STROKE PREVENTION IN ATRIAL FIBRILLATION

Thrombosis Canada
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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.

The risk of arterial thromboembolism can be significantly reduced with anticoagulant therapy (warfarin, apixaban, dabigatran, edoxaban or rivaroxaban) and, to a lesser extent, with antiplatelet therapy. Selection of antithrombotic therapy should be guided by 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 patients' annual risk for thromboembolism without anticoagulant therapy. These models were developed for patients with non-valvular AF. The most frequently used score is the $CHADS_2$ score (see **Table 1**). A modification of this score is the CHA_2DS_2-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 $CHADS_2$ score or a CHA_2DS_2-VASc score ≥1, the risk of arterial thromboembolism (and resulting morbidity/mortality) without anticoagulation outweighs the risk of bleeding from anticoagulants.

TABLE 1: $CHADS_2$ SCORE FOR ASSESSMENT OF RISK OF STROKE OR SYSTEMIC EMBOLISM IN PATIENTS WITH NON-VALVULAR AF

Risk Factor	Points
Congestive Heart Failure	1
History of **H**ypertension	1
Age ≥ 75 years	1
Diabetes	1
Prior History of **S**troke or TIA	2
TOTAL score	

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., NSAID or alcohol use, frequent falls). There are prognostic models for the estimation of bleeding risk in patients with AF on warfarin therapy (e.g. HAS-BLED, available on Thrombosis Canada website, http://thrombosiscanada.ca/?page_id=502).

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 suggest improved efficacy and safety of these agents compared with warfarin. Practical advantages of DOACs* 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 in case of major bleeding (an antidote for dabigatran (idaruzicumab) is now approved by Health Canada but is not widely available, while antidotes for rivaroxaban, apixaban, and edoxaban are still in advanced development) and varying degrees of renal elimination requiring dose adjustment in patients with renal insufficiency (see **Table 2**). Patients taking these anticoagulants require periodic monitoring of renal function. Like warfarin, DOACs increase the risk for bleeding.

There have been no clinical trials directly comparing one DOAC to another and there is no evidence to suggest superior efficacy or safety of one agent over the other. Practical issues regarding the everyday use of DOACs are addressed in the Thrombosis Canada Guide NOACs/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 >age 75 years and at increased risk for bleeding or in the elderly (e.g. age ≥ 80 years) Measure CrCl every 12 months
	30-49	110 or 150 mg twice daily	Consider 110 mg dose in patients > age 75 years and at increased risk for bleeding or in the elderly (e.g. age ≥ 80 years) Measure CrCl every 6 months *and* with acute illness Consider avoiding if deteriorating renal function

*NOACs/DOACs = Non-vitamin K antagonist Oral AntiCoagulants, also known as Direct Oral AntiCoagulants

	< 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 *and* with acute illness Consider avoiding if deteriorating renal function
	< 30	Avoid rivaroxaban	Consider warfarin as alternative anticoagulant
Apixaban	≥ 50	5 mg twice daily	2.5 mg twice daily in patients with 2 of following: (1) creatinine ≥ 133 µmol/L; (2) age ≥ 80 years; (3) body weight ≤ 60 kg Measure CrCl every 12 months
	25-49	5 mg twice daily	2.5 mg twice daily in patients with 2 of following: (1) creatinine ≥ 133 µmol/L; (2) age ≥ 80 years; (3) body weight ≤ 60 kg Measure CrCl every 6 months *and* with acute illness
	15-24	No dose recommendations can be made	Very limited clinical data with apixaban Consider warfarin as alternative anticoagulant
	< 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.
	30-50	30 mg daily	Measure CrCl every 6 months *and* with acute illness Consider avoiding if deteriorating renal function
	<30	Avoid edoxaban	Consider warfarin as an alternative anticoagulant

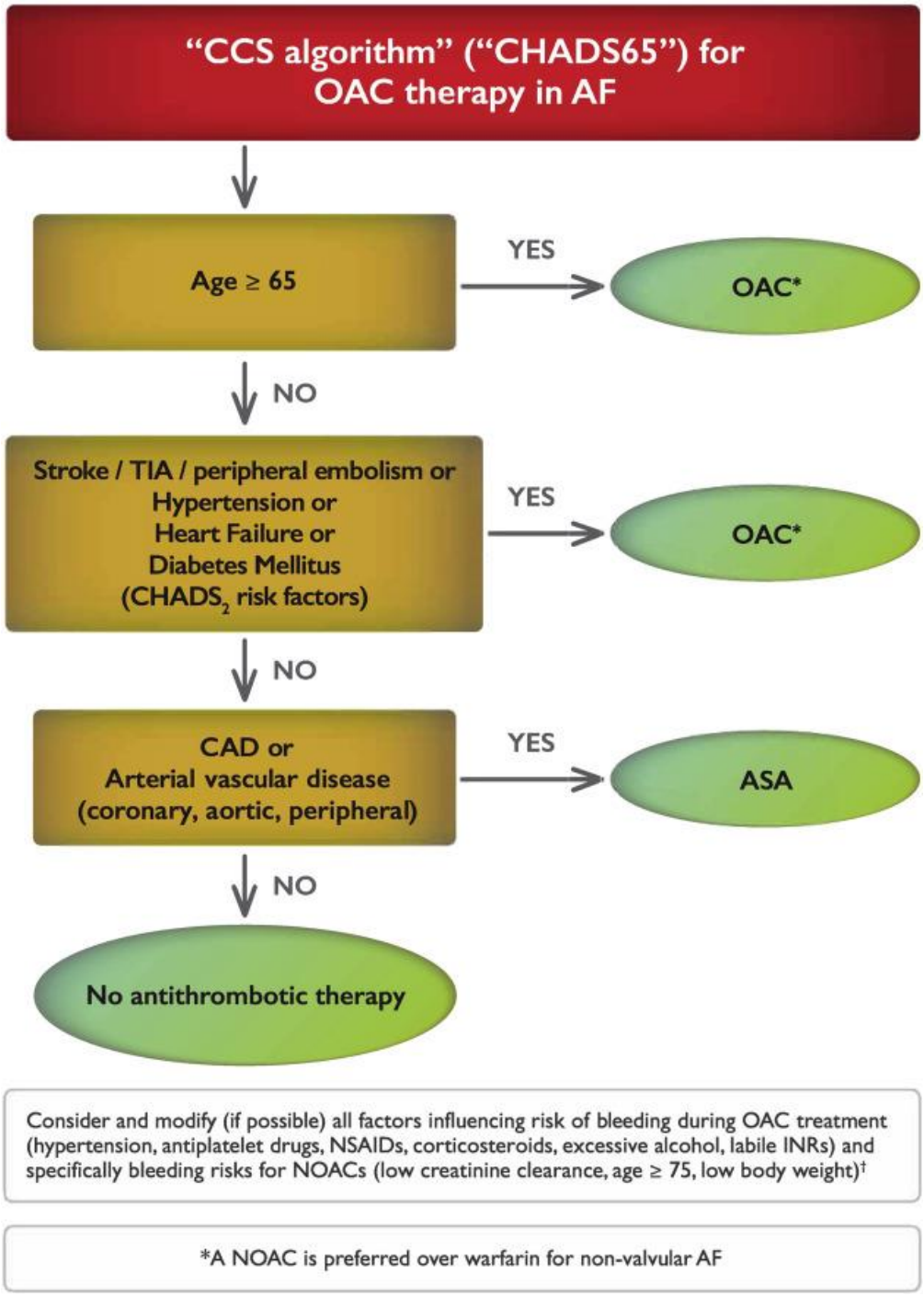
Antiplatelet agents: In patients with AF at low risk of stroke, who decline oral anticoagulation, or in whom oral anticoagulation is considered contraindicated due to bleeding risk, low dose aspirin (80-100 mg/day) may be considered. However, aspirin provides less protection than an anticoagulant and is also associated with an increased 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 ($CHADS_2$ score = 0)** and no other risk factors, no antithrombotic therapy is needed. In patients < age 65 who have coronary artery or vascular disease, ASA 81 mg daily should be used.

For patients with non-valvular AF with **intermediate/high risk of stroke ($CHADS_2$ score ≥1)**, 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.



The simplified "Canadian Cardiovascular Society Algorithm" ("CHADS-65") for deciding which patients with atrial fibrillation (AF) or atrial flutter should receive oral anticoagulation (OAC) therapy. It recommends OAC for most patients 65 years of age and for younger patients with a Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack (CHADS2) score 1; aspirin (acetylsalicylic acid; ASA) for patients < 65 years of age with a CHADS2 score ¼ 0 with arterial vascular disease (coronary, aortic, or peripheral); and no antithrombotic therapy for patients < 65 years of age with a CHADS2 score ¼ 0 and no arterial vascular disease. Bleeding risks should be modified whenever possible. A non-vitamin K antagonist oral anticoagulant (NOAC) is recommended in preference to warfarin for OAC therapy in NVAF patients. CAD, coronary artery disease; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack. **(CANADIAN JOURNAL OF CARDIOLOGY 2016 32, 1170-1185DOI: (10.1016/J.CJCA.2016.07.591))**

SPECIAL CONSIDERATIONS:

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

In patients with coronary artery disease, antithrombotic management should be individualized.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

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

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Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.