

Objective:

To guide clinicians in the selection of antithrombotic therapy for the prevention of ischemic stroke and arterial thromboembolism in patients with atrial fibrillation.

Background:

Atrial fibrillation (AF) is the most common pathologic arrhythmia and increases in prevalence with increasing age (prevalence of 10-15% in patients who are ≥ 80 years). The most devastating complication of AF is arterial embolism of a left atrial thrombus resulting in ischemic stroke, peripheral limb ischemia, or other end organ damage. AF is associated with a 3- to 6-fold increased risk of stroke or non-central nervous system (CNS) systemic embolism. Furthermore, ischemic strokes in patients with AF are larger and more frequently associated with death and disability than strokes that occur in the absence of AF. Therefore, stroke prevention is a critical part of AF treatment.

The risk of arterial thromboembolism can be significantly reduced with anticoagulant therapy (warfarin, apixaban, dabigatran, edoxaban or rivaroxaban) and, to a much lesser extent, with antiplatelet therapy. Selection of antithrombotic therapy should be guided by an assessment of presumed thrombotic risk, assessment of presumed bleeding risk on antithrombotic therapy and patient preference.

Thrombotic Risk: Prognostic models incorporating patient age and co-morbidities provide validated estimates of the annual risk for thromboembolism without anticoagulant therapy. These models were developed for patients with non-valvular AF, which refers to AF occurring in the absence of a mechanical heart valve or rheumatic heart disease with severe mitral stenosis or regurgitation. The most frequently used score is the CHADS₂ score (see **Table 1**). A modification of this score is the CHA₂DS₂-VASc score which incorporates age 65-75 years (1 point), age ≥ 75 (2 points), female sex (1 point), and presence of vascular disease (1 point). These risk calculators are available on the Thrombosis Canada website [http://thrombosiscanada.ca/?page_id=502]. In general, in patients with a CHADS₂ score or a CHA₂DS₂-VASc score ≥ 1 , the risk of arterial thromboembolism (and resulting morbidity/mortality) without anticoagulation outweighs the risk of bleeding from anticoagulants.

Table 1: CHADS₂ Score for Assessment of Risk of Stroke or Systemic Embolism in Patients with Non-Valvular AF

Risk Factor	Points
Recent Congestive Heart Failure	1
History of Hypertension	1
Age ≥ 75 years	1
Diabetes	1
Prior History of Stroke or TIA	2
TOTAL score	

The Canadian Cardiovascular Society and this guide use the “CHADS-65” scoring system as the basis for its recommendations (see **Recommendations** and **Figure 1**).

Bleeding Risk: Bleeding risk should also be assessed in all patients. However, in most cases, bleeding risk should not preclude the use of anticoagulant therapy. The risk-benefit ratio almost always favours anticoagulation unless the risks for bleeding are very high and the risk of thromboembolism is very low. Patients at increased risk for bleeding, typically, are also those who will benefit the most from anticoagulation to prevent stroke, and attempts should be made to modify bleeding risk factors (i.e. appropriate blood pressure control, reduce NSAID or alcohol use, discontinue concomitant antiplatelet therapy if not needed, assess fall risk). There are prognostic models for the estimation of bleeding risk in patients with AF on warfarin therapy (e.g. HAS-BLED, available on the Thrombosis Canada website [<https://thrombosiscanada.ca/tools/?calc=has-bled>]), which can help to identify potentially reversible risk factors for bleeding.

Agents and Dosing:

Anticoagulants: Warfarin (with target INR of 2-3) was the anticoagulant of choice for the prevention of stroke in patients with AF for many years. **The newer direct oral anticoagulants (DOACs), which consist of apixaban, dabigatran, edoxaban, and rivaroxaban are used increasingly for this indication, and are suggested in preference to warfarin in the Canadian Cardiovascular Society’s guidelines for the management of AF.** Large randomized trials indicate non-inferior or superior efficacy and safety compared with warfarin. Practical advantages of DOACs (also known as NOACs, non-vitamin K oral anticoagulants) over warfarin include fixed, once- or twice-daily oral dosing without the need for routine coagulation monitoring, few known or defined drug interactions, no known food interactions, and lower risks of intracranial bleeding. Potential disadvantages include lack of readily available reversal agents for rivaroxaban, apixaban, and edoxaban in case of major bleeding (although andexanet alfa has been licensed for this indication in the United States) and varying degrees of renal elimination requiring dose adjustment in patients with renal insufficiency (see **Table 2**). An antidote for dabigatran (idarubicumab) is approved by Health Canada and is

widely available. Patients taking DOACs require periodic monitoring of renal function. Like warfarin, DOACs increase the risk for bleeding.

There have been no head-to-head clinical trials comparing one DOAC with another and there is no evidence to suggest superior efficacy or safety of one agent over another. Practical issues regarding the everyday use of DOACs are addressed in the **Clinical Guide:** [DOACs: Comparison and Frequently Asked Questions](#).

Table 2: DOAC drug dosing for patients with AF according to renal function†

DOAC	CrCl (mL/min)	DRUG DOSE	COMMENT
Dabigatran	≥ 50	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding or in the elderly (e.g. age ≥ 80 years or >75 years with additional bleeding risk factors) Measure CrCl every 12 months
	30-49	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding (e.g. age ≥ 80 years or >75 years with additional bleeding risk factors) Measure CrCl every 6 months <u>and</u> with acute illness Consider avoiding if deteriorating renal function
	< 30	Avoid dabigatran	Consider warfarin as alternative anticoagulant
Rivaroxaban	≥ 50	20 mg daily	Measure CrCl every 12 months
	30-49	15 mg daily	Measure CrCl every 6 months <u>and</u> with acute illness Consider avoiding if deteriorating renal function
	15 - 30	15 mg daily approved	Use with caution due to limited clinical data; if used, measure CrCl every 3 months <u>and</u> with acute illness Consider warfarin as alternative anticoagulant
	<15	Avoid rivaroxaban	Consider warfarin as an alternative anticoagulant
Apixaban	≥ 50	5 mg twice daily	2.5 mg twice daily in patients with 2 or more of the following: Age ≥ 80 years; Body weight ≤ 60 kg; Creatinine ≥ 133 µmol/L
	30-49	5 mg twice daily	Measure CrCl every 12 months for CrCl > 50 or every 6 months for CrCl 30-50 <u>and</u> with acute illness
	15-30	No dose recommendations can be made	Very limited clinical data with apixaban
	< 15	Avoid apixaban	Consider warfarin as alternative anticoagulant
Edoxaban	≥50	60 mg daily	Reduce dose to 30 mg daily if weight <60 kg or if concomitant use of P-gp inhibitor (except amiodarone and verapamil). Measure CrCl every 12 months.
	15-50	30 mg daily	Measure CrCl every 6 months <u>and</u> with acute illness Consider avoiding if deteriorating renal function
	<15	Avoid edoxaban	Consider warfarin as an alternative anticoagulant

Antiplatelet agents:

In patients with AF at low risk of stroke, who decline oral anticoagulation, or in whom oral anticoagulation is considered contraindicated due to bleeding risk, low dose aspirin (80-100 mg/day) may be considered. However, aspirin provides less protection than an anticoagulant and increases bleeding risk.

Recommendations:

See **Figure 1** below (from the Canadian Cardiovascular Society Update of AF guidelines).

For patients age <65 with non-valvular AF at **low risk of stroke (CHADS₂ score = 0)** and no other risk factors, no antithrombotic therapy is needed. In patients age <65 who have coronary artery or other vascular disease, ASA 81 mg daily should be used.

For patients with non-valvular AF age ≥65 or <65 with any of the CHADS₂ risk factors, anticoagulation with a DOAC or warfarin (target INR 2.0-3.0) is indicated. The Canadian Cardiovascular Society states that a DOAC is the preferred choice. For patients who are unsuitable for or who decline anticoagulants, ASA 81 mg daily is suggested.



Special Considerations:

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Patients with AF and valvular heart disease (severe mitral stenosis, mechanical heart valves, rheumatic heart disease) are at significantly increased risk for ischemic stroke, and warfarin is recommended for this indication. Treatment with a DOAC is not recommended in patients with valvular AF and these drugs are not approved for this use.

In patients with coronary artery disease, antithrombotic management should be individualized and based on an assessment of risk of atrial fibrillation-related stroke, ischemic coronary event, and clinically relevant bleeding associated with the use of antithrombotic agents.

Other Relevant Thrombosis Canada Clinical Guides:

- [Apixaban \(Eliquis®\)](#)
- [Dabigatran \(Pradaxa®\)](#)
- [DOACs: Coagulation Test](#)
- [DOACs: Comparison and Frequently Asked Questions](#)
- [DOACs: Management of Bleeding](#)
- [DOACs: Peri-Operative Management](#)
- [Edoxaban \(Lixiana®\)](#)
- [Rivaroxaban \(Xarelto®\)](#)
- [Warfarin](#)
- [Warfarin: Management of Out-of-Range INR](#)

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