REVIEW ARTICLE

Prevention of stroke and systemic embolization in atrial fibrillation: a Canadian perspective

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KEY WORDS

atrial fibrillation, clinical practice guidelines, oral anticoagulants, stroke prevention, vitamin K antagonists

ABSTRACT

Atrial fibrillation (AF) has a prevalence of about 1% in the general population, but is much more common in the elderly. The annual overall risk of stroke is about 4.5% without antithrombotic therapy, but the risk in an individual patient varies from under 1% to about 20%, depending on the presence of well-recognized risk factors. The risk of stroke, usually followed by major neurological deficit or death, is reduced by about two-thirds by oral vitamin K antagonist (VKA) therapy and about 20% by aspirin. This risk reduction generally outweighs the risk of major hemorrhage caused by oral anticoagulation. New oral anticoagulants (dabigatran, rivaroxaban, and apixaban) obviate many of the difficulties experienced by patients and doctors in the use of oral VKAs. Comparisons with warfarin in recent large randomized clinical trials have demonstrated advantages of efficacy and safety, which vary somewhat from one agent to another but all offer excellent alternatives to VKAs for stroke prevention. Recent clinical practice guidelines recommend these agents as alternatives to VKAs.

Background Atrial fibrillation (AF) is characterized electrocardiographically by a completely irregular atrial rhythm, no discernable P-waves, and a ventricular rate which is dependent on the conduction properties of the atrioventricular node. The prevalence of AF is from 1% to 2% in the general population, is uncommon in the young, and rises to above 10% among patients aged 80 years and older.[1] Patients may experience abnormal awareness of cardiac contractions and symptoms of reduced cardiac output (particularly on exertion). Persons with AF have a 4- to 5-fold increased risk of stroke,[1] a 3-fold increased risk of heart failure,[2] and a 2-fold increased risk of death.[2] Appropriate management of a person with AF is focused on the identification of the presence of AF on at least 1 electrocardiogram and determination of the pattern of AF (first onset, paroxysmal [self-terminating or cardioversion within 7 days], persisting [>7 days], long-standing persistent [>1 year], or permanent [accepted by a patient and physician]). The physician should assess the severity of symptoms and degree of functional impairment, the risk of thromboembolism, and the presence of common comorbidities. The focus in therapy is on alleviating symptoms with appropriate control of ventricular rate, in selected patients control of the atrial arrhythmia, and in most patients therapy to prevent thromboembolism. Major advances in the understanding about the risk of thromboembolism and new oral anticoagulants (OACs) for its prevention have prompted the present review.

Risk of stroke Stroke and non-central nervous system (CNS) embolism have long been known to be important complications of AF. In several case series, from 50% to 70% of embolic strokes were found to result in either death or severe neurological deficit.[3] The Framingham study documented a 4.5% annual incidence of stroke among patients with AF.[4] Among the placebo groups in 5 landmark randomized clinical trials (RCTs) in patients with nonvalvular AF, there was a mean 4.5% annual incidence of stroke (range, 3%–7%) and a mean 5% annual incidence of stroke plus other systemic emboli (range, 3%–7.4%).[5] Over half of the strokes resulted in death or permanent disability. In the United States, the proportion of strokes attributable to AF is 1.5% in the age group 50 to 59 years, rises to 23.5% in the age group 80 to 89 years, and is 15% overall.[1]

The $CHADS_2$ index[6] was developed from the findings of an overview of the RCTs of

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TABLE 1 Risk factors and assigned score values for the $CHADS_2$[6] and CHA_2DS_2-VASc[8] schemes

Prevention of stroke in atrial fibrillation / atrial flutter			
$CHADS_2$	score	CHA_2DS_2-VASc	score
congestive heart failure	1	congestive heart failure	1
hypertension	1	hypertension	1
age ≥75 years	1	age ≥75 years	2
diabetes mellitus	1	diabetes mellitus	1
stroke/TIA/thromboembolism	2	stroke/TIA/thromboembolism	2
maximum score	6	vascular disease	1
		age 56–74 years	1
		female	1
		maximum score	9

Abbreviations: TIA – transient ischemic attack

warfarin therapy in AF. It assigns 1 point each for congestive heart failure, hypertension, age >75 and diabetes and 2 points for history of stroke or transient ischemic attack (TIA). It has been well validated, with the annual stroke rate increasing by about 2% for each 1-point increase in the $CHADS_2$ score (from 1.9% with a score of 0 to 18.2% with a score of 6)[6,7] (**TABLE 1**).

The 2010 European Society of Cardiology (ESC) AF guidelines[2] incorporated the Birmingham 2009 system (CHA_2DS_2-VASc) for the prediction of stroke risk.[8] The CHA_2DS_2-VASc is similar to the $CHADS_2$, but gives 2 points for age ≥75 years and 1 point each for age 65–74 years, vascular disease (prior myocardial infarction [MI], peripheral artery disease, or aortic plaque), and female sex (**TABLE 1**). Olesen et al.[9] published a detailed comparison of $CHADS_2$ and CHA_2DS_2-VASc schema performance among all nonvalvular AF patients hospitalized in Denmark between 1997 and 2000. The $CHADS_2$ and CHA_2DS_2-VASc scores were evaluated in relation to the rates of hospitalization or death due to thromboembolism at 1, 5, and 10 years. All 3 new risk-score components (age 65–74 years, vascular disease, and female sex) contributed significantly to risk prediction in a univariate analysis, but female sex did not make a significant contribution in a multivariate model. The value of assigning a point for female sex continues to be debated.[10] The *c*-statistics were similar for both schemas when individual scores were used, but the CHA_2DS_2-VASc performed better when patients were categorized as low (score, 0), moderate (score, 1) or high (score, ≥2) risk, principally because of more precise estimates of thromboembolic risk in patients with the $CHADS_2$ scores of 0 or 1.

About 20% of AF patients have a $CHADS_2$ score of 0,[9,11] conferring an annual stroke risk of 1.9%. However, there is a large range of stroke risk among patients with a $CHADS_2$ score of 0, and appropriate therapy may range from OACs to aspirin to no antithrombotic. Only about 8.5% of AF patients have a CHA_2DS_2-VASc score of 0, with an annual stroke risk of 0.5%.[9,11] The main advantage of the CHA_2DS_2-VASc schema is to allow the identification of these patients, most of whom do not require antithrombotic therapy. Patients with a $CHADS_2$ of 1 or higher have a stroke risk well over 2%/year and require OACs. Most patients with a CHA_2DS_2-VASc score of 1 have sufficient risk to justify the use of OACs. However, if the CHA_2DS_2-VASc score of 1 is based only on vascular disease or female sex, the stroke risk is under 1.5%/year and aspirin should be considered. Patients with a CHA_2DS_2-VASc of 2 and higher clearly have sufficient stroke risk to justify use of an OAC

Paroxysmal atrial fibrillation The SPAF trial[12] found similar annual rates of ischemic stroke in patients with "recurrent" (3.2%) and "chronic" (3.3%) AF, as did a report from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W).[13] However, it is possible that the risk of stroke is lower in patients whose episodes of AF are brief (<1 day) and self-terminating. Recent studies using rhythm detection hardware have documented the stroke risk associated with intermittent and brief episodes of AF. The TRENDS study[14] enrolled patients with rhythm-monitoring pacemakers or implantable cardioverter-defibrillators and ≥1 stroke-risk factor (mean $CHADS_2$, 2.2). AF burden was defined as the longest total daily duration of atrial tachycardia (AT, probable AF) documented during 30 days of monitoring. During a mean follow-up of 1.4 years, the risk ratio (RR) for stroke/TIA/systemic thromboembolism (STE) was 0.98 (stroke/TIA incidence, 1.1%/year) with an AF burden of <5.5 hours of AT vs. those with no AT. However, when the AF burden was 5.5 hours or longer, the RR for stroke was 2.2 (stroke/TIA/STE incidence, 2.4%/year). The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)[15] enrolled patients aged 65 years and older with hypertension for a mean follow-up of 2.8 years after implantation of first pacemaker or ICD. Device-detected AT (>190 bpm lasting >6 minutes) occurred in 36% and was associated with an increased risk of stroke/STE

TABLE 2 The HAS-BLED scoring system for risk of bleeding on oral anticoagulation therapy[20]

Bleeding risk – HAS-BLED Score		
letter	clinical characteristic	points
H	hypertension	1
A	abnormal liver or renal function 1 point each	1 or 2
S	stroke	1
B	bleeding	1
L	labile INRs	1
E	elderly (age >65 years)	1
D	drugs or alcohol 1 point each	1 or 2
		maximum score – 9

Abbreviations: INR – international normalized ratio

(RR, 2.5 vs. patients without AT; incidence, 2.1%/year). Episodes as short as 6 minutes were markers for stroke/STE. The short-term risk of stroke appears to be higher in patients with recent-onset AF than in those with AF lasting more than 1–2 years.[16,17]

Atrial flutter A retrospective analysis of a large database of elderly hospitalized patients found little difference in the risk ratios for stroke with atrial flutter (AFl; 1.4) and AF (1.6).[18] By 8 years of follow-up, more than half of the patients with AFl had developed AF, and these patients were more likely to experience a stroke. Although there are no rigorous prospective data on the incidence of stroke among patients with AFl, nor are there RCTs of the value of anticoagulation, it is generally recommended that patients with AFl be risk-stratified and treated in the same manner as patients with AF.[2,19]

Risk of hemorrhage The efficacy of antithrombotic therapy to prevent ischemic stroke must be balanced against the risk of major hemorrhage, particularly cerebral, which is often fatal. The bleeding risk increases as antithrombotic intensity increases from 1) aspirin or clopidogrel (75 mg/day) alone, to 2) combination aspirin plus clopidogrel, to 3) dabigatran 110 mg twice daily, to 4) apixaban, to 5) dabigatran 150 mg twice daily, rivaroxaban, and vitamin K antagonists (VKAs). For VKAs, the bleeding risk depends upon the international normalized ratio (INR), the quality of monitoring, the duration of therapy (higher risk during initial few weeks of therapy), and the stability of dietary and other factors that may alter VKA potency. Bleeding risk is likely higher in common clinical practice than in the rigorous setting of a clinical trial or a dedicated, expert anticoagulation service.

Bleeding risk in a patient receiving anticoagulant therapy may be predicted using the HAS-BLED schema.[20] A score is assigned based on the presence of Hypertension, Abnormal liver or renal function, history of Stroke or Bleeding, Labile INRs, Elderly age (>65 years) and concomitant use of Drugs that promote bleeding or excess alcohol. The score allows clinicians to calculate an individual patient risk of major bleeding ranging from about 1% (score, 0–1) to 12.5% (score, 5) (TABLE 2). The HAS-BLED schema is simpler to remember and easier to use than other more complicated (e.g., HEMORR$_2$HAGES)[21] or less-validated (e.g., ATRIA [Anticoagulation and Risk Factors in Atrial Fibrillation])[22] schemas and seems to predict bleeding somewhat better.[23]

The application of a bleeding-risk schema ensures that important risk factors are systematically considered. The relative risks of stroke vs. major bleeding with various antithrombotic therapies may be estimated. Many of the factors that determine stroke risk are also predictors of bleeding, but stroke risks usually exceed those of major bleeding. Furthermore, 70% of strokes with AF are either fatal or leave severe residual deficits, whereas major bleeding is less often fatal and is less likely to leave significant residual effects in survivors. Patients at increased risk of major bleeding warrant extra caution and closer monitoring of antithrombotic therapy. Only when the stroke risk is low and the bleeding risk particularly high (e.g., a young patient with AF and few or no stroke risk factors, but a high risk of major hemorrhage, e.g., malignancy, prior major hemorrhage or participation in contact sports) does the risk–benefit ratio favor no antithrombotic therapy. Patient preferences are of great importance in deciding on antithrombotic therapy in relation to benefits and risks.

Trials of vitamin K antagonists and aspirin Prior to 1990, anticoagulation was usually prescribed for AF patients who had mitral stenosis, a prosthetic heart valve, prior arterial embolism, or who were to undergo electrical cardioversion. Anticoagulation was generally not prescribed long-term for patients with nonrheumatic AF. In the late 1980s, the observations of the Framingham Study, together with evidence for the efficacy and increased safety of regimens of lower-dose warfarin prompted the initiation of 5 RCTs of warfarin vs. control or placebo for the primary prevention of thromboembolism among patients with nonrheumatic (nonvalvular) AF.

An overview[5] of the initial 5 RCTs of oral VKAs compared with no treatment found that the incidence of ischemic stroke was reduced from 4.5%/year to 1.4%/year (relative risk reduction [RRR], 68%, 95% confidence interval [CI], 50%–79%, P <0.001). The rate of major hemorrhage with VKA was 1.3%/year vs. 1%/year in controls. The most recent meta-analysis of such trials[24] included 1 additional trial (of secondary prevention of stroke) and calculated an RRR of 64% (95% CI, 49%–74%) for the more clinically meaningful outcome of all stroke (ischemic or hemorrhagic). The absolute risk reduction (ARR) was 2.7%/year in primary prevention trials and 8.4%/year in the only secondary prevention trial. There was an excess of

0.3%/year (*P* = nonsignificant) of major extracranial hemorrhage with VKA but a statistically significant ARR of mortality of about 1.6%/year.

The Hart meta-analysis[24] also summarized trials of aspirin vs. no treatment; the RRR for all stroke was 19% (95% CI, –1% to 35%), with an ARR of 0.8%/year in primary prevention trials and 2.5%/year in secondary prevention trials. There were no significant differences in major extracranial hemorrhage or mortality. An update of this overview[25] assessed trials of VKA vs. aspirin; the RRR for all stroke was 39% (95% CI, 19%–53%) in favor of VKA, equivalent to an ARR of about 0.9%/year for primary prevention and 7%/year for secondary prevention. There were no significant differences in major extracranial hemorrhage or mortality.

Warfarin adjusted to an INR of 2 to 3 has been compared with various regimens of lower-dose warfarin plus aspirin,[24,25] and to warfarin at lower intensity and low fixed dose,[24,25] but none of these regimens was as effective. It had been expected that in patients suitable for warfarin therapy, the combination of aspirin plus clopidogrel might be noninferior to warfarin for the prevention of stroke, while offering the advantages of less bleeding and greater convenience. However, in the ACTIVE-W trial[26] for the composite outcome of stroke, non-CNS embolus, MI, and vascular death, the RR was 1.44 (95% CI, 1.18–1.76, *P* = 0.0003) for clopidogrel/aspirin (75 mg and 75–100 mg/day) vs. warfarin (INR, 2–3). Somewhat surprisingly, for major bleeding the RR was 1.10 (95% CI, 0.83–1.45) with the combination.

It had also been expected that in patients not suitable for warfarin therapy, aspirin/clopidogrel might be more effective than aspirin alone. This was confirmed by the ACTIVE-A trial[27]: after a mean of 3.6 years, the risk of major vascular events was reduced by the combination (RR, 0.89; 95% CI, 0.81–0.98; *P* =0.01). However, major bleeding was increased by the combination (2.0% vs. 1.3%/year; RR, 1.57, 95% CI, 1.29–1.92; *P* <0.01).

Trials of newer oral anticoagulants VKAs are difficult for both patients and physicians to use effectively and safely. Many factors affect the pharmacokinetics and pharmacodynamics of VKAs; accordingly, the degree of INR prolongation by a given dose of VKA is unpredictable and measurement is required at least monthly. Even with careful monitoring, it is difficult to achieve therapeutic range INRs above 65% of the time, and AF patients typically experience major bleeding at a rate of about 3.0%/year.[28]

Several new OACs have been developed to obviate some of the problems associated with VKAs.[28] Dabigatran, rivaroxaban, and apixaban have undergone extensive clinical evaluation and been found to be safe and efficacious.[29-31] They exert their anticoagulant effects by combining reversibly with either thrombin (dabigatran) or factor Xa (rivaroxaban and apixaban). Maximal blood levels and anticoagulant effects are observed quickly following oral intake. After drug discontinuation, anticoagulant effects diminish quickly because of short serum and receptor-inhibition half-lives. Their absorption is largely unaffected by food or other medications, and their elimination-kinetics are affected by few agents. Dose recommendations vary little among patients and anticoagulation monitoring is not required. Dose reductions are advised for patients with reduced renal function, advanced age, or small BMI. In contrast to VKAs, clinically useful measurement of anticoagulant effect is challenging and no specific antidotes are yet available.

Dabigatran is approved in Canada, the United States, and Europe for the prevention of stroke and STE in AF and AFl. In the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY),[29] 18,113 AF patients (mean $CHADS_2$, 2.1) were randomized to dabigatran (110 mg vs. 150 mg twice-daily, double blind) or open-label warfarin and followed for a median of 2.0 years. The principal-outcome rates (stroke or STE) were 1.69%/year with warfarin, 1.53%/year with dabigatran 110 mg (RR, 0.91; 95% CI, 0.74–1.11), and 1.11%/year with dabigatran 150 mg (RR, 0.66; 95% CI, 0.53–0.82; *P* <0.001 vs. warfarin). Major-bleeding rates were 3.36%/year with warfarin, 2.71% with dabigatran 110 mg (RR vs. warfarin 0.8, *P* = 0.003), and 3.11% with dabigatran 150 mg (RR vs. warfarin, 0.93; *P* = 0.31). Net clinical-benefit rates (composite of stroke, STE, pulmonary embolism, MI, death, or major bleeding) were 7.64%/year with warfarin, 7.09%/year with dabigatran 110 mg (RR vs. warfarin, 0.92; CI, 0.84–1.02), and 6.91%/year with dabigatran 150 mg (RR vs. warfarin, 0.91; CI, 0.82–1.00). Patients taking dabigatran had more gastrointestinal bleeding, twice the likelihood of dyspepsia, and discontinued therapy almost 50% more often in the first year of therapy.

Rivaroxaban is approved in Canada, the United States, and Europe for the prevention of stroke and STE in AF/AFl. The double-blind ROCKET-AF trial (Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation)[30] randomized 14,264 AF patients (mean $CHADS_2$, 3.5) to rivaroxaban 20 mg once daily (15 mg once daily when creatinine clearance [CrCl] was 30–49 ml/min) or warfarin (median follow-up, 1.9 years). Principal efficacy-outcome rates (composite of stroke or STE) were 2.2%/year with warfarin and 1.7%/year with rivaroxaban (RR vs. warfarin, 0.79; CI, 0.66–0.96). In a secondary, intention-to-treat analysis, the respective rates were 2.4% vs. 2.1% (RR 0.88; CI, 0.75–1.03; *P* = 0.12 for superiority). Major bleeding rates were 3.4%/year with warfarin vs. 3.6% with rivaroxaban (RR, 1.04). There was significantly less intracranial, but more gastrointestinal bleeding with rivaroxaban. No net clinical-benefit data were reported. MI rates were 1.12%/year with warfarin vs. 0.91%/year with rivaroxaban (RR, 0.81; *P* = 0.121). Adverse events occurred in

81.4% of rivaroxaban subjects vs. 83.1% of those on warfarin, with only epistaxis and hematuria significantly more common with rivaroxaban.

Apixaban is not yet approved in Canada, the United States, or Europe for stroke prevention in AF. In the ARISTOTLE trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation),[31] 18,113 AF patients (mean $CHADS_2$, 2.1) were randomized (double-blind) to apixaban 5 mg twice daily (2.5 mg twice daily for 2 or more of: 1. age ≥80, 2. weight ≤60 kg, 3. serum creatinine ≥133 μmol/l) or to warfarin and followed for a median of 1.8 years. Principal-outcome rates (stroke or STE) were 1.60%/year with warfarin vs. 1.27%/year with apixaban (RR vs. warfarin, 0.79; CI, 0.66–0.95; P <0.01 for superiority). Major-bleeding rates were 3.09%/year with warfarin vs. 2.13% with apixaban (RR, 0.69; P <0.001), with substantial and statistically significant reductions in intracranial and gastrointestinal bleeding. Net clinical-benefit outcome rates (composite of stroke, STE, major bleeding and all-cause mortality) were 4.11%/year with warfarin vs. 3.17%/year with apixaban (RR, 0.85; CI, 0.78–0.92; P <0.001). MI rates were 0.61%/year with warfarin vs. 0.53%/year with apixaban (RR, 0.88; P = 0.37). Overall adverse-event rates occurring were 81.5% (apixaban) vs. 83.1% (warfarin), with no adverse event categories more frequent on apixaban.

In the Apixaban versus Acetylsalicylic Acid to Prevent Strokes trial (AVERROES),[32] 5599 AF patients (mean $CHADS_2$, 2.0) unsuitable for warfarin therapy were randomized double-blind to apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) vs. aspirin and followed for a median of 1.1 year. The trial was stopped early because of marked outcome differences. Principal-outcome rates (stroke or STE) were 3.7%/year with aspirin vs. 1.6%/year with apixaban (RR vs. aspirin, 0.45; CI, 0.32–0.62; P <0.001). The rates of major bleeding were 1.2%/year with aspirin vs. 1.4% with apixaban (RR, 1.13; P <0.57), with no significant differences in intracranial or gastrointestinal bleeding.

Compared with warfarin, both dabigatran and apixaban are more efficacious for the prevention of stroke and STE, while rivaroxaban is noninferior to warfarin. Apixaban causes less major bleeding than warfarin, while in comparison with warfarin there is no more major bleeding with either dabigatran 150 mg or rivaroxaban. There is significantly less intracranial bleeding with each of the new agents than with warfarin.

Current recommendations for antithrombotic therapy Both the ESC[2] and the Canadian Cardiovascular Society (CCS)[19] recommend that patients with AF or AFl, whether paroxysmal, persistent, or permanent, be stratified for risk of stroke using the $CHADS_2$ score and for risk of bleeding on anticoagulation using the HAS-BLED score and that most should receive antithrombotic therapy. Both the ESC and the CCS recommend OACs for patients with a $CHADS_2$ equal to 2 or higher. The ESC recommends that patients with a $CHADS_2$ of 1 or less be further stratified using the CHA_2DS_2-VASc. If a CHA_2DS_2-VASc is 1 or less, then the recommendation is for either OAC or aspirin, with OAC preferred. If a CHA_2DS_2-VASc is equal to 0, the recommendation is either no antithrombotic therapy or aspirin, with no antithrombotic therapy preferred. The CCS recommends OACs for most patients with a $CHADS_2$ score of 1, with aspirin as a reasonable alternative in some patients as indicated by risk–benefit. If a $CHADS_2$ is 0, it is recommended that the additional CHA_2DS_2-VASc risk factors of age 65–74 years, vascular disease, and female sex be considered and that appropriate therapy could range from OAC to aspirin to no antithrombotic agent (**FIGURE**).

The 2012 guidelines of the CCS[19] recommend that when OAC therapy is indicated, most patients should receive dabigatran or rivaroxaban (or apixaban when it becomes available) in preference to a VKA. The recommendation is based on comparisons with warfarin showing that dabigatran (150 mg) and apixaban have greater efficacy and rivaroxaban has similar efficacy for stroke prevention; dabigatran and rivaroxaban have no more major bleeding and apixaban has less; all 3 new OACs have less intracranial bleeding; and all 3 are much simpler to use. The recently updated 2012 guidelines of the ESC[33] make an essentially identical recommendation.[33] A 2011 focused update of the American Heart Association Guidelines[34] gave a class I recommendation to the use of dabigatran as an alternative to warfarin in patients who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (CrCl, <15 ml/min) or advanced liver disease (impaired baseline clotting function). Although there are differences in the mechanisms of action of the new OACs, in their pharmacokinetics and pharmacodynamics and in the specific findings in the clinical trials of these agents, indirect comparisons do not show major differences[35] and practice guidelines do not recommend the choice of any specific agent over another.[19,33]

Elderly patients Advanced age (>75 years) is a risk factor for both ischemic stroke and major hemorrhage. In RE-LY,[29] the efficacy of dabigatran over warfarin was no different among patients aged 75 years and older and those less than 75 years. In the overall cohort, there was no significant difference in major bleeding between warfarin and dabigatran 150 mg, but there was a significant interaction between age and the choice of therapy[36] with 150 mg doses of dabigatran causing more major bleeding than warfarin among patients aged 75 years and older. It seems prudent to prescribe dabigatran at 110 mg for patients aged 75 years and above. For both rivaroxaban and apixaban, efficacy against stroke/STE and safety for the avoidance of major hemorrhage is not significantly different between patients aged 75 years and older vs. those younger than 75 years.[30,31]

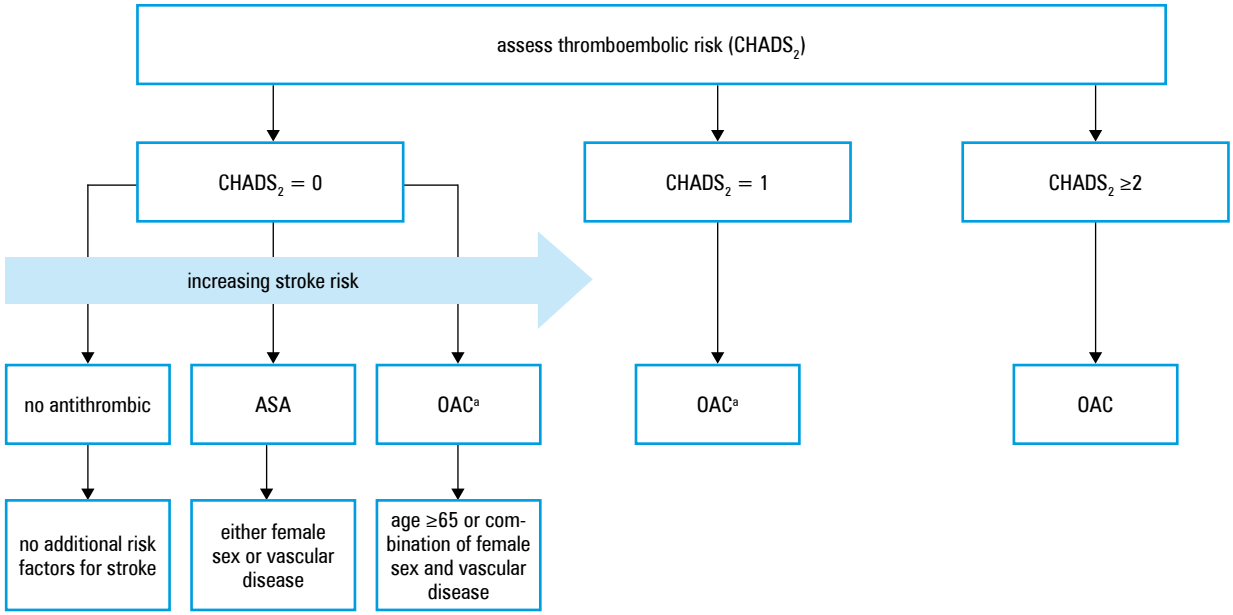

FIGURE The Canadian Cardiovascular Society algorithm[19] for choice of antithrombotic therapy in patients with atrial fibrillation (with permission from Elsevier)
a ASA is a reasonable alternative in selected patients as indicated by risk–benefit analysis
Abbreviations: ASA – acetylsalicylic acid, OAC – oral anticoagulant

Coronary artery disease When an AF patient also has coronary artery disease (CAD), optimal antithrombotic therapy must address both conditions. For primary prevention of coronary events, low-intensity warfarin (INR, ≥1.5) and aspirin are equally effective.[37] Although no RCTs have specifically addressed antithrombotic management of patients with AF who also have CAD, it seems reasonable that patients with AF who have stable CAD should receive antithrombotic therapy based upon their risk of stroke (aspirin for $CHADS_2$, 0; OAC for $CHADS_2$, ≥1)[19]

For secondary prevention post-MI, warfarin alone (INR, 2.8–4.8) is at least as efficacious as aspirin alone in preventing coronary events.[37] RCTs have shown the benefits of aspirin plus clopidogrel for up to 1 year following an acute coronary syndrome (ACS), with or without percutaneous coronary intervention (PCI), and for PCI (both elective and post-ACS).[37] There has been no rigorous comparison of the combination of aspirin and clopidogrel vs. warfarin for patients post-ACS, but RCTs have shown that aspirin plus clopidogrel is more effective than warfarin (alone or in combination with aspirin) post-PCI. There are no RCTs that have compared various antithrombotic regimens among patients with AF, but the so called triple therapy (a combination of OAC, aspirin, and a thienopyridine) is often prescribed. Such patients should receive antithrombotic therapy based on a balanced assessment of their risks of stroke, of recurrent coronary events, and of bleeding associated with the use of combinations of antithrombotic therapies. The issues regarding antithrombotic therapies for patients with CAD plus AF have been extensively discussed in recent evidence-based guidelines.[38-40]

The finding in RE-LY[29] of a significant excess of MIs on dabigatran raised concerns, which were augmented by a meta-analysis of 7 dabigatran trials showing a significant excess of MI, although significantly lower mortality.[41] A recent publication from RE-LY[42] found that net clinical benefit favored dabigatran over warfarin. There was no suggestion of excess MI in the trials of either rivaroxaban or apixaban, and it is generally agreed that the benefits over warfarin of all 3 new OACs are likely to outweigh harm in most patients with AF, including those with CAD.[19]

Chronic kidney disease AF patients may also have chronic kidney disease (CKD), which can affect drug metabolism, rates of bleeding, and rates of stroke.[43-45] Management of AF patients therefore requires accurate assessments of renal function and recognition of comorbid CKD to optimize the efficacy and safety of antithrombotic therapies. The results of RCTs of stroke/STE prevention support the use of new OACs in patients with mild-to-moderate CKD, but there are no RCT data in patients with severe CKD (estimated glomerular filtration rate, <30 ml/min). Observational studies of warfarin for stroke prevention in AF patients with CKD have provided inconsistent results. A group of leading renal experts have advised that, in the absence of more rigorous data, routine anticoagulation of dialysis-dependent CKD patients with AF for primary prevention of stroke is not indicated.[46]

Cardioversion Although the management of the arrhythmia of AF focuses primarily on rate control, cardioversion is commonly undertaken in appropriately selected patients. Evidence from rigorous case series and cohort studies indicates that cerebral and systemic thromboembolism are clear risks associated with both electrical and pharmacological cardioversion.[47] Accordingly, guidelines generally recommend that patients should receive an OAC at therapeutic levels for at least 3 weeks prior to cardioversion and that it should be continued for 4 weeks subsequently.[2,47] New-onset AF is generally thought not to warrant

OAC if cardioversion is undertaken within 48 hours from onset. In some patients at particularly high risk of stroke, it may be appropriate to administer 3 weeks of OAC precardioversion even when the duration of AF is less than 48 hours. In situations of hemodynamic compromise from rapid AF, urgent cardioversion may be warranted with no or only a short duration of anticoagulation even when the AF has been present for more than 48 hours. There is good evidence that the absence of left atrial thrombus on transesophageal echocardiography (TEE) indicates a very low risk of stroke in association with cardioversion.[48] Accordingly, TEE-guided cardioversion may be appropriate with the availability of expert TEE and the use of 4 weeks of OAC following cardioversion.[2,42]

Invasive procedures A patient with AF may require a surgical or diagnostic procedure with an associated risk of major bleeding. The risk of thromboembolism during interrupted or reduced antithrombotic therapy must be weighed against the risk of major bleeding if therapy is maintained.[47] It is reasonable to consider first the risk of stroke in such a patient. If it is low ($CHADS_2$, ≤2), the antithrombotic agent may be discontinued before the procedure (aspirin or clopidogrel for 7–10 days, warfarin for 5 days if the INR is from 2 to 3, and dabigatran or rivaroxaban for 2 days), and reinstated once post-procedure hemostasis is established (about 24 hours). If the risk of bleeding is low and the operator is expert, it may be appropriate to continue the antithrombotic therapy without interruption. When the risk of stroke is high, the antithrombotic therapy may be continued uninterrupted if the risk of major bleeding is low and the operator is expert. If the risk of bleeding is higher and the clinical consequences greater, some form of bridging therapy may be necessary in conjunction with the procedure, with the minimal possible duration of absence of antithrombotic therapy.

Summary AF is common, and the prevalence increases sharply with the age over 65 years. The annual risk of stroke averages 4.5%, but with a wide range depending on the presence of well-recognized risk factors. The risk of stroke, usually followed by major neurological deficit or death, is reduced about two-thirds by VKA and about 20% by aspirin. Dabigatran, rivaroxaban, and apixaban are new OACs which obviate many of the difficulties for patients and doctors in the use of VKA. They offer advantages of efficacy and safety, which vary somewhat from one agent to another and offer excellent alternatives to VKA for stroke prevention.

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ARTYKUŁ POGLĄDOWY

Zapobieganie występowaniu udaru niedokrwiennego mózgu i zatorowości systemowej w migotaniu przedsionków: kanadyjski punkt widzenia

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antagoniści witaminy K, doustne leki przeciwkrzepliwe, migotanie przedsionków, wytyczne praktyki klinicznej, zapobieganie udarowi niedokrwiennemu mózgu

STRESZCZENIE

Częstość występowania migotania przedsionków (*atrial fibrillation* – AF) wśród ogółu populacji ocenia się na około 1%, jednak jest to zjawisko znacznie częstsze wśród osób starszych. Roczne ryzyko wystąpienia udaru niedokrwiennego mózgu w przypadku niestosowania leków przeciwkrzepliwych wynosi w przybliżeniu 4,5%, ale wartość ta może oscylować między <1% a 20% u poszczególnych chorych, w zależności od występowania dobrze znanych czynników ryzyka. Ryzyko wystąpienia udaru niedokrwiennego mózgu, najczęściej prowadzącego do znacznego upośledzenia czynności układu nerwowego lub śmierci, może być zmniejszone o 2/3 w przypadku podawania doustnych antagonistów witaminy K (*vitamin K antagonist* – VKA) i o 20% w przypadku podawania aspiryny. Korzyści wynikające ze zmniejszenia tego ryzyka na ogół przeważają nad ryzykiem krwotoków wywołanych przez doustne antykoagulanty. Nowe doustne leki przeciwkrzepliwe (dabigatran, riwaroksaban i apiksaban) pozwalają uniknąć wielu trudności napotykanych dotychczas podczas stosowania doustnych VKA. Duże randomizowane próby kliniczne przeprowadzone w ostatnim okresie potwierdziły przewagę tych leków nad warfaryną w zakresie ich skuteczności i bezpieczeństwa, których zakres różni się nieznacznie między poszczególnymi preparatami, ale wszystkie stanowią doskonałą alternatywę dla VKA w zapobieganiu udarowi niedokrwiennemu. Najnowsze wytyczne praktyki klinicznej zalecają te leki jako alternatywę dla VKA.

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