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

QUEBEC'S MEDICAL PROTOCOL

No. 628003

Warfarin Adjustment

Developed in collaboration with an advisory committee consisting of Québec clinicians and experts.

Validated by the Comité d'excellence clinique en usage optimal du médicament, des protocoles médicaux nationaux et des ordonnances (UOM-PMNO) of the Institut national d'excellence en santé et en services sociaux (INESSS).

CLINICAL SITUATION OR TARGET POPULATION

Person 18 years of age or older on warfarin anticoagulation therapy

CONTRAINDICATIONS TO THE APPLICATION OF THIS PROTOCOL

Pregnancy and breastfeeding

INSTRUCTIONS

1. ASSESS HEALTH STATUS WHEN MAKING THE ADJUSTMENT[1]

1.1 Thromboembolic risk factors

Inquire about thromboembolic risk factors.

MAIN THROMBOEMBOLIC RISK FACTORS		
Transient	**Hereditary or genetic**	**Acquired**
• Major surgery • General anesthesia • Malignant neoplasm • Trauma • Acute spinal cord injury • Fracture of the hip, pelvis or a lower limb • High doses of estrogens, oral contraceptives • Pregnancy and postpartum • Myocardial infarction • Stroke • Chemotherapy • Dehydration • Flight lasting more than 6 to 8 hours • Electrical or pharmacological cardioversion for treating atrial fibrillation or flutter	• Resistance to activated C protein (factor V Leiden) • Hyperhomocysteinemia • Antithrombin deficiency • Protein C deficiency • Protein S deficiency • Prothrombin gene mutation G20210A	• Age (↑ with age > 40 years) • Neoplasia • Prolonged immobility • Heart failure • Venous obstruction • History of deep vein thrombosis (DVT) or pulmonary embolism (PE) • Obesity (BMI ≥ 30 kg/m^2) • Varicose veins • Heparin-induced thrombocytopenia • Polycythemia vera • Splenectomy • Inflammatory bowel disease • Chronic venous insufficiency • Valve replacement (especially a mechanical valve) • History of atrial fibrillation or flutter • Transient ischemic attack (TIA) • History of stroke • Antiphospholipid syndrome

[1] If necessary, consult Appendix I for assessing thromboembolic risk in patients with atrial fibrillation, Appendix II for assessing the risk of bleeding complications, and Appendix IV for additional information on warfarin.

1.2 Bleeding risk factors

Inquire about any bleeding risk factors.

MAIN BLEEDING RISK FACTORS		
• Age > 65 years • History of bleeding • History of gastrointestinal bleeding • History of stroke • History of TIA • Decompensated heart failure • Liver failure • Severe kidney failure (eGFR < 30 ml/min/1.73 m^2) • Neoplasia	• Uncontrolled hypertension • Anemia • Thrombocytopenia (platelet count < 50 × 10^9/l) or platelet dysfunction • Recent trauma or surgery (≤ 1 month) • Frequent falls • Alcohol abuse • Unstable INR • Intensity of anticoagulation therapy (the most important factor for intracranial bleeding; risk ↑ with INR > 4) • Duration of anticoagulation therapy	• Concomitant use of a drug that can potentiate the anticoagulant effect or modify hemostasis (e.g., antiplatelet agents) or cause insult to the gastroduodenal mucosa [e.g., nonsteroidal antiinflammatory drugs (NSAIDs)]

1.3 Factors that can modify anticoagulation therapy and its effects on the international normalized ratio (INR)[1]

Inquire about factors that can modify anticoagulation therapy and its effects on the INR.

MAIN FACTORS THAT CAN MODIFY ANTICOAGULATION THERAPY AND ITS EFFECTS ON THE INR	
Variation factor	**Effect on the INR**
Poor compliance with drug therapy (error or missed dose)	↓ or ↑ INR, depending on the case
Drug interaction (see Appendix IV)	↓ or ↑ INR OR ↑ bleeding risk, depending on the drug taken
Physical activity	If ↑ physical activity, (↓ INR)
Change in diet or irregular eating pattern	If ↑ vitamin K intake, (↓ INR) If ↓ vitamin K intake, (↑ INR)
Alcohol consumption	Variation in the INR
Smoking (change in habits)	Possible ↑ INR on smoking cessation Possible ↓ INR on smoking resumption
Heart failure with hepatic congestion	↓ in warfarin metabolism (↑ INR)
Hypothyroidism	↓ clotting factor catabolism (↓ INR)
Hyperthyroidism	↑ clotting factor catabolism (↑ INR)
Fever	↑ clotting factor catabolism (↑ INR)
Gastrointestinal disorders (diarrhea and vomiting)	↓ vitamin K absorption (↑ INR)
Liver failure	Altered clotting factor synthesis ↓ warfarin metabolism (↑ INR)

[1] If necessary, see Appendix III, which contains sample questions for warfarin-treated patients aimed at identifying factors that may have caused their INR to fluctuate or at detecting symptoms or warning signs.

2. INVESTIGATION

2.1 Laboratory tests for adjusting warfarin

The following laboratory tests should be ordered:

FREQUENCY OF LABORATORY TESTS FOR ADJUSTING WARFARIN
At the start of treatment
INR every 2 to 3 days until the target therapeutic range is reached, then INR every week x 3, then INR every other week x 2, then INR every 4 weeks
INR stable (is usually within the target therapeutic range)[1]
INR every 4 weeks Depending on the patient's clinical condition, INR every 4 to 12 weeks[2]
INR unstable (INR nontherapeutic)
Frequency of INR measurement as per the dose adjustment tables

[1]The health professional should tell a warfarin-treated patient that the INR measurement will need to be done sooner than according to the scheduled interval if there are any changes in their health or to their medication or diet.

[2] Measuring the INR at intervals greater than 4 weeks is not appropriate for all patients (e.g., it should not be done in patients with a psychiatric disorder, a cognitive impairment or a known therapeutic adherence problem).

3. RECOMMENDED PROCEDURE FOR ADJUSTING THE WARFARIN DOSE

3.1 General principles

- It is preferable to keep INR values in the middle of the target therapeutic range in order to maintain a safety zone in the event of INR variation. The approach to be used will depend on **whether or not a factor responsible for the INR deviating from the therapeutic range is identified** and on whether or not this factor **persists**.
- Assess the INR trends before deciding on a dose adjustment.
- Avoid large dose variations, as they can cause high INR variability.
- Consider checking the INR more frequently when the difference between two consecutive results is greater than or equal to 0.8.
- In the adjustment tables below, the recommended interval to the next INR measurement is the maximum interval. When using a low-molecular-weight heparin (LMWH) or a large loading dose (for 2 or more days) or if the patient has a particular clinical condition, consideration should be given to a shorter INR testing interval.
- **Regardless of the INR value, in the presence of bleeding considered significant or of symptoms or signs of thromboembolism or that prompt suspicion of a stroke, the patient should be referred, if necessary, to the professional or clinical facility that will be able to manage the patient appropriately.**

3.2 Adjusting the warfarin dose in the presence of a temporary variation factor

When a **temporary factor** that can explain the INR variation can be clearly established and when this factor (e.g., infection, diarrhea, etc.) is completely resolved, priority should be given to a rapid return to within the target therapeutic range and then to resuming the usual dose.

When required, the loading dose is **approximately 1.5 times the scheduled dose on the day of the adjustment** (e.g., for a patient taking a dose of 5 mg QD, the loading dose would be 7.5 mg.).

In the presence of a **temporary factor** that can explain the INR variation, only the recommendations in the 'Recommended temporary dose adjustment' column in the adjustment tables below are to be applied.

3.3 Adjusting the warfarin dose if the presence of a variation factor cannot be established or if an identified factor is likely to persist

If the presence of a factor that can explain the INR variation cannot be established or if a factor is identified but is likely to persist (e.g., the addition of a drug that can potentially interact with warfarin), **immediately modifying the weekly warfarin dose** is justified.

A temporary dose adjustment (loading dose or omitting a dose, depending on the INR) can be added (but not always) to the modification to the weekly dose. The need to make or not make a temporary dose adjustment depends on the clinical context.

If the presence of a factor that can explain the INR variation cannot be established or if a factor is identified but is likely to persist, the recommendations in the column 'Recommended percent adjustment to the weekly dose' in the adjustment tables below should be applied. The relevance of also following the recommendations in the column 'Recommended temporary dose adjustment' should be assessed in light of the clinical context.

3.4 Adjustment tables

TARGET THERAPEUTIC RANGE: INR OF 2.0 TO 3.0			
Context	**In all cases, *in the presence of a temporary variation factor***	**In all cases, *if the presence of a variation factor cannot be established or if an identified factor is likely to persist*** Depending on the clinical context (e.g., rapid or significant INR variation), combine the recommended percent adjustment to the weekly dose with the recommended temporary dose adjustment (left column) to promote a rapid return to within the target therapeutic range.	
INR measured	**Recommended temporary dose adjustment**	**Recommended percent adjustment to the weekly dose**	**Next INR measurement[1]**
Subtherapeutic INR			
≤ 1.49	Loading dose x 2 or 3 days[2] Consider using an LMWH[3]	↑ 15% to 20%[2]	2 to 3 days
1.50 to 1.69	Loading dose x 2 days[2] Consider using an LMWH[3]	↑ 10% to 12.5%[2]	5 to 7 days
1.70 to 1.79	Loading dose x 1 or 2 days	↑ 10% to 12.5%	5 to 7 days
1.80 to 1.99	Loading dose x 1 day	↑ 5% to 7.5%	2 to 4 weeks
Supratherapeutic INR			
3.01 to 3.39	No dose omission[4]	No adjustment. Continue the anticoagulation therapy as is.[4]	2 to 4 weeks
3.40 to 3.79	Omit one dose x 1 day or give a half-dose x 1 day	↓ 5%	1 to 2 weeks
3.80 to 4.59	Omit one dose x 1 day	↓ 5% to 7.5%	5 to 7 days
4.60 to 4.99	Omit the dose x 2 days	↓ 10% to 15%	3 to 5 days
≥ 5.0	Stop warfarin and pay special attention[2] Consider using vitamin K[5]		1 to 3 days

[1] In the adjustment table above, the recommended interval to the next INR measurement is the maximum interval. When using an LMWH or a high loading dose (for 2 or more days) or in the presence of a particular clinical condition, consider a shorter INR testing interval.

[2] For the purpose of a joint follow-up with a nurse applying an individual adjustment prescription (IAP), the authorized prescriber who wrote the prescription (or the responding health professional) must be contacted that same day to determine the best course of action in light of the patient's clinical status.

[3] In patients with a high thromboembolic risk, especially those with a mechanical valve or a history of stroke, consider using an LMWH until the INR returns to within the target therapeutic range.

[4] If the temporary variation factor is not resolved when a first INR result between 3.01 and 3.39 is obtained or if several consecutive INR results are in this range, consideration should be given to making the adjustment pertaining to a result between 3.40 and 3.79.

[5] Depending on the thrombotic risk, in patients with a high bleeding risk or in the presence of significant active bleeding, consider using vitamin K.

TARGET THERAPEUTIC RANGE: INR OF 2.5 TO 3.5			
Context	**In all cases, *in the presence of a temporary variation factor***	**In all cases, *if the presence of a variation factor cannot be established or if an identified factor is likely to persist*** Depending on the clinical context (e.g., rapid or significant INR variation), combine the recommended percent adjustment to the weekly dose with the recommended temporary dose adjustment (left column) to promote a rapid return to within the target therapeutic range.	
INR measured	**Recommended temporary dose adjustment**	**Recommended percent adjustment to the weekly dose**	**Next INR measurement[1]**
Subtherapeutic INR			
≤ 1.49	Loading dose x 2 or 3 days[2] Start an LMWH[3]	↑ 15% to 20%[2]	2 to 3 days
1.50 to 1.89	Loading dose x 2 days[2] Consider the use of an LMWH[3]	↑ 10% to 12.5%[2]	2 to 3 days
1.90 to 2.19	Loading dose x 1 or 2 days[2] Consider the use of an LMWH[3]	↑ 7.5% to 10%[2]	5 to 7 days
2.20 to 2.29	Loading dose x 1 or 2 days	↑ 7.5% to 10%	5 to 7 days
2.30 to 2.49	Loading dose x 1 day	↑ 3% to 5%	2 to 4 weeks
Supratherapeutic INR			
3.51 to 3.99	No dose omission[4]	No adjustment. Continue the anticoagulation therapy as is.[4]	2 to 4 weeks
4.00 to 4.49	Omit one dose x 1 day or give a half-dose x 1 day	↓ 2.5% to 5%	1 week
4.50 to 5.39	Omit one dose x 1 day	↓ 5% to 7.5%	5 to 7 days
5.40 to 5.99	Omit the dose x 2 days and pay special attention[2] Consider using vitamin K[5]		3 to 5 days
≥ 6.00	Stop warfarin and pay close attention[2] Consider using vitamin K[5]		1 to 3 days

[1] In the adjustment table above, the recommended interval to the next INR measurement is the maximum interval. When using an LMWH or a high loading dose (for 2 or more days) or in the presence of a particular clinical condition, consider a shorter INR testing interval.

[2] For the purpose of a joint follow-up with a nurse applying an individual adjustment prescription (IAP), the authorized prescriber who wrote the prescription (or the responding health professional) must be contacted that same day to determine the best course of action in light of the patient's clinical status.

[3] In patients with a high thromboembolic risk, especially those with a mechanical valve or a history of stroke, consider using an LMWH until the INR returns to within the target therapeutic range.

[4] If the temporary variation factor is not resolved when a first INR result between 3.51 and 3.99 is obtained or if several consecutive INR results are in this range, consideration should be given to making the adjustment pertaining to a result between 4.00 and 4.49.

[5] Depending on the thrombotic risk, in patients with a high bleeding risk or in the presence of significant active bleeding, consider using vitamin K.

4. FOLLOW-UP

Certain basic concepts about the treatment and certain precautions should be discussed with patients receiving warfarin anticoagulation therapy.

FOLLOW-UP
Basic concepts concerning the therapy
• Indication for anticoagulants • Reason for anticoagulation therapy, target therapeutic range and duration of treatment • Reason for and importance of blood draws for INR measurements • Anticoagulant dosage and administration schedule • Use of an anticoagulation diary • Functioning of the anticoagulation therapy unit • Option of self-monitoring or self-management of the therapy (for information on this topic, click here) • Missed doses: - Missed dose remembered on the same day: take the scheduled dose. - Missed dose remembered on the following day: do not double the dose.
Precautions
• Adverse effects • Signs of bleeding • If bleeding occurs, apply pressure on the bleeding site for at least 10 minutes • Use of a method of contraception, if applicable • Lifestyle: diet, alcohol and tobacco consumption, and physical activity • Vigilance in the event of a head injury • Interactions with prescription and over-the-counter medications and natural products • Importance of informing all health professionals (pharmacist, dentist, physician and nurse) of being on an anticoagulant • Importance of the patient carrying or wearing an anticoagulant card or bracelet • Storing medications • How and when to contact the medical clinic, physician or specialized nurse practitioner (SNP)

5. SITUATIONS REQUIRING SPECIAL ATTENTION, FURTHER INVESTIGATION OR A REEVALUATION

- ► Active cancer[1]
- ► A history of thrombotic event during appropriate anticoagulation therapy
- ► A recent history of major bleeding (< 1 month)
- ► Patient on dialysis
- ► Patient preparing for a surgical or dental procedure or an invasive examination
- ► Use of a low-molecular-weight heparin (LMWH)
- ► Alcohol problem or abuse
- ► Emergence of a contraindication to the use of warfarin during the therapy
- ► Persistent INR lability (three consecutive INR results outside the target therapeutic range)
- ► Noncompliance with the therapy observed on a regular basis
- ► Signs or symptom of major bleeding, of thromboembolism or of a stroke
- ► Concomitant use of an antiplatelet agent

[1] During the first 6 months of treatment or if the cancer remains active (extensive, metastatic or treated with chemotherapy).

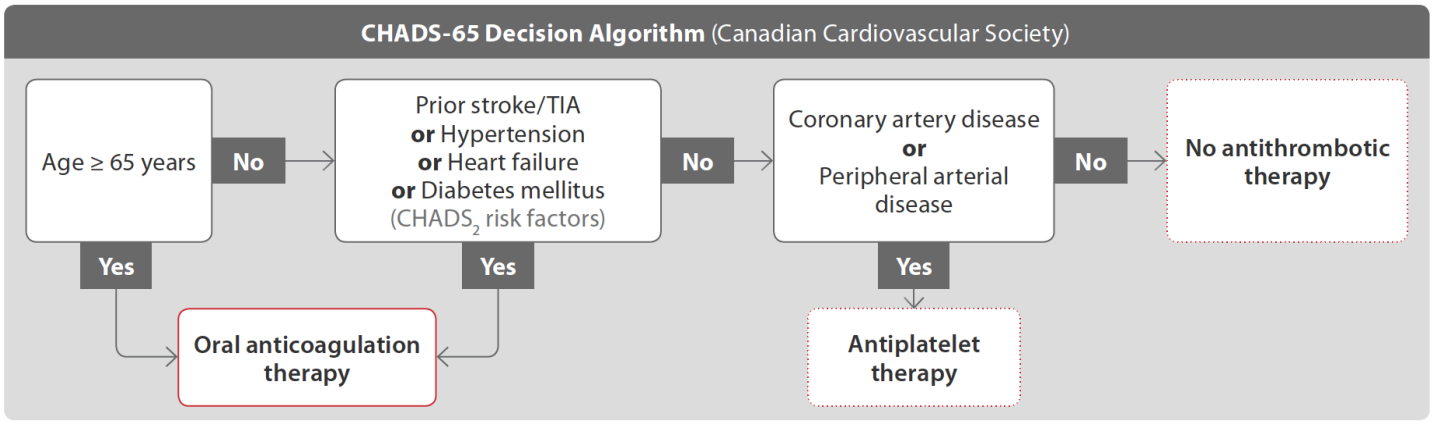
REFERENCES

This national medical protocol is based on the latest scientific data and best practice recommendations, which were enhanced with contextual information and experiential knowledge provided by Québec clinicians and experts. For further details on the process used to develop this protocol and to consult the references, see the report in support of this protocol.

APPENDIX I – ASSESSING THROMBOEMBOLIC RISK IN PATIENTS WITH ATRIAL FIBRILLATION

The CHADS-65 decision algorithm was created by the Canadian Cardiovascular Society for the purpose of determining which patients with atrial fibrillation or flutter should receive oral anticoagulation therapy.

The CHA_2DS_2-VASc is a tool for assessing the risk of stroke in patients with nonvalvular atrial fibrillation (NVAF). The summation of the points given for the risk factors that are present yields the overall risk.



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

APPENDIX II – ASSESSING THE RISK OF BLEEDING COMPLICATIONS

In patients with atrial fibrillation, pay special attention to the following risk factors in order to minimize the bleeding risk:

Modifiable risk factors	Potentially modifiable risk factors
Hypertension (especially if the blood pressure is greater than 160 mm Hg)	**Anemia**
INR unstable or within the therapeutic range less than 60% of the time in patients treated with a VKA	**Renal failure**
Use of drugs that promote bleeding (such as antiplatelet agents and nonsteroidal antiinflammatory drugs (NSAIDs))	**Hepatic failure**
Alcohol abuse (8 or more drinks per week)	**Thrombocytopenia or platelet dysfunction**

Furthermore, clinical tools, each with its limitations, are currently available to guide clinicians in their risk assessment for bleeding complications in patients with atrial fibrillation (AF). One of these tools, HAS-BLED, is used to assess the bleeding risk in AF patients without mitral valvulopathy who are receiving warfarin anticoagulation therapy. The summation of the points given for the different risk factors that are present yields the overall risk.

BLEEDING RISK ASSESSMENT (HAS-BLED)		
Clinical characteristic	**Points**	**Risk interpretation**
Hypertension: SBP > 160 mm Hg	1	Low risk (0 or 1) Moderate risk (2) High risk (≥ 3)
Abnormal renal or hepatic function (1 point each) • Chronic dialysis, renal transplantation or creatinine > 200 µmol/l • Chronic liver disease (e.g., cirrhosis) or bilirubin > 2 x upper limit of normal and AST/ALT/ALP > 3 x upper limit of normal	1 or 2	
History of stroke	1	
Bleeding: history or predisposition	1	
Labile INR: time within the therapeutic range < 60%	1	
Age > 65 years	1	
Alcohol or medications (1 point each) • Alcohol abuse > 8 drinks/week • Antiplatelet agents[1], NSAIDs	1 or 2	
Maximum score	9	

Adapted from Pisters *et al.*, 2010.
[1] Examples: acetylsalicylic acid (ASA), clopidogrel, prasugrel, ticagrelor and ticlopidine.

In the context of deep vein thromboembolism or pulmonary embolism, the risk assessment for bleeding complications in a patient receiving warfarin anticoagulation therapy is based on the judgement of the clinician, who may consider the following main factors in the assessment: age, history of bleeding, renal failure, thrombocytopenia, etc.

APPENDIX III – SAMPLE QUESTIONS FOR WARFARIN-TREATED PATIENTS AIMED AT IDENTIFYING FACTORS THAT MAY HAVE CAUSED THEIR INR TO FLUCTUATE OR AT DETECTING SYMPTOMS OR WARNING SIGNS

Here are some sample questions for warfarin-treated patients aimed at identifying factors that may have caused their INR to fluctuate or at detecting symptoms or warning signs.

QUESTIONS
How have you taken your warfarin in the past 2 weeks (number of tablets, colour, number of times per day)? Have you forgotten to take any doses? Did you make any dose changes?
Have you made any changes to your medication? • Antibiotics • Natural products • Over-the-counter medications (e.g., acetylsalicylic acid, nonsteroidal antiinflammatory drugs or acetaminophen) • Dietary supplements • Vitamins • Medication provided in the context of a research study
Have you been sick (e.g., fever, diarrhea, vomiting or recently hospitalized)? Did you experience an intensely stressful situation recently (e.g., bereavement, moving or a divorce)?
Have you changed your alcohol consumption (including wine, beer and liquor)?
Have you started, resumed or stopped smoking?
Have you changed your diet? Have you changed your intake of green vegetables?
Has your level of physical activity changed significantly?
If necessary, and depending on the clinical context and the INR result, ask the patient if there have been any symptoms or warning signs, using plain language adjusted to their level of understanding: • *Signs or symptoms of bleeding*, such as minor bleeding (e.g.., epistaxis, ecchymoses or bleeding gums), hemoptysis, hematuria, intracerebral bleeding (e.g., a sudden, intense headache or a neurological impairment), gastrointestinal bleeding (e.g., red blood in stool, black stool or brownish, coffee-ground emesis), intra-abdominal bleeding (e.g., unexplained abdominal pain) or fainting • *Signs or symptoms of venous thromboembolism*, such as pain in the affected area (e.g., in the calf, on the inside of the thigh or in the inguinal area), swelling or hardening in the affected area, redness and heat in the affected area, shortness of breath, or chest pain • *Signs or symptoms that prompt suspicion of a stroke*, such as new facial asymmetry, a new motor impairment, or speech problems

APPENDIX IV – ADDITIONAL INFORMATION ON WARFARIN

The additional information on warfarin presented below is not exhaustive.

USE OF WARFARIN IN SPECIFIC POPULATIONS

WARFARIN		
USE IN SPECIFIC POPULATIONS		
Clcr (ml/min) *	**15 to 30**	✓
	< 15	✓
Active cancer[1]		Preference should be given to an LMWH or a direct oral anticoagulant (DOAC), depending on the context
Antiphospholipid syndrome		✓
Weight > 120 kg		✓
Gastric bypass		✓
Parietal gastrectomy		✓
PE and hemodynamic instability[2]		After heparin therapy
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		⚠[3]
Mild (Child-Pugh A) or moderate (Child-Pugh B) liver failure		⚠[3]
Recent AF-related ischemic stroke		Consider initiating a DOAC or a vitamin K antagonist (VKA) (e.g., warfarin) within the 2 weeks following the ischemic stroke if such treatment is considered safe, based on a consultation with a specialist

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

*Creatinine clearance values should be calculated using the Cockcroft-Gault formula.
[1] During the first 6 months of treatment or if the cancer remains active (extensive, metastatic or treated with chemotherapy).
[2] Patient whose blood pressure is less than 90 mm Hg for more than 15 minutes and in whom systemic fibrinolytic therapy might be considered.
[3] When considered safe, based on a consultation with a specialist.

MAIN ADVERSE EFFECTS

WARFARIN
MAIN ADVERSE EFFECTS[1]
• Bleeding (minor or major) • Occult bleeding

[1]Consider adding a proton pump inhibitor (PPI) in patients at risk for gastrointestinal bleeding, such as those requiring concomitant treatment with warfarin and an antiplatelet agent or with warfarin and a nonsteroidal antiinflammatory drug (NSAID).

THE MOST SIGNIFICANT DRUG INTERACTIONS

Drug interactions with warfarin are very numerous.

The potential for drug interactions should be assessed when making any addition or change to a patient's medications. If necessary, consult the appropriate references and/or a pharmacist.

It is advisable to reduce warfarin doses as soon as treatment with sulfamethoxazole, amiodarone or metronidazole is initiated.

Apixaban, dabigatran, rivaroxaban and edoxaban are direct oral anticoagulants (DOACs). Their continuous use with warfarin is contraindicated.

Close INR monitoring during significant drug interactions

- Check the INR **4 to 5 days** after **initiating** the treatment, **modifying** the dose or **discontinuing** it.

WARFARIN		
THE MOST SIGNIFICANT DRUG INTERACTIONS REQUIRING CLOSE MONITORING OF INR VALUES		
Class of drug	**Result**	**Next INR measurement/Details**
Antibiotics and antifungals		
Clarithromycin	↑ INR	INR 4 to 5 days after initiation, dose modification, or discontinuation
Erythromycin	↑ INR	
Systemic azole antifungals (fluconazole (with the exception of single-dose treatment), itraconazole, ketoconazole, posaconazole and voriconazole)	↑ INR	
Metronidazole	↑ INR	
Quinolones	↑ INR	
Rifampicin	↓ INR	The time to interaction varies and can be up to several weeks. Check the INR every 4 to 5 days until it stabilizes[1].
Sulfamethoxazole	↑ INR	INR 4 to 5 days after initiation, dose modification, or discontinuation
Antiarrhythmics		
Amiodarone	↑ INR	Check the INR every 4 to 5 days until it stabilizes[1] after initiating amiodarone or at each dose modification and up to 4 weeks after discontinuing it, depending on the INR variation.
Propafenone	↑ INR	INR 4 to 5 days after initiation, dose modification, or discontinuation
Antipyretic analgesics		
Acetaminophen	↑ INR	Interaction observed particularly during variable dosing and at high doses. There is the potential for an interaction at doses greater than 2 g/day.
Class of nonsteroidal antiinflammatory drugs (NSAIDs)	↑ bleeding risk	Avoid this combination, unless the benefits outweigh the risks. Monitor closely for signs and symptoms of bleeding.
Class of selective cyclo-oxygenase 2 (COX-2) inhibitors (celecoxib)	↑ INR ↑ bleeding risk	INR 4 to 5 days after initiation, dose modification, or discontinuation
Tramadol	↑ INR ↑ bleeding risk	
Antiplatelet agents		
Acetylsalicylic acid (ASA)	↑ bleeding risk	Combination may be useful only if the benefits outweigh the risks. Monitor closely for signs and symptoms of bleeding. Assess regularly the clinical appropriateness of continuing the combination.
Clopidogrel	↑ bleeding risk	
Prasugrel	↑ bleeding risk	
Ticagrelor	↑ bleeding risk	
Ticlopidine	↑ bleeding risk	

WARFARIN		
THE MOST SIGNIFICANT DRUG INTERACTIONS REQUIRING CLOSE MONITORING OF INR VALUES		
Class of drug	**Result**	**Next INR measurement/Details**
Anticonvulsants		
Carbamazepine	↓ INR	INR 4 to 5 days after initiation, dose modification, or discontinuation
Phenobarbital	↓ INR	
Phenytoin	↑ or ↓ INR	Check the INR every 4 to 5 days until it stabilizes[1].
Primidone	↓ INR	INR 4 to 5 days after initiation, dose modification, or discontinuation
Fibrates		
Fenofibrate	↑ INR	INR 4 to 5 days after initiation, dose modification, or discontinuation
Gemfibrozil	↑ INR	
Antidepressants		
Fluoxetine	↑ INR ↑ bleeding risk	INR 4 to 5 days after initiation, dose modification, or discontinuation
Class of selective serotonin reuptake inhibitors (SSRIs)	↑ bleeding risk	Monitor closely for signs and symptoms of bleeding.

[1]The INR is usually within the target therapeutic range.

THE MOST FREQUENT INTERACTIONS WITH NATURAL PRODUCTS

It is best to avoid using any natural products.

WARFARIN	
NATURAL PRODUCTS THAT INCREASE THE INR OR THE BLEEDING RISK	**NATURAL PRODUCTS THAT DECREASE THE INR**
• Alfalfa • Cranberry juice • Danshen • Devil's claw • Dong quai • Fenugreek • Garlic capsules • Ginger • Ginkgo biloba • Matricaria • Papain • Vitamin E (doses > 400 units/day)	• Coenzyme Q10 • Ginseng • Green tea (only in large quantities) • St. John's wort