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Society Guidelines

Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control

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ABSTRACT

The Canadian Cardiovascular Society (CCS) published the complete set of 2010 Atrial Fibrillation (AF) Guidelines in the January, 2011 issue of the *Canadian Journal of Cardiology*. During its deliberations, the CCS Guidelines Committee engaged to a timely review of future evidence, with periodic composition of focused updates to address clinically important advances. In 2011, results were published from 3 pivotal AF trials: the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke

RÉSUMÉ

La Société canadienne de cardiologie (SCC) a publié l'ensemble des lignes directrices de 2010 en matière de fibrillation auriculaire (FA) dans le numéro de janvier 2011 du *Journal canadien de cardiologie*. Au cours de ses discussions, le comité des lignes directrices de la SCC s'est engagé à revoir régulièrement les nouvelles données par la rédaction périodique de mises à jour ciblées portant sur les avancées cliniques importantes. En 2011, les résultats de 3 essais pivots sur la FA ont été publiés : le ROCKET-AF (*Rivaroxaban Once Daily Oral Direct Factor*

The development of the 2010 Canadian Cardiovascular Society (CCS) Atrial Fibrillation (AF) Guidelines included a commitment to a timely review of emerging evidence, with the periodic production of focused updates to address clinically important advances. In 2011, results were published from 3 pivotal AF trials: the **R**ivaroxaban **O**nce Daily Oral Di-

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*A complete list of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines Committee primary and secondary panels is available in Supplemental Appendix S1.

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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and Embolism Trial in Atrial Fibrillation (ROCKET-AF), the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, and the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS), comparing dronedarone with placebo in patients with permanent AF and additional cardiovascular disease risk-factor burden. Each of these large randomized trials provided clear results with major implications for AF management. Other important evidence that has emerged since the 2010 Guidelines includes findings about prediction instruments for AF-associated stroke and bleeding risk, stroke risk in paroxysmal-AF patients, risk-benefit considerations related to oral anticoagulation in patients with chronic kidney disease, and risk/benefit considerations in the use of antiplatelet agents, alone and in combination with each other or with oral anticoagulants, in AF patients. The Guidelines Committee judged that this extensive and important new evidence required focused updating of the 2010 Guidelines with respect to stroke prevention and rate/rhythm control. This report presents the details of the new recommendations, along with the background and rationale.

Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), l'étude ARISTOTLE (*Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation*) et le PALLAS (*Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy*), qui compare le dronédarone au placébo chez les patients ayant une FA permanente et des facteurs de risque cardiovasculaire additionnels. Chacun de ces essais hasardisés de grande envergure a fourni des résultats clairs sur les importantes conséquences de la prise en charge de la FA. Les autres données probantes importantes qui sont ressorties depuis la publication des lignes directrices 2010 incluaient les conclusions sur les outils de prédiction du risque d'accident vasculaire cérébral et d'hémorragie associé à la FA, du risque d'accident vasculaire cérébral chez les patients ayant une FA paroxystique, les considérations risques-avantages liés à l'anticoagulation orale chez les patients ayant une maladie rénale chronique (MRC) et les considérations risques-avantages de l'utilisation d'agents antiplaquettaires, seuls ou en combinaison avec d'autres agents antiplaquettaires ou agents anticoagulants oraux, chez les patients ayant une FA. Le comité des lignes directrices a estimé que ces nouvelles données probantes, importantes et exhaustives exigeaient une mise à jour ciblée des lignes directrices 2010 en ce qui a trait à la prévention des accidents vasculaires cérébraux, le maintien du rythme et la maîtrise de la fréquence. Ce rapport présente de manière détaillée les nouvelles recommandations, ainsi que leur fondement et leurs justifications.

rect Factor Xa Inhibition **C**ompared With Vitamin **K** Antagonist for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation (ROCKET-AF) trial, **A**pixaban for **R**eduction **i**n **St**roke and **O**ther **T**hromboembo**l**ic **E**vents in Atrial Fibrillation (ARISTOTLE) study, and the **P**ermanent **A**trial Fibri**lla**tion Outcome **S**tudy Using Dronedarone on Top of Standard Therapy (PALLAS) trial, comparing dronedarone with placebo in patients with permanent AF and additional cardiovascular disease. Each of these 3 large randomized trials provided clear results with major implications for the management of AF. After reviewing these 3 trials and other emergent data, the CCS-AF Guidelines Committee has recommended important changes to the guidelines, specifically with respect to stroke prevention and rate and rhythm control. This focused update provides the details and rationale for the new recommendations.

The present recommendations were developed with the same methods used for the initial guidelines.[1] The primary panel was reassembled and maintained a wide representation from primary and specialty care (internal medicine, cardiology, neurology, and emergency medicine). For continuity, the panel included many of the 2010 members. Conflict of interest declarations were updated and the primary panel included members without conflicts of interest on both the Stroke Prevention and Rate/Rhythm Control writing subgroups. Consistent with prior CCS AF guidelines, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was maintained in place of the American College of Cardiology/American Heart Association/Heart Rhythm Society grading system to evaluate evidence and strength of recommendations. Dissemination of the current update will follow the same multidimensional approach as the 2010 Guidelines, which resulted in over 10,000 downloads of manuscripts, slides, and the executive summary in the past year.

Updated Guidelines for Stroke Prevention

Predicting stroke risk

The **C**ongestive **H**eart Failure, Hypertension, **A**ge $>$ 75, **D**iabetes Mellitus, and Prior **S**troke or Transient Ischemic Attack ($CHADS_2$) index[2] 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 2.0% for each 1-point increase in $CHADS_2$ score (from 1.9% with a score of 0 to 18.2% with a score of 6).[2,3] A recent systematic review[4] of 12 risk stratification schemas assesses additional validation studies performed since publication of the risk schemas, including 6 validations of the $CHADS_2$. A modified version of the $CHADS_2$ schema[5] gives increasing points to various age categories with up to 6 points for age $\geq$ 85 years, 6 points for stroke/TIA, 1 point for each of female sex and diabetes mellitus, but nothing for hypertension or heart failure. The modifications increased granularity for lower score groups and were associated with a slightly higher c-statistic than the standard $CHADS_2$. The 2010 European Society of Cardiology (ESC) AF guidelines[6] incorporated the Birmingham 2009 system (**C**ongestive Heart Failure, **H**ypertension, **A**ge $\geq$ 75 Years, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, **A**ge 65 to 74 Years, **S**ex **C**ategory [CHA_2DS_2-VASc]) for the prediction of stroke risk.[7] The CHA_2DS_2-VASc is similar to the $CHADS_2$, but gives 2 points for age $\geq$ 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. CHA_2DS_2-VASc was validated and compared with $CHADS_2$ and other standard schemas in a subset of 1577 patients in the Euro Heart Survey on AF population. When patients with AF were categorized as low (score = 0), intermediate (score = 1), or high risk (score = 2), the c-statistic was 0.59 for $CHADS_2$ and 0.61 for the CHA_2DS_2-VASc.[7] Because the c-statistic ranges from values of 0.5 to 1, with 0.5 indicating no predictive value and 1 perfect prediction, both systems showed similar but weak predictive value. The 2010 ESC guidelines recommended that $CHADS_2$ be applied first, with CHA_2DS_2-VASc applied only if the $CHADS_2$ score is under 2, to refine the stroke-risk definition in lower-risk individuals. The 2010 CCS Guidelines,[8] recommended that the $CHADS_2$ schema be

used for stroke risk prediction, in view of its simplicity, extensive validation, and wide use.

Several large new validation studies of stroke-risk schemas have been considered in this 2012 CCS guidelines update. A 2008 systematic review[4] of 12 risk-stratification schemes noted that none had been compared in a single cohort of adequate size and diversity. Two subsequent studies validated and compared several stroke-prediction schemas in large populations of AF patients. Van Staa et al.[9] analyzed several risk-prediction schemas in a 79,844-patient cohort from the UK General Practice Research Database and found that the c-statistics associated with the standard $CHADS_2$, the modified $CHADS_2$, and the CHA_2DS_2-VASc indicated very similar moderate predictive value. Olesen et al.[10] published a detailed comparison of $CHADS_2$ and CHA_2DS_2-VASc schemas performance among all nonvalvular AF patients hospitalized in Denmark between 1997 and 2000. $CHADS_2$ and CHA_2DS_2-VASc scores were evaluated in relation to rates of hospitalization or death due to thromboembolism at 1, 5, and 10 years. All 3 new risk-score components (age 65-74, vascular disease, and female sex) contributed significantly to risk prediction in 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.[11] 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 $\geq$ 2) risk, principally because of more precise estimates of thromboembolic risk in patients with $CHADS_2$ scores of 0 or 1.

Whereas the stroke-risk for the $CHADS_2 = 0$ group was 1.9% per year in the original validation,[2] subsequent validations found lower 1-year stroke-risks, between 0.5 and 1.7%.[4,9,10] There is a large range of stroke-risk among patients with $CHADS_2 = 0$, among whom appropriate therapy may range from oral anticoagulants (OACs) to acetylsalicylic acid (ASA) to no antithrombotic agent. Whereas about 20% of AF patients have a low-risk $CHADS_2$ score ($CHADS_2 = 0$),[9,10] the prevalence of CHA_2DS_2-VASc = 0 AF patients is about 8.5%[9,10] with a mean stroke-risk $\leq$ 0.5% per year. The principal value of CHA_2DS_2-VASc applies in these patients, most of whom do not require antithrombotic therapy. Patients with a $CHADS_2 \geq 1$ have a stroke-risk well over 2% per year and require OACs. Although most patients with a CHA_2DS_2-VASc score of 1 have sufficient risk to justify the use of OACs, a single CHA_2DS_2-VASc point based on vascular disease or female sex implies a stroke risk $<$ 1.5% per year and ASA should be considered. Patients with a CHA_2DS_2-VASc $\geq$ 2 clearly have sufficient stroke risk to justify use of an OAC.

There is extensive evidence that the stroke-risk of paroxysmal AF patients is similar to that among patients with persistent or permanent AF. Is there a threshold AF burden to require antithrombotic therapy? In the TRENDS study[12] patients with rhythm-monitoring pacemakers or implantable cardioverter defibrillators and $\geq$ 1 stroke-risk factor (mean $CHADS_2 = 2.2$) were followed for a mean of 1.4 years. AF-burden was quantified as the longest total daily duration of atrial tachycardia (AT) (probable AF) during a 30-day monitoring period. The risk ratio (RR) for stroke/TIA/systemic thromboembolism (STE) with an AF-burden of $<$ 5.5 hours of AT vs those with no AT was 0.98 (stroke/TIA incidence 1.1% per year). The RR for AF-burden $\geq$ 5.5 hours was 2.20 (stroke/TIA/STE incidence 2.4% per year). The **As**ymptomatic Atrial Fibrillation and **S**troke **E**valuation in Pacemaker Patients and the Atrial Fibrillation **R**eduction Atrial Pacing **T**rial (ASSERT) study[13] enrolled 2580 patients with age $\geq$ 65 years and hypertension followed for a mean of 2.8 years after implantation of first pacemaker or implantable cardioverter defibrillator. Device-detected AT ($>$190 beats per minute lasting $>$ 6 minutes) occurred in 36%, and was associated with an increased risk of clinical AF (RR 5.56 vs patients without AT) and stroke/STE risk of 2.1% per year (RR 2.5 vs patients without AT). These 2 studies demonstrate a clear association between device-detected AT and stroke/STE. The ASSERT trial demonstrates that episodes as short as 6 minutes are markers for the development of clinical AF and for stroke/STE risk. However, the absolute stroke risk was lower in ASSERT patients than in clinical AF patients and there was typically a delay of many months between the appearance of device-detected AT and the occurrence of stroke/STE. In the absence of data from randomized trials of OAC in this population, it remains unclear if treatment of this very early phase of AF prevents stroke/STE.

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 depends on the specific antithrombotic agent and a variety of patient characteristics. Hemorrhagic risks increase as antithrombotic intensity increases from (1) ASA (75-325 mg/day) or clopidogrel (75 mg/day) alone, to (2) combination ASA plus clopidogrel, to (3) dabigatran 110 mg twice per day [bid], to (4) dabigatran 150 mg/day, rivaroxaban, and vitamin-K antagonists (VKAs), which carry similar risks. Apixaban appears to have a lower risk of major bleeding than 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 rigourous setting of a clinical trial or a dedicated, expert anticoagulation service.

The 2010 ESC and CCS AF guidelines[6,8] recommended the **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly ($>$ 65 Years), **D**rugs/Alcohol Concomitantly (HAS-BLED) score schema[14] for predicting bleeding risk. HAS-BLED is 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 HAS-BLED score allows clinicians to assign individualized patient risks of major bleeding from about 1% (score 0-1) to 12.5% (score 5). The HAS-BLED schema has been further validated in a large elderly, hospitalized population.[15] The annual major bleeding rate was surprisingly high; 5.11% in the non-OAC group and 5.27% in the OAC group. The c-statistic associated with the 3-level grouping of patients was high (about 0.8).

The **Ant**icoagulation and **R**isk Factors **i**n **A**trial Fibrillation (ATRIA) score[16] assigns points to the following variables: anemia (3), severe renal disease (3), age $\geq$ 75 years (2), prior hemorrhage (1), and hypertension (1). The annual rates of

major bleeding in the validation cohort were: 0.83% (0-3 points), 2.41% (4 points), and 5.32% (5-10 points). The c-statistics for continuous scores and for categories were 0.74 and 0.69 respectively, better than for 6 other published schemes. Surprisingly, no comparison was made to the HAS-BLED score. The HAS-BLED schema is simpler to remember and easier to use, and we suggest it as the best available for hemorrhage risk prediction over other more complicated (eg, **H**epatic or Renal Disease, **E**thanol Abuse, **M**alignancy, **O**lder [Age > 75 Years], **R**educed Platelet Count or Function, **R**ebleeding Risk, **H**ypertension [Uncontrolled], **A**nemia, **G**enetic Factors, **E**xcessive Fall Risk, and **S**troke [HEMORR$_2$HAGES]) or less-validated (eg, ATRIA) schemas.

The application of a bleeding risk schema is useful to ensure that important risk factors are systematically considered. The score can be useful in comparing the relative risks of stroke vs major bleeding with various antithrombotic therapies. 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 (eg, a young patient with AF and few or no stroke risk factors, but a high risk of major hemorrhage because of malignancy, prior major hemorrhage, or participation in contact sports) does the risk/benefit ratio favour no antithrombotic therapy. Patient preferences are of great importance in deciding on stroke prevention therapy in relation to benefits and risks.

Newer OACs

The limitations of warfarin as an OAC are well known. The degree of INR prolongation by a given dose of warfarin is unpredictable because of numerous factors affecting pharmacokinetics and pharmacodynamics. INR measurements are required at least monthly to maintain a safe/effective INR. Even with careful monitoring, it is difficult to achieve therapeutic range INRs > 65% of the time, and AF patients typically experience major bleeding at a rate of about 3.0 % per year.[17]

Several new OACs have been developed to obviate some of the problems associated with VKAs.[17] Dabigatran, rivaroxaban, and apixaban have undergone extensive clinical evaluation and been found to be safe and efficacious.[18-20] 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 after 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 indicated for patients with reduced renal function, advanced age, or low body mass index. Two disadvantages are (1) clinically useful measurement of anticoagulant effect is challenging, and (2) no specific antidotes are yet available.

Efficacy and safety of new OACs in AF patients

Dabigatran is approved in Canada, the USA, and Europe for the prevention of stroke and STE in AF and atrial flutter (AFL). In the **R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y** (RE-LY) trial[18] 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% per year with warfarin, 1.53% per year with dabigatran 110 mg (RR 0.91; 95% confidence interval [CI], 0.74-1.11), and 1.11% per year with dabigatran 150 mg (RR 0.66; 95% CI, 0.53-0.82; $P < 0.001$ vs warfarin). (Throughout this report, when RR is followed by a range, it indicates 95% CI). Major bleeding rates were 3.36% per 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% per year with warfarin, 7.09% per year with dabigatran 110 mg (RR vs warfarin 0.92; 0.84-1.02), and 6.91% per year with dabigatran 150 mg (RR vs warfarin 0.91; 0.82-1.00). Patients taking dabigatran had more gastrointestinal (GI) 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 USA, and Europe for the prevention of stroke and STE in AF/AFL. The double-blind ROCKET-AF trial[19] randomized 14,264 AF patients (mean $CHADS_2 = 3.5$) to rivaroxaban 20 mg once daily (15 mg once daily when CrCl was 30-49 mL/minute) or warfarin (median follow-up 1.9 years). Principal efficacy outcome rates (composite of stroke or STE were 2.2% per year with warfarin and 1.7% per year with rivaroxaban (RR vs warfarin 0.79; 0.66-0.96). In a secondary, intention-to-treat analysis, the respective rates were 2.4% vs 2.1% (RR 0.88; 0.75-1.03; $P = 0.12$ for superiority). Major bleeding rates were 3.4% per year with warfarin vs 3.6% with rivaroxaban (RR 1.04). There was significantly less intracranial, but more GI, bleeding with rivaroxaban. No net clinical benefit data were reported. MI rates were 1.12% per year with warfarin vs 0.91% per year with rivaroxaban (RR 0.81; $P = 0.121$). Adverse events occurred in 81.4% of rivaroxaban subjects vs 83.1% taking warfarin, with only epistaxis and hematuria significantly more common with rivaroxaban.

Apixaban is not yet approved in Canada for stroke prevention in AF. In the ARISTOTLE trial,[20] 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% per year with warfarin vs 1.27% per year with apixaban (RR vs warfarin 0.79; 0.66-0.95; $P < 0.01$ for superiority). Major bleeding rates were 3.09% per year with warfarin vs 2.13% with apixaban (RR 0.69; $P < 0.001$), with substantial and statistically significant reductions in intracranial and GI bleeding. Net clinical benefit outcome rates (composite of stroke, STE, major bleeding, and all-cause mortality) were 4.11% per year with warfarin vs 3.17% per year with apixaban (RR 0.85; 0.78-0.92; $P < 0.001$). MI rates were 0.61% per year with warfarin vs

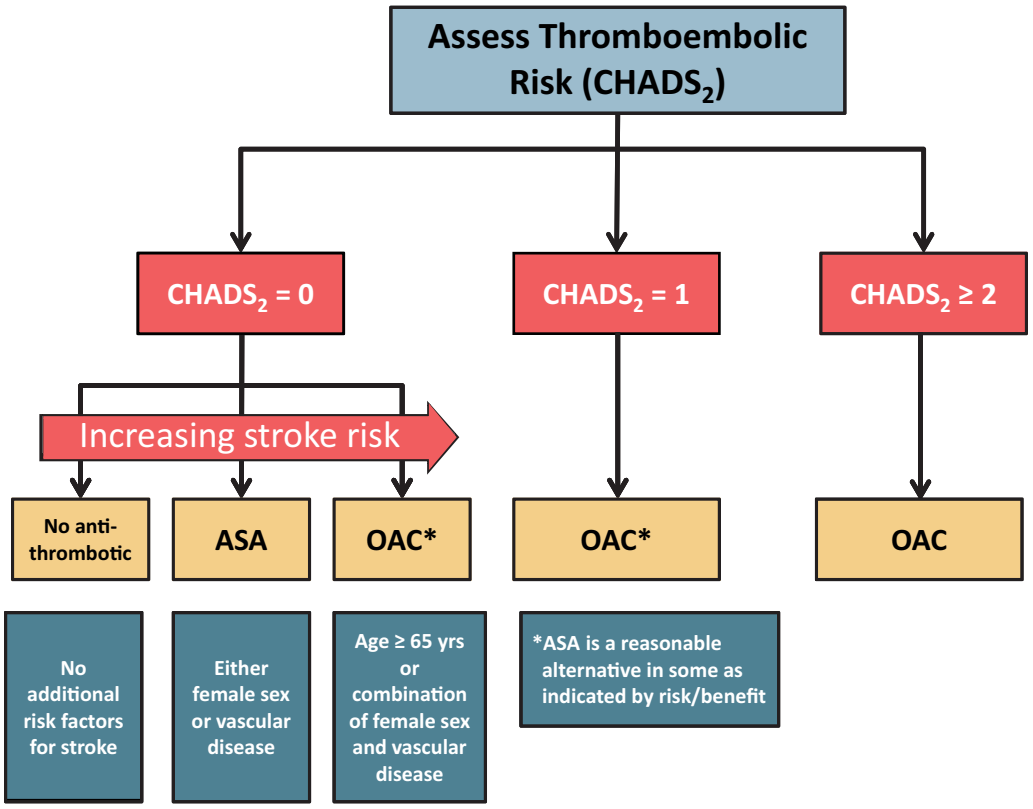

Figure 1. Summary of recommendations for antithrombotic agent use based on Congestive Heart Failure, Hypertension, Age > 75, Diabetes Mellitus, and Prior Stroke or Transient Ischemic Attack ($CHADS_2$) score. Additional risk factors of age > 65, vascular disease, and female sex are integrated to increase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

0.53% per year with apixaban (RR 0.88; $P = 0.37$). Overall adverse event rates were 81.5% (apixaban) vs 83.1% (warfarin), with no adverse event categories more frequent in patients taking apixaban.

In the **A**pixaban **Ver**sus Acetylsalicylic Acid (ASA) to P**r**event Str**o**k**e**s in Atrial Fibrillation Patient**s** Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial,[21] 5590 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) or to the combination of ASA plus clopidogrel, and followed for a median of 1.1 years. The trial was stopped early because of marked outcome differences. Principal outcome rates (stroke or STE) were 3.7% per year with ASA/clopidogrel vs 1.6% per year with apixaban (RR vs ASA/clopidogrel 0.45; 0.32-0.62; $P < 0.001$). The rates of major bleeding were 1.2% per year with ASA/clopidogrel vs 1.4% with apixaban (RR 1.13; $P < 0.57$), with no significant differences in intracranial or GI bleeding.

In summary, compared with warfarin, both dabigatran and apixaban are more efficacious than warfarin 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.

The recommendations made by previous national guidelines exercises were based upon a total of 2900 patients in the randomized trials of warfarin vs control, 3990 patients in the trials of ASA vs control and 3647 patients in the trials of warfarin vs ASA. The 3 recent trials randomized over 50,000 subjects to 1 of the new agents vs warfarin, and 5500 to apixaban vs ASA/clopidogrel. The 5 major primary prevention trials of warfarin compared with control showed an absolute risk reduction (ARR) for stroke of 2.7% per year, and a number-needed-to-treat (NNT) of 37 to avoid 1 stroke during 1 year of treatment.[22] In RE-LY, the ARR for dabigatran vs warfarin was 0.58% per year (NNT = 172) and in ARISTOTLE the ARR for apixaban vs warfarin was 0.33% per year (NNT = 303). For intracranial hemorrhage, the ARRs are small (dabigatran ARR 0.44% per year, NNT = 227; rivaroxaban ARR 0.2% per year, NNT = 500; and apixaban ARR 0.47% per year, NNT = 213).

RECOMMENDATION (Fig. 1)

We recommend that all patients with AF or AFL (paroxysmal, persistent, or permanent), should be stratified using a predictive index for stroke risk (eg, $CHADS_2$) and for the risk of bleeding (eg, HAS-BLED), and that most patients should receive either an OAC or ASA (Strong Recommendation, High-Quality Evidence).

We suggest, that when OAC therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban

(once approved by Health Canada), in preference to warfarin (Conditional Recommendation, High-Quality Evidence).

Values and preferences. This recommendation places a relatively high value on comparisons with warfarin showing that dabigatran 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 hemorrhage and are much simpler to use. The recommendation places less value on the following features of warfarin: long experience with clinical use, availability of a specific antidote, and a simple and standardized test for intensity of anticoagulant effect. The preference for 1 of the new OACs over warfarin is less marked among patients already receiving warfarin with stable INRs and no bleeding complications.

We recommend that patients at high risk of stroke ($CHADS_2 \geq 2$) should receive OAC therapy (Strong Recommendation, High-Quality Evidence).

We recommend that most patients at intermediate risk of stroke ($CHADS_2 = 1$) should receive OAC therapy (Strong Recommendation, High-Quality Evidence).

We suggest, based on individual risk/benefit considerations, that ASA is a reasonable alternative for some (Conditional Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places relatively greater weight on the absolute reduction of stroke risk with OACs compared with ASA and less weight on the absolute increased risk for major hemorrhage with OACs compared with ASA.

We suggest that patients at low risk of stroke ($CHADS_2 = 0$) should have additional risk factors for stroke considered (including age 65-74 years, female sex, and presence of vascular disease) (Conditional Recommendation, Moderate-Quality Evidence).

We suggest OAC therapy for patients at highest risk within this category (age greater than age 65 or the combination of female sex and vascular disease); ASA (75-325 mg/day) for patients at lower risk within this category (female sex or vascular disease); and no antithrombotic therapy for those patients at lowest risk in this category (no additional risk factors) (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. Among patients at higher risk, this recommendation places greater weight on the strokes prevented by OAC and ASA and less weight on the major bleeds caused. Among patients at lowest risk, this recommendation places greater weight on the inconvenience, costs, and risks (major hemorrhage) with OAC and ASA and relatively less weight on the strokes prevented.

Elderly patients

Advanced age (> 75 years) is a clear risk factor for both ischemic stroke and major hemorrhage. In the overall cohort of the RE-LY trial, there was no significant difference in major bleeding between warfarin and dabigatran 150 mg. There was a significant interaction between age and the choice of therapy.[23] The efficacy of dabigatran was no different among patients aged ≥ 75 years and those < 75 years, but because 150 mg doses of dabigatran may cause more major bleeding among patients older than 75 years, it seems prudent to prescribe dabigatran at 110 mg. For both rivaroxaban and apixaban, efficacy against stroke/STE and safety for the avoidance of major hemorrhage is not significantly different between patients ≥ 75 years vs those < 75 years.[19, 20]

Practical tip. Among patients > 75 years and certainly those > 80 years, dose reduction of the new OACs, especially dabigatran, should be considered.

As experience with the new OACs increases, a number of practical issues around their use will become clearer. Practical tips are provided to assist the practitioner in using new OACs where reasonable data exist to guide therapy. Further data are needed to guide bridging prior to and after surgical procedures, DC cardioversion, monitoring of anticoagulant effect, and reversal when bleeding occurs using new OACs. Likewise, advice for dose-reduction related to low body mass index and in the presence of hepatic dysfunction is needed.

Coronary artery disease

AF patients with concomitant coronary artery disease (CAD) present issues of concomitant antithrombotic therapy in the settings of primary prevention, stable CAD, acute coronary syndrome (ACS), or percutaneous coronary intervention (PCI). There is good randomized clinical trial (RCT) evidence[24] for the use of ASA, clopidogrel, combination ASA plus clopidogrel, and warfarin for patients with various manifestations of CAD. For primary prevention of coronary events, low-intensity warfarin (INR ≥ 1.5) is as effective as ASA. For secondary prevention post-MI, warfarin alone (INR 2.8–4.8) is at least as efficacious as ASA alone in preventing coronary events.[24] RCTs have shown the benefits of ASA plus clopidogrel for up to 1 year following an ACS (with or without PCI) and for PCI (both elective and post-ACS).[24] There has been no rigourous comparison of the combination of ASA and clopidogrel vs warfarin for patients post ACS, but RCTs have shown that ASA plus clopidogrel is more effective than warfarin (alone or in combination with ASA) post-PCI.

No RCTs have specifically addressed antithrombotic management of patients with AF who also have CAD. For patients who require both OAC for stroke prophylaxis and antiplatelet therapy to prevent coronary events, so-called "triple therapy" (a combination of OAC, ASA, and a thienopyridene) is often prescribed, no studies have compared new OACs with placebo or ASA in primary CAD prevention, stable CAD, ACS, or PCI. However, from the trials of new OACs vs warfarin for AF, data are available on the comparative rates of coronary events overall and in subsets of CAD patients.

The RE-LY trial initially reported a higher incidence of MI with dabigatran 150 mg dose vs warfarin (RR 1.38; 1.00-1.91; $P = 0.048$).[18] A recent meta-analysis incorporating the RE-LY data found a similar result but also noted a reduction in all-cause mortality associated with dabigatran.[25] An updated analysis of RE-LY[26] found only a trend toward more frequent MIs on dabigatran (RR 1.27; 0.94-1.71; $P = 0.12$). Analysis of the composite outcomes of (1) MI, unstable angina, cardiac arrest, or cardiac death (RR 0.98; 0.85-1.12; $P = 0.77$), (2) composite cardiac events plus stroke and STE (RR 0.88; 0.78-0.98; $P = 0.03$), and (3) net clinical benefit (RR 0.90; 0.82-0.99; $P = 0.02$) favoured dabigatran over warfarin. When patients were

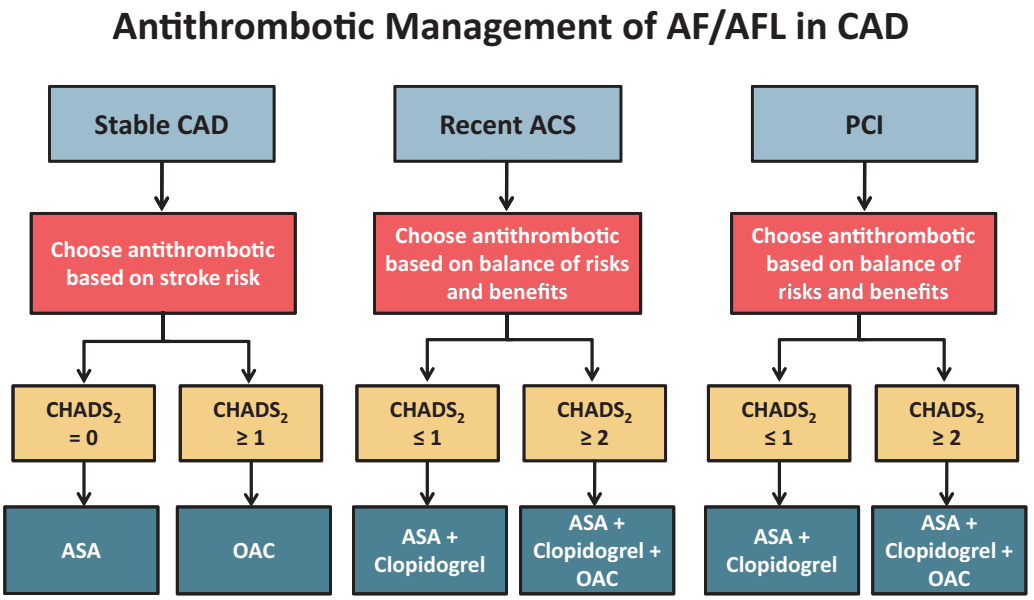

Figure 2. A summary of our recommendations for antithrombotic management in settings of CAD. ACS, acute coronary syndrome; AF, atrial fibrillation; AFL, atrial flutter; ASA, acetylsalicylic acid (aspirin); CAD, coronary artery disease; $CHADS_2$, Congestive Heart Failure, Hypertension, Age > 75, Diabetes Mellitus, and Prior Stroke or Transient Ischemic Attack; OAC, oral anticoagulant; PCI, percutaneous coronary intervention.

categorized as having a baseline history of CAD and/or previous MI, there were no statistically significant interactions between allocated therapy and any of the major outcomes. In ROCKET-AF[19], the MI RR for rivaroxaban vs warfarin was 0.81 ($P = 0.121$). In ARISTOTLE,[20] the MI RR for apixaban vs warfarin was 0.61 ($P = 0.37$). The available data from the RCTs of new OACs vs warfarin in AF do not suggest mitigation of the efficacies for the prevention of stroke in patients with CAD, nor does it suggest an excess of coronary events among those receiving any of the new OACs. Therefore, the qualifier that warfarin is preferred over dabigatran for patients at increased risk of coronary events presented in the 2010 CCS Guidelines, has been removed.

There have been 3 recently published randomized phase II dose-finding trials of triple therapy (using 1 of the new OACs) vs ASA/clopidogrel,[27-29] each of which found a substantial and significant increase in major bleeding rates with triple therapy. In none of the studies was there a significant reduction nor a suggestion of an increase in the principal coronary-ischemic outcome events. The patient cohorts in these studies were younger than the AF populations in studies comparing new OACs with warfarin and the patients did not have strong indications for anticoagulant therapy (eg, AF). A phase III study[30] of rivaroxaban "triple therapy" vs ASA plus clopidogrel found a statistically significant reduction of the primary composite outcome (cardiovascular death, MI, or stroke) but a significant increase of major bleeding. A similar phase III study of apixaban[31] was stopped early because of high rates of major bleeding. The risk of major bleeding is definitely increased with the addition of any of the new OACs to antiplatelet therapy, as is observed with warfarin as part of "triple therapy."

In summary, no RCTs have directly addressed the management of patients with both AF and CAD. In the absence of RCTs, guidelines must be derived from reasonable extrapolations from the available RCTs in AF and CAD alone and from evidence of lesser quality among patients with both AF and CAD. The 2010 CCS Consensus recommended that warfarin be used in preference to dabigatran in those patients with AF and CAD requiring OAC therapy. The available evidence now suggests that 1 of the new OACs could be used in preference to warfarin when an OAC is indicated for the prevention of stroke in a patient with concomitant AF and CAD. Recommendations with respect to ACS and PCI remain unchanged. A full discussion can be found in the 2010 Guidelines.[8] The issues regarding antithrombotic therapies for patients with CAD plus AF have been extensively discussed in recent evidence-based guidelines.[32-34]

RECOMMENDATION (Fig. 2)

We suggest that patients with AF/AFL who have stable CAD should receive antithrombotic therapy selected based upon their risk of stroke (ASA for most $CHADS_2 = 0$ and OAC for most $CHADS_2 \geq 1$) (Conditional Recommendation, Moderate-Quality Evidence).

We suggest that patients with AF/AFL who have experienced ACS or who have undergone PCI, should receive antithrombotic therapy selected based on a balanced assessment of their risks of stroke, of recurrent coronary artery events, and of hemorrhage associated with the use of combinations of antithrombotic therapies, which in patients at higher risk of stroke may include ASA plus clopidogrel plus OAC (Conditional Recommendation, Low-Quality Evidence).

Stroke prevention in non-valvular AF in patients with chronic kidney disease

Chronic kidney disease (CKD) commonly afflicts patients with AF,[35-37] and can influence drug metabolism,[38] rates of bleeding,[39] and rates of stroke.[40] Management of AF-patients

Table 1. Therapeutic choices in patients with chronic kidney disease and stroke risk factors ($CHADS_2 \geq 1$)

GFR	Warfarin	Dabigatran	Rivaroxaban	Apixaban*
GFR ≥ 60 mL/min	Dose adjusted for INR 2.0-3.0[41]	150 mg bid or 110 mg bid[18]	20 mg daily[19]	5 mg bid[20]
GFR 50-59 mL/min	Dose adjusted for INR 2.0-3.0[41]	150 mg bid or 110 mg bid[18]	20 mg daily[19]	5 mg bid[20]
GFR 30-49 mL/min	Dose adjusted for INR 2.0-3.0[41]	150 mg bid or 110 mg bid[18]	15 mg daily[19]	5 mg bid (for GFR > 25 mL/min only)[20] Consider 2.5 mg bid†
GFR 15-29 mL/min (not on dialysis)	No RCT data‡	No RCT data§	No RCT data¶	5 mg bid (for GFR > 25 mL/min only)[20] Consider 2.5 mg bid†
GFR < 15 mL/min (on dialysis)	No RCT data‡	No RCT data¶	No RCT data¶	No RCT data

bid, twice daily; $CHADS_2$, Congestive Heart Failure, Hypertension, Age > 75, Diabetes Mellitus, and Prior Stroke or Transient Ischemic Attack score; GFR, glomerular filtration rate; INR, international normalized ratio; RCT, randomized clinical trial.

* Not yet approved by Health Canada.

† Consider Apixaban 2.5 mg po bid if GFR ≤ 25 mL/min, especially if age > 80 or body weight < 60 kg.[20]

‡ Dose adjusted warfarin has been used, but observational data regarding safety and efficacy is conflicting (see text).

§ Modelling studies suggest that dabigatran 75 mg bid might be safe for patients with GFR 15-29 mL/min, but this has not been validated in a prospective cohort.[18]

¶ No published studies support a dose for this level of renal function; product monographs suggest the drug is contraindicated for this level of renal function.

therefore requires accurate assessments of renal function and recognition of comorbid CKD to make safe and effective therapeutic choices. More detailed discussion of assessment of estimated glomerular filtration rate (eGFR), the effect of CKD on rates of stroke and hemorrhage, and therapies for stroke prevention in AF is in the Supplementary Material.

Clinical trials. Clinical trials of antiplatelet agents or OACs in AF have not systematically enroled patients with severe CKD (glomerular filtration rate [GFR] < 30 mL/minute) (see Supplemental Table S1). Data from RCTs of stroke/STE prevention (Table 1) support OAC use in patients with mild to moderate CKD, but there are no RCT data in patients with severe CKD (GFR < 30 mL/minute).

Observational studies. Observational studies of warfarin for stroke prevention in AF patients with CKD have provided inconsistent results. An observational study of 399 patients with CKD and AF, including 93 patients on dialysis and 132 with an eGFR of < 15 mL/minute per $1.73m^2$, suggested a significantly lower rate of stroke with warfarin vs no warfarin and no significant increase in hemorrhage.[42] Two other small observational studies did not identify benefit with warfarin in dialysis patients with AF.[43,44] Some reports suggest that in AF patients on dialysis, warfarin use is associated with harm. In an observational study of 2188 dialysis patients, warfarin use was associated with increased stroke risk, especially in those > 75 years old (RR 2.17; 1.04-4.53).[45] Another study in 1671 dialysis patients found a similarly increased rate of both ischemic (5.8% warfarin use vs 2.3% nonuse) and hemorrhagic stroke (1.2% warfarin use vs 0.5% nonuse).[46] A large retrospective cohort study evaluated 41,425 patients with incident hemodialysis but not necessarily AF, and found increased mortality with warfarin (RR 1.27; 1.18-1.37), clopidogrel (RR 1.24; 1.13-1.35), and ASA (RR 1.06; 1.01-1.11).[47] Although observational studies are prone to confounders and bias, the findings are disconcerting and highlight an urgent need for RCTs of antithrombotic therapies for stroke prevention in patients with severe CKD and also AF. The Kidney Disease: Improving Global Outcomes authors have advised that, pending further data, "routine anticoagulation of dialysis-dependent CKD patients with AF for primary prevention of stroke is not indicated."[48]

RECOMMENDATION

We recommend that patients with AF who are receiving OAC:

Have their renal function assessed at least annually by measuring serum creatinine and calculating eGFR (Strong Recommendation, Moderate-Quality Evidence).

Be regularly considered for the need for alteration of OAC drug and/or dose changes based on eGFR (Strong Recommendation, Moderate-Quality Evidence).

For antithrombotic therapy of CKD patients, therapy should relate to eGFR as follows:

eGFR > 30 mL per minute: We recommend that such patients receive antithrombotic therapy according to their $CHADS_2$ score as detailed in recommendations for patients for patients with normal renal function (Strong Recommendation, High-Quality Evidence).

eGFR 15-30 mL per minute and not on dialysis: We suggest that such patients receive antithrombotic therapy according to their $CHADS_2$ score as for patients with normal renal function. The preferred agent for these patients is warfarin (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places a relatively higher value on prevention of ischemic stroke than on bleeding complications associated with antithrombotic therapy, as well as the limited data available for new OACs in CKD patients. No therapy may be appropriate for some patients with eGFR 15-30 mL per minute (not on dialysis), with a stronger preference for avoiding bleeding complications than preventing ischemic stroke.

eGFR < 15mL per minute (on dialysis): We suggest that such patients not routinely receive either OAC (Conditional Recommendation, Low-Quality Evidence) or ASA for stroke prevention in AF (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places a relatively higher weight on observational data linking warfarin and ASA use with mortality in patients on dialysis, and relatively lower weight on the potential for these agents to prevent ischemic stroke. Therapy with OACs or antiplatelet drugs may be appropriate for some patients with eGFR

< 15 mL per minute (on dialysis) in whom there is a stronger preference for avoiding ischemic stroke.

Practical tip. Patients with eGFR 30-50 mL per minute need more frequent measures of eGFR and may need OAC dose reductions with conditions that may transiently reduce eGFR. This is especially true in the elderly (age older than 75 years) as bleeding risk increases with age.[23]

Updated Guidelines for Rate/Rhythm Control

Updated risk/benefit assessment for dronedarone

The "**A** Placebo-Controlled, Double-Blind, Parallel Arm **T**rial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular **H**ospitalization or Death From Any Cause in Pati**en**ts With **A**trial Fibrillation/Atrial Flutter" (ATHENA) trial evaluated the safety and efficacy of dronedarone therapy in 4628 higher risk patients with AF or AFL (paroxysmal or persistent with sinus rhythm restoration planned).[49] After a mean follow-up of 21 ± 5 months, there was a reduction in the primary outcome variable (death or first cardiovascular hospitalization) from 39.4% (placebo group) to 31.9% (dronedarone group; RR 0.76; 0.69-0.84; $P < 0.001$). There was also a statistically significant reduction in cardiovascular mortality (RR 0.71; 0.51-0.98; $P = 0.03$) and death from cardiac arrhythmia (RR 0.55; 0.34-0.88; $P = 0.01$). In a post hoc analysis there was a statistically significant reduction in stroke (RR 0.66; 0.46-0.96, $P = 0.03$).[50] There were 473 patients in ATHENA that developed permanent AF: these patients had a similar response to dronedarone therapy as the overall study population with respect to the primary outcome.[51]

The latter observation led to the hypothesis that dronedarone has beneficial effects independent of AF prevention perhaps mediated by ventricular rate-slowing, blood pressure lowering, adrenergic blockade, and/or ventricular fibrillation prevention. This hypothesis was tested in the PALLAS trial; a double-blind, placebo-controlled, parallel group RCT involving higher risk permanent AF patients.[52] The PALLAS trial intended to enrol 10,800 patients during a 2-year period with 1 additional year of follow-up. The trial was prematurely terminated for safety reasons after enrolment of 3236 patients. PALLAS had 2 coprimary outcomes; the composite of stroke, MI, STE, or death from cardiovascular causes (termed the first coprimary outcome) and the composite of death or first unplanned cardiovascular hospitalization (the second coprimary outcome). After a median follow-up of 3.5 months, there were increases in the first coprimary outcome from 1.2% in the placebo group to 2.7% in the dronedarone group (RR 2.29; 1.34-3.94, $P = 0.002$) and in the second coprimary outcome from 4.1% (placebo group) to 7.8% (dronedarone group; RR 1.95; 1.45-2.62; $P < 0.001$). The composites included statistically significant increases in first unplanned cardiovascular hospitalization (RR 1.97; 1.44-2.70; $P < 0.001$), first unplanned heart failure hospitalization (RR 1.97; 1.44-2.70; $P < 0.001$), death from any cause (RR 1.81; 1.10-2.99; $P = 0.05$), stroke (RR 2.32; 1.11-4.88; $P = 0.02$), and a statistically nonsignificant increase in ACS (RR 1.89; 0.80-4.45; $P = 0.14$).

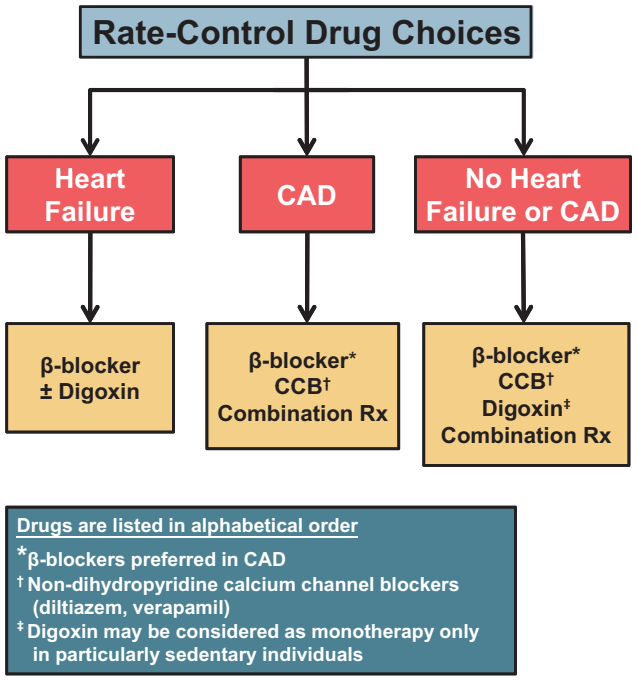

Figure 3. Summary of recommendations for choice of rate-control agents for various conditions. CAD, coronary artery disease; CCB, calcium channel blocking agents; Rx, therapy.

There was also a statistically significant increase in any reported liver function abnormality from 1.7% in the placebo group to 3.8% in the dronedarone group ($P < 0.001$). Acute liver injury has also been reported in the postmarket release experience with the drug.[53]

The results of PALLAS thus stand in stark distinction to those of ATHENA. The mechanism for this dichotomy has not been determined. Working on the premise that both results are valid for their respective populations, considerations of potential mechanisms for this dichotomy have focused on differences between the 2 study populations. One clear difference is that ATHENA enroled patients with paroxysmal or persistent AF/AFL while PALLAS enroled patients with permanent AF/AFL. Accordingly, dronedarone should not be used in patients with permanent AF/AFL for the purpose of rate control. This is a change from the 2010 version of the guidelines in which dronedarone was listed as a second-line choice for rate control (see Fig. 3 for an updated rate-control guideline schema).

PALLAS patients were also significantly older, with a higher proportion of males and a higher prevalence of CAD compared with ATHENA. Of particular note, PALLAS patients were more likely to have symptomatic congestive heart failure (54% vs 21%), a left ventricular ejection fraction ≤ 0.40 (21% vs less than 12%), and were more likely to be receiving concomitant therapy with digoxin (33% vs 14%). Considering the magnitude of each of these differences, and the prior results of the **An**tiarrhythmic Trial With **Dro**nedarone in **M**oderate to Severe Congestive Heart Failure **E**valuating Morbidity **D**ecrea**s**e (ANDROMEDA) showing increased mortality in patients with severe heart failure and left ventricular dysfunction,[54] dronedarone should not be used in patients with a history of heart failure symptoms or a left ventricular ejection fraction < 0.40. PALLAS showed that dronedarone significantly increases

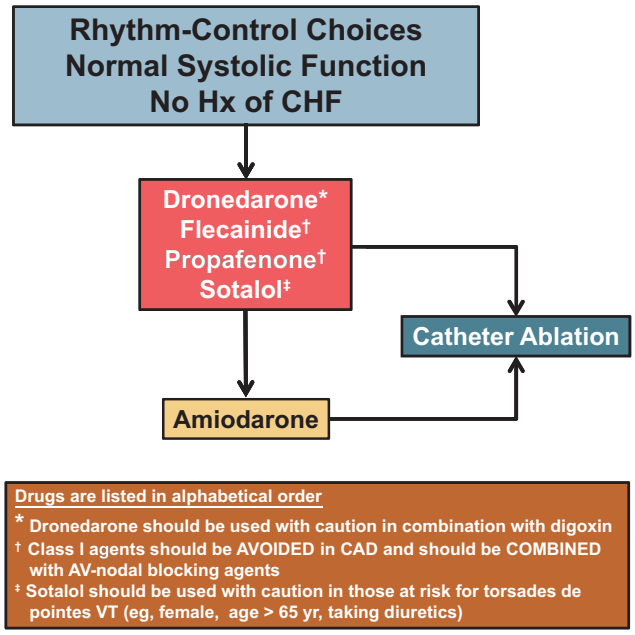

Figure 4. Summary of recommendations for choice of rhythm-control therapy in patients with normal systolic left ventricular function and no history of congestive heart failure. AV, atrioventricular; CAD, coronary artery disease; CHF, congestive heart failure; Hx, history; VT, ventricular tachycardia.

serum digoxin concentrations and data to be published soon will demonstrate a particular increase in harm from the interaction of dronedarone and digoxin. There are 3 new recommendations that were not a part of the 2010 version of the guidelines.[55] (See Figs. 4 and 5 for updated rhythm-control drug recommendations).

RECOMMENDATION

We recommend that dronedarone not be used in patients with permanent AF nor for the sole purpose of rate control (Strong Recommendation, High-Quality Evidence).

We recommend dronedarone not be used in patients with a history of heart failure or a left ventricular ejection fraction $\leq$ 0.40 (Strong Recommendation, Moderate-Quality Evidence).

We suggest dronedarone be used with caution in patients taking digoxin (Conditional Recommendation, Moderate-Quality Evidence).

Values and preferences. These recommendations recognize that the mechanism(s) for the differences between the results of the ATHENA and the PALLAS trials have not yet been determined. These recommendations are based on the known differences between the 2 patient populations and are also informed by the results of the ANDROMEDA trial.

Based on this new evidence, it has become clear that dronedarone, like all antiarrhythmic drugs, has important risks and limitations. These risks and limitations are important determinants in choosing an agent and are highlighted throughout the guidelines. For example, flecainide and propafenone should be avoided in patients with atherosclerotic heart disease and heart failure. Sotalol is used with caution in patients at risk of QT-interval prolongation and torsades de pointes, and amiodarone is used with caution because of its risk of long-term noncardiac side effects. Like the other available agents, dronedarone remains a useful antiarrhythmic drug option for appropriately chosen AF patients. These considerations are reflected in the Practical Tip below and are summarized in Figures 4 and 5.

Practical tip. Dronedarone is a reasonable choice for rhythm control in selected patients with AF. Typically, these would be patients with nonpermanent (predominantly paroxysmal) AF with minimal structural heart disease. Consideration should be given to monitoring for liver enzyme elevations within 6 months of initiating therapy with dronedarone.

Updated choices for rate control

It is generally assumed that "uncontrolled AF" is undesirable, because it may lead to worsened symptoms and an increased risk of heart failure. Atrioventricular nodal blocking drugs are administered on the assumption that a slower ventricular response leads to improved subjective and objective outcomes. The 2010 Guidelines emphasize the lack of evidence for this concept, and the revised resting ventricular rate target for AF patients is now set at 100 beats per minute or less.[55]

Either β-blocking drugs or nondihydropyridine calcium channel-blocking drugs (diltiazem, verapamil) can be used to achieve ventricular rate control. Although some new data have become available, there remains insufficient evidence to routinely recommend 1 agent over another. β-blockers are generally more "effective" at slowing ventricular rates both at rest and during exercise than calcium channel blockers, but their use is associated with a higher risk of adverse effects, primarily fatigue and exercise intolerance.[56-58] In a combined analysis of randomized trials of β-blockers and calcium channel blockers

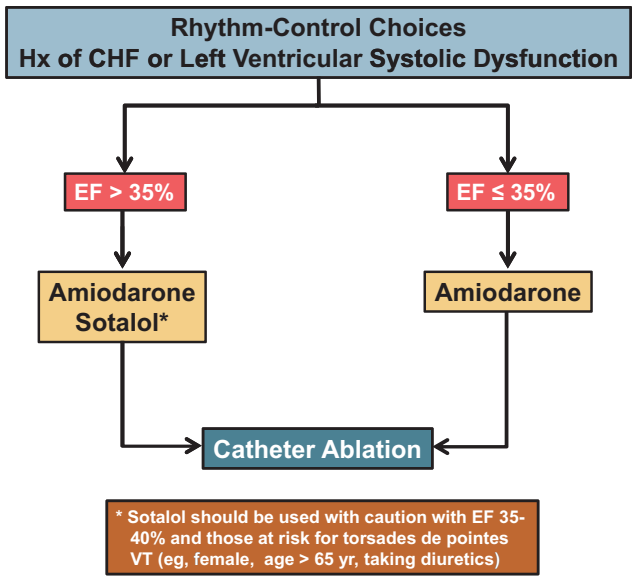

Figure 5. Summary of recommendations for choice of rhythm-control therapy in patients with a history of congestive heart failure (current or remote) or left ventricular systolic dysfunction. CHF, congestive heart failure; EF, ejection fraction; Hx, history; VT, ventricular tachycardia.

vs placebo or digoxin or for rate control in AF, β-blocker use did not improve exercise tolerance during AF in any study, and led to a reduction in maximum exercise capacity in a minority of studies.[58] Conversely, rate-slowing calcium channel blockers did not reduce exercise tolerance in any of the studies, and resulted in improved exercise tolerance in a substantial proportion.

An additional consideration in selection of drugs for rate control is the Canadian Hypertension Education Program recommendation not to use β-blockers as initial antihypertensive therapy in patients older than 60 years.[59] Because 60%-80% of patients with AF have hypertension as a cause or comorbidity, it seems reasonable to use a long-acting, rate-slowing calcium channel blocker for both hypertension and rate control, adding other agents (eg, an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or diuretic) if necessary to achieve recommended blood pressure targets.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca, and at doi: 10.1016/j.cjca.2012.01.021.