STROKE PREVENTION IN ATRIAL FIBRILLATION

Thrombosis Canada
Thrombose Canada

TARGET AUDIENCE: All Canadian health care professionals.

OBJECTIVE:

To guide clinicians in the selection of antithrombotic therapy for the secondary prevention of ischemic stroke and arterial thromboembolism in patients with atrial fibrillation. Selection of therapy should be guided by assessment of presumed thrombotic risk, bleeding risk on antithrombotic therapy and patient preference.

ABBREVIATIONS:

AF	atrial fibrillation
ASA	acetyl salicylic acid
CI	confidence interval
CNS	central nervous system
CrCl	creatinine clearance
HR	hazard ratio
INR	international normalized ratio
NOAC	new oral anticoagulant
RR	relative risk

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 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. Risk of thromboembolism is increased by a number of identifiable clinical variables including, but not limited to, advancing age, structural heart disease (particularly mitral valve disease), congestive heart failure, diabetes, hypertension and prior arterial thromboembolic events. Both persistent and paroxysmal atrial fibrillation increase risk for thromboembolism and stroke.

AF can be classified as valvular, pertaining mainly to patients with mitral stenosis or mechanical prosthetic heart valves, or non-valvular, which encompasses the remaining vast majority of patients with atrial fibrillation.

Both oral anticoagulation and antiplatelet medication reduce the risk of stroke in patients with AF but are associated with an increased risk of bleeding. The risk of arterial thromboembolism can be significantly reduced by anticoagulant therapy (warfarin, dabigatran, rivaroxaban and apixaban) and, to a lesser extent, by antiplatelet therapy (see ASA, clopidogrel, prasugrel, ticagrelor guides). 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 vascular disease (1 point). In general, risk of arterial thromboembolism (and resulting morbidity/mortality) without anticoagulation outweighs the risk of bleeding from anticoagulants in patients with a $CHADS_2$ score or CHA_2DS_2-VASc score ≥ 1. The decision to anticoagulate should be made after a full discussion between the patient and physician of the benefits and risks of therapy (see below) and patient preferences.

Table 1: $CHADS_2$ Score for Assessment of Risk in Patients with Non-valvular AF

Risk Factor	Points
Recent **C**ongestive Heart Failure	1
History of **H**ypertension	1
Age ≥ 75 years	1
Diabetes	1
Prior History of **S**troke or TIA	2

AGENTS AND DOSING:

Please see specific sections on individual antithrombotic therapies elsewhere in these guides for a full description of dosing, monitoring, side-effects, etc.

Approved therapeutic agents:

Acetyl Salicylic Acid (ASA): Pooled data from 8 randomized, controlled trials suggest that ASA (50-325 mg/day) compared with no therapy results in 2, 5, 9 and 20 fewer non-fatal strokes (ischemic or hemorrhagic) per year per 1,000 patients treated for $CHADS_2$ scores of 0, 1, 2 and ≥ 3, respectively. ASA would be expected to result in approximately 3 more non-fatal extracranial bleeds per 1,000 patients treated per year. Bleeding rates may be higher in patients with greater co-morbidity/higher $CHADS_2$ score. There is no difference in mortality for the overall treated population with ASA therapy (6 fewer deaths; 95% CI 13 fewer to 3 more).

Warfarin: Pooled data from 11 randomized, controlled trials suggest that warfarin (target INR 2.0-3.0) compared with ASA therapy results in 3, 9, 19 and 40 fewer non-fatal strokes (ischemic or hemorrhagic) per 1,000 treated for $CHADS_2$ score of 0, 1, 2 and ≥ 3, respectively. Warfarin would be expected to result in approximately 3 more non-fatal extracranial bleeds per 1,000 treated per year. Bleeding rates are likely higher in patients with greater co-morbidity/higher $CHADS_2$ score.

No significant difference in mortality is anticipated in the overall treated population. Effects on mortality may be more pronounced in patients at higher risk of stroke.

Dabigatran: The RELY study compared dabigatran, an oral direct thrombin inhibitor, 150 mg twice daily and 110 mg twice daily, to warfarin (target INR 2.0-3.0) in 18,113 patients with non-valvular AF and one additional risk factor for stroke. Dabigatran 150 mg twice daily was associated with a statistically-significant 34% decrease in the risk of non-fatal stroke or systemic embolism (HR 0.66, 95% CI 0.53-0.82), no difference in the risk of major bleeding, and a trend towards decreased mortality (RR 0.89, 95% CI 0.79-1.01) compared with warfarin therapy. Dabigatran 110 mg twice daily was associated with a similar stroke rate compared with warfarin but with a 20% lower risk of major bleeding complications (HR 0.80, 95% CI 0.69-0.93). Treatment with dabigatran at both the 150 mg and 110 mg doses was associated with a reduction in intracranial bleeding compared with warfarin.

Dabigatran is indicated for the prevention of stroke and systemic embolism in patients with AF, in whom anticoagulation is appropriate. Among patients at increased risk for bleeding or age $\geq$ 80 years, a dose reduction of dabigatran to 110 mg twice daily should be considered (see **Table 2**).

Apixaban: The ARISTOTLE trial compared apixaban, an oral factor Xa inhibitor, at 5 mg twice daily (or 2.5 mg twice daily in selected patients; see **Table 2**), with warfarin (target INR 2.0-3.0) in 18,201 patients with non-valvular AF at increased risk for stroke. Apixaban was associated with a 21% decrease in stroke (HR 0.79; 95% CI 0.66-0.95), a 31% decrease in major bleeding (HR 0.69, 95% CI 0.60-0.80), and an 11% decrease in all-cause mortality (HR 0.89, 95% CI 0.80-0.99). Treatment with apixaban was associated with a reduction in intracranial bleeding compared with warfarin.

The AVERROES trial compared apixaban, at 5 mg twice daily (or 2.5 mg in selected patients: see **Table 2**), with ASA, 81 mg daily, in patients with non-valvular AF at increased risk for stroke in whom warfarin therapy was deemed unsuitable. Compared with ASA, apixaban was associated with a 55% decrease in stroke (HR 0.45, 95% CI 0.32-0.62), and without a significant increase in major bleeding (HR 1.13, 95% CI 0.74-1.75).

Apixaban is indicated for the prevention of stroke and systemic embolism in patients with AF, in whom anticoagulation is appropriate.

Rivaroxaban: The ROCKET-AF study compared rivaroxaban, an oral factor Xa inhibitor, 20 mg daily (or 15 mg daily in selected patients; see **Table 2**), to warfarin (target INR 2.0-3.0) in 14,264 patients with non-valvular AF and increased risk of stroke. Rivaroxaban was non-inferior to warfarin for the primary endpoint of stroke or systemic embolism (RR 0.88, 95% CI 0.74-1.03). There was no significant difference in major bleeding or mortality. Treatment with rivaroxaban was associated with a reduction in intracranial bleeding compared with warfarin.

Rivaroxaban is indicated for the prevention of stroke and systemic embolism in patients with AF, in whom anticoagulation is appropriate.

Table 2: New Oral Anticoagulant (NOAC) Drug Dosing for Patients with AF According to Renal Function†

NOAC	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) Measure CrCl every 12 months
	30-50	110 or 150 mg twice daily	Consider 110 mg dose in patients at increased risk for bleeding (e.g. age ≥ 80 years) Measure CrCl every 6 months *and* 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 *and* with acute illness Consider avoiding if deteriorating renal function
	<30	avoid rivaroxaban	Consider warfarin as alternative anticoagulant
Apixaban	>50	5 mg twice daily	Measure CrCl every 12 months
	25-50	5 mg twice daily	2.5 mg twice daily in patients with creatinine ≥ 133 µmol/L who are also ≥ 80 years or ≤ 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

†It is advised to consult with a specialist if there is uncertainty about the appropriate NOAC drug and dose regimen and if warfarin provides a better oral anticoagulation option for individual patients.

Aspirin plus Clopidogrel: The ACTIVE-W trial evaluated dual antiplatelet therapy with ASA (75-100 mg/day) plus clopidogrel (75 mg/day) versus warfarin in patients with non-valvular AF. This trial was stopped early as warfarin was found to be superior to dual antiplatelet therapy with respect to the primary outcome (stroke, systemic embolism, MI, or vascular death) without a significant difference in the risk of major bleeding.

The ACTIVE-A study evaluated dual antiplatelet therapy with ASA plus clopidogrel versus ASA alone in patients with non-valvular AF considered unsuitable for warfarin (physician decision, risk of bleeding, patient preference). Dual antiplatelet therapy was associated with a decreased risk of ischemic stroke (1.9% vs 2.8%, $p < 0.001$), a non-significant increase in hemorrhagic stroke (0.17% to 0.23%), and an increase in major bleeding (2.0% vs 1.3%, $p < 0.001$).

RECOMMENDATIONS:

See **Figure 1** below.

For patients 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 with prior vascular disease or of female sex, ASA 81 mg daily should be used. Patients ≥ 65 years of age, or female plus prior vascular disease require anticoagulation with a warfarin or a NOAC such as dabigatran, rivaroxaban or apixaban. The NOACs are preferred over warfarin for patients with AF.

For patients with non-valvular AF with intermediate risk of stroke ($CHADS_2$ score =1) we suggest anticoagulation with warfarin (target INR 2.0-3.0) or a NOAC. A NOAC is the preferred choice. For patients who are unsuitable for or who decline anticoagulants, we suggest ASA 81 mg daily.

For patients with non-valvular AF at high risk of stroke ($CHADS_2$ score ≥ 2) we recommend anticoagulation with warfarin (target INR 2.0-3.0) or a NOAC. Treatment with a NOAC is preferred over warfarin. For patients who are unsuitable for or who decline anticoagulants, we suggest ASA (81 mg/day) plus clopidogrel (75 mg/day).

Bleeding risk should be assessed in all patients, but in most cases it should not preclude the use of anticoagulant therapy unless the risk is considered very high. Patients at increased risk for bleeding, typically, are those who also will benefit the most from anticoagulation to prevent stroke. When the risk is high, other measures should be taken to avoid bleeding such as blood pressure control, gait stabilization, alcohol and non-steroidal anti-inflammatory drug avoidance and proton pump inhibitor use.

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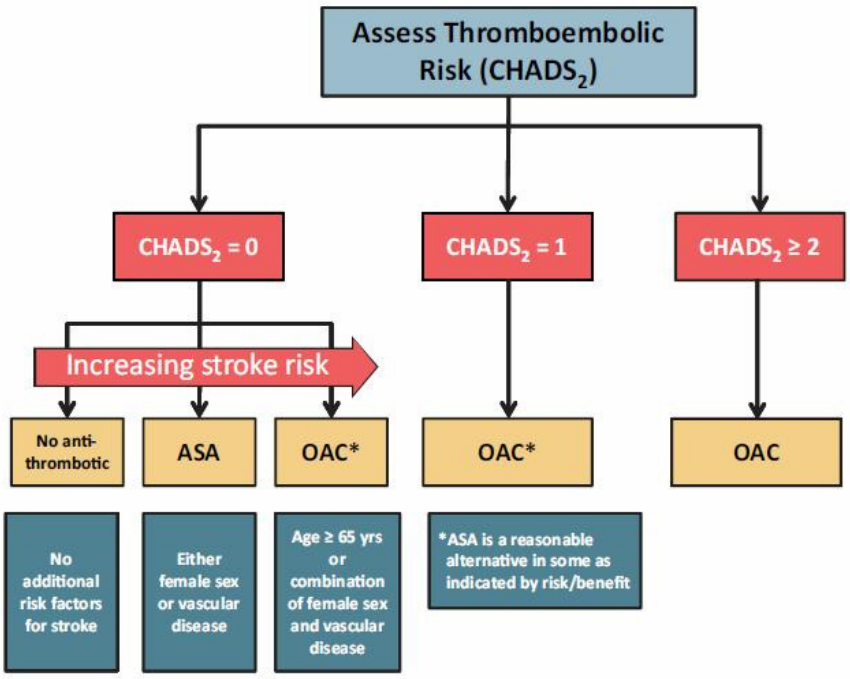

Figure 1. Summary of recommendations for antithrombotic agent use based on Congestive Heart Failure, Hypertension, Age > 75, Diabetes Mellitus, and Prior Stroke or Transient Ischemic Attack ($CHADS_2$) score. Additional risk factors of age > 65, vascular disease, and female sex are integrated to increase granularity at low $CHADS_2$ score ($CHADS_2 = 0$). ASA, acetylsalicylic acid (aspirin); OAC, oral anticoagulant.

Dabigatran, Apixaban and Rivaroxaban are preferred over Warfarin

SPECIAL CONSIDERATIONS:

Patients with AF and valvular heart disease (mitral stenosis, mechanical prosthetic heart valves) are at significantly increased risk for ischemic stroke, and warfarin is recommended. Treatment with a NOAC (dabigatran, rivaroxaban, apixaban) is not recommended in patients with AF and valvular heart disease or mechanical heart valves, and these drugs are not approved for their use.

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

PEDIATRICS:

Children with AF should be referred to a pediatric cardiologist for management. There are no studies establishing safety and efficacy of antithrombotic therapy in children with AF.

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