✗	✗[6]
Nursing women		✗	✗	✗	✗	✓
Mechanical valve prosthesis		✗	✗	✗	✗	✓
Rheumatic heart disease or moderate to severe mitral stenosis		✗	✗	✗	✗	✓
Severe liver failure (Child-Pugh C) or liver failure accompanied by a coagulopathy		✗	✗	✗	✗	⚠[5]
Gastric bypass		✗	✗	✗	✗	✓

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

3. The creatinine clearance should be calculated using the Cockcroft-Gault formula.
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. When deemed safe following a specialist consultation.
6. 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.

IMPORTANT PRECAUTIONS

	Apixaban	Edoxaban	Rivaroxaban	Dabigatran	Warfarin
Prior to initiating treatment	Assess **renal function (CrCl)** and **order a complete blood count.**				
Concomitant treatment with an antiplatelet agent	❗ Consider adding a proton pump inhibitor (PPI) in patients requiring concomitant treatment with a DOAC and acetylsalicylic acid or clopidogrel. ❗ Consideration should be given to withdrawing antiplatelet therapy in patients with stable coronary artery disease (defined as having had no acute coronary syndrome for at least 1 year).				
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 **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.	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.

FOLLOW-UP

	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.

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.

	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

Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European heart journal 2016;37(38):2893-962.

Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C, et al. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Canadian Journal of Cardiology 2018;34(11):1371-92.

Thrombosis Canada. Stroke prevention in atrial fibrillation. Thrombosis Canada 2018. September 10 2018. Available at: http://thrombosiscanada.ca/clinicalguides/.

Wein T, Lindsay MP, Côté R, Foley N, Berlingieri J, Bhogal S, et al. Canadian stroke best practice recommendations: Secondary prevention of stroke, sixth edition practice guidelines, update 2017. International Journal of Stroke 2018;13(4):420-43.

To consult all the references:

See the report in support of the OUG and the systematic review report.

Institut national d'excellence en santé et en services sociaux
Québec

Embolic risk assessment

Congestive heart failure	**+1**
Documented moderate to severe systolic dysfunction; signs and symptoms of heart failure with a reduced ejection fraction; or recent decompensated heart failure that required hospitalization irrespective of the ejection fraction.	
History of hypertension	**+1**
Resting blood pressure > 140 mmHg (systolic) or > 90 mmHg (diastolic) on at least 2 occasions or patient currently on pharmacological antihypertensive therapy.	
Age ≥ 75 years	**+2**
Diabetes mellitus	**+1**
Fasting plasma glucose concentration ≥ 7 mmol/l (1.26 g/l) or patient treated with an oral hypoglycemic agent or insulin.	
History of stroke, transient ischemic attack (TIA) or peripheral embolism	**+2**
Stroke: focal neurological deficit of sudden onset diagnosed by a neurologist, lasting more than 24 hours and caused by ischemia. TIA: focal neurological deficit of sudden onset diagnosed by a neurologist, lasting less than 24 hours. Peripheral embolism: thromboembolism outside the brain, heart, eyes and lungs, or pulmonary embolism (defined by the responsible physician).	
Vascular disease	**+1**
Coronary artery disease, peripheral artery disease or aortic plaque.	
Age 65-74 years	**+1**
Sex (female)	**+1**

Risk assessment for bleeding complications

Modifiable risk factors	Potentially modifiable risk factors
Hypertension (especially if the blood pressure is > 160 mmHg)	**Anemia**
Unstable INR or time in the therapeutic range less than 60% in patients treated with VKAs	**Kidney failure**
Use of drugs that promote bleeding (e.g., antiplatelet agents and nonsteroidal antiinflammatory drugs (NSAIDs))	**Liver failure**
Excess alcohol consumption (8 or more drinks a week)	**Thrombocytopenia or platelet dysfunction**

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%	—

Return to optimal use guide