

# The 2014 Atrial Fibrillation Guidelines Companion: A Practical Approach to the Use of the Canadian Cardiovascular Society Guidelines

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## ABSTRACT

The Canadian Cardiovascular Society (CCS) Atrial Fibrillation Guidelines Program has generated a comprehensive series of documents regarding the management of atrial fibrillation (AF) between 2010 and 2014. The guidelines provide evidence-based consensus management recommendations in a broad range of areas. These guidelines have proven useful in informing clinical practice, but often lack detail in specifications related to practical application, particularly for areas in which the evidence base is limited or conflicting. Based on feedback from the community, the CCS Atrial Fibrillation Guidelines Committee has identified a number of areas that require clarification to address commonly asked practical questions related to guidelines application. In the present article a number of such questions are presented and suggestions about how they can be answered are suggested. Among the issues considered are: (1) What duration of AF is clinically significant? (2) How are the risk factors in the CCS Algorithm for selecting anticoagulation therapy derived and defined? (3) How is valvular heart disease defined and how do different forms of valve disease affect the choice of anticoagulant therapy for AF patients? (4) How should we quantify renal dysfunction and how does it affect therapeutic choices? The response to these questions and the underlying logic are provided, along with an indication of future research needed where no specific approach can presently be recommended based on the literature.

The Canadian Cardiovascular Society (CCS) Atrial Fibrillation Guidelines Program has generated a comprehensive document regarding the management of atrial fibrillation (AF) in 2010, with subsequent focused updates to address clinically important advances in 2012 and 2014.<sup>1-3</sup> These documents contained evidence-based and formal recommendations according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria, with “Practical Tips” to guide implementation. Based on feedback from the community, we identified areas that require clarification to addresses commonly asked practical questions related to clinical application of the guidelines. In this document we address these issues with a question and answer format. The responses use published evidence whenever possible, but where evidence is limited we have relied on the expertise of the CCS Atrial Fibrillation Guidelines Panel (see [Supplemental Appendix S1](#) for a list of panel members) to provide practical guidance.

### What Duration of AF Is Clinically Significant?

The detection of an irregularly irregular heart rhythm on heart rhythm monitoring (eg, via ambulatory electrocardiogram [ECG] or implantable electronic device) suggests a diagnosis of AF.

There is extensive evidence for a relationship between the duration of AF paroxysms and stroke risk.<sup>4,5</sup> Oral anticoagulation with vitamin-K antagonists or a novel nonvitamin K antagonists (NOACs) reduce stroke risk, but carry the disadvantages of increased risk of bleeding, cost, and/or a need for monitoring. Therefore, it would be useful to define a standard arrhythmia duration for the diagnosis of AF, and to justify the initiation of stroke prevention therapy.

AF duration of 30 seconds (or for the duration of the ECG recording if the duration is < 30 seconds) is commonly used for the arrhythmic diagnosis of AF.<sup>6</sup> Similarly, the stroke prevention literature commonly uses a minimum AF duration of 30 seconds before cryptogenic stroke is attributed to AF.<sup>7,8</sup> Accordingly, the CCS Atrial Fibrillation Guidelines primary panel concluded that a duration of 30 seconds or more of continuous AF should be required for diagnostic purposes.

However, the minimum duration of AF that justifies prophylactic antithrombotic therapy, particularly oral anticoagulation, is less clear. The CCS Atrial Fibrillation Guidelines panel made a conditional recommendation that oral anticoagulation be initiated in patients with subclinical AF lasting > 24 hours and 1 or more CCS Algorithm risk factors.<sup>3</sup> However, clinical studies have shown that even brief episodes of AF might be associated with increased stroke risk. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) study found that  $\geq 6$  minutes of atrial tachyarrhythmia detected using pacemaker surveillance over 3 months is associated with an increased stroke risk (hazard ratio [HR], 2.49; 95% confidence interval [CI], 1.28- 4.85), although the absolute risk was lower than those found in epidemiological studies of patients with a clinical diagnosis of AF.<sup>5</sup> A quartile analysis of the ASSERT data found that stroke risk increased substantially among patients with episodes > 3.64 hours in duration. A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics (TRENDS) study similarly suggested a clinically relevant increase in stroke risk to 2.4% per year in patients with a total atrial tachycardia/AF duration of > 5.5 hours on any given day in the preceding 30 days in a patient population with a mean Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack (CHADS<sub>2</sub>) score of 2.2.<sup>4</sup> These studies indicate that the stroke risk increases substantially with AF durations of several hours or more.

Of course, duration of AF and the presence of risk factors influence the risk of stroke. In a patient with a high CHADS<sub>2</sub> score, even brief episodes of AF might justify stroke prevention therapy. This consideration has been incorporated into proposed intervention algorithms, such as those proposed by Botto et al.,<sup>9</sup> and Boriani et al.<sup>10</sup> Although these algorithms are based on limited data and are not definitive, they illustrate how the practitioner might integrate patient-specific risk (bleeding and stroke) with AF duration to inform clinical decision-making.

However, in the absence of any controlled trial data, no evidence-based cutoff can be identified for the AF duration that merits oral anticoagulation. Clearly, further evidence is needed to unambiguously determine the contributions of AF duration and CHADS<sub>2</sub> score to risk of stroke.

### **How Were the Risk Factors in the CCS Algorithm Derived?**

The accuracy of various schemas for the prediction of stroke risk in patients with nonvalvular AF (NVAF), the validity of their individual components for estimation of annual stroke incidence, and differences among national guidelines with respect to their recommendations for antithrombotic therapies are actively debated.<sup>11-13</sup> Accordingly, it is timely to review the origins of the most widely used risk prediction schemas and the data underlying recommendations for antithrombotic therapies.

Analyses based on the Framingham cohort and subsequent randomized clinical trials revealed that NVAF is an independent risk factor for stroke, with an annual incidence of approximately 4.1%-4.5%,<sup>14</sup> and a combined risk of stroke and systemic embolism of 5.0%.<sup>15</sup> Because the net benefit of aspirin and warfarin for stroke prevention is mitigated by an enhanced risk of major bleeding, investigators have attempted to delineate stroke risk factors in specific NVAF patient subgroups to allow the estimation of risk-benefit ratios in individual patients. The Stroke Prevention in Atrial Fibrillation (SPAF) trials investigators found that age, previous stroke, congestive heart failure (CHF), and hypertension independently predicted the annual incidence of stroke over a range from 0.9% to 20%.<sup>16</sup> The Atrial Fibrillation Investigators (AFI), used data from the control groups of randomized controlled trials (RCTs) of warfarin, and found independent associations with stroke risk for the same risk predictors and for that of diabetes mellitus, with annual stroke rates ranging from 1.0% to 8.1%.<sup>15</sup> The findings from these 2 studies were integrated as the CHADS<sub>2</sub> index, and validated to predict stroke risk.<sup>17</sup>

Subsequently the Congestive Heart Failure, Hypertension, Age (>75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age (65-74 years), Sex (Female) (CHA<sub>2</sub>DS<sub>2</sub>-VASc) schema, which incorporated refinements of previously determined risk factors and added vascular disease and female sex, was validated,<sup>18,19</sup> has been widely implemented,<sup>20</sup> and has evolved since its initial validation.<sup>21</sup> The CCS Atrial Fibrillation Guidelines update in 2012 recommended use of the CHADS<sub>2</sub> schema,<sup>2</sup> but differentiated among patients at low risk based on interpretations of risk factors derived from the CHA<sub>2</sub>DS<sub>2</sub>-VASc validations.<sup>22</sup> In the 2014 update of the CCS guidelines, a simplified schema for risk prediction, the CCS Algorithm, was recommended for selection of antithrombotic therapies (Fig. 1).<sup>3</sup>

Although the recommendations of various guidelines groups for antithrombotic therapies are in general agreement about patients with moderate to high risk of stroke, there is greater variation for patients at lower stroke risk. There is also variation in the choice of stroke risk schema<sup>3,21,23,24</sup> and in the selection and interpretation of data on the stroke risk associated with individual components of overall stroke risk.<sup>11,13</sup>

### Definitions of risk factors

The original definitions of the individual components of the various risk prediction schemas are provided in [Supplemental Table S1](#). These definitions were largely determined by the information in the databases from which the various risk prediction schemas were derived.

**CHF.** The definition of CHF differs substantially among schemas, with a tendency for broader inclusion criteria in more recent versions. In the SPAF trials,<sup>16</sup> the diagnosis of CHF was based on standard clinical and radiological criteria. In the AFI publication,<sup>15</sup> CHF was defined based on the definitions used in each of the 5 stroke prevention trials. When the results of the SPAF and AFI analyses were integrated into the original CHADS<sub>2</sub> schema and validated in the National Registry of Atrial Fibrillation database, CHF was defined based on hospitalization with a primary diagnosis of CHF (using International Classification of Diseases, Ninth Revision, Clinical Modification codes) within the preceding 100 days.<sup>17</sup> When the CHA<sub>2</sub>DS<sub>2</sub>-VASc schema was developed, CHF was broadly defined as presence of signs and symptoms of right and/or left ventricular heart failure combined with objective evidence of cardiac dysfunction.<sup>18</sup> When the European Society of Cardiology (ESC) AF guidelines were updated in 2012, the definition of CHF was broadened even further: documented moderate to severe systolic dysfunction, or recent heart failure that required hospitalization irrespective of ejection fraction. It is not clear whether the evolved definition had been further

validated,<sup>21</sup> although ejection fraction has not been shown to predict stroke events in heart failure patients.<sup>25</sup>

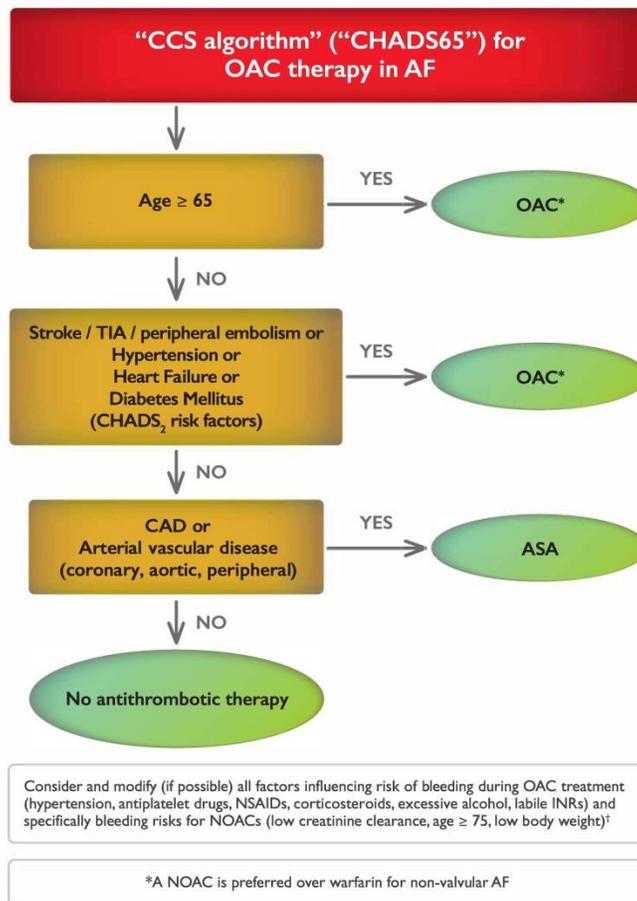
**Hypertension.** In the SPAF trials and in the AFI publication, hypertension was defined as a systolic blood pressure > 160 mm Hg at randomization.<sup>15,16</sup> When the results of the SPAF trials and AFI analyses were integrated into the original CHADS<sub>2</sub> index, hypertension was simply defined as a history of hypertension.<sup>17</sup> When the CHA<sub>2</sub>DS<sub>2</sub>-VASc schema was developed, hypertension was defined as a resting blood pressure > 140 mm Hg systolic and/or > 90 mm Hg diastolic on at least 2 occasions, or current antihypertensive drug treatment.<sup>18</sup> This definition appears to have remained unchanged.

**Age.** Although the definition of age does not vary among the schemas, the reliability of the values assigned depends on the rigour of the applicable derivation and validation cohorts. The National Registry of Atrial Fibrillation database used to define and validate the CHADS<sub>2</sub> schema included only patients aged ≥ 65 years who were eligible for Medicare.<sup>17</sup> Accordingly, older age was determined to be 75 years or older compared with the rest of the database aged 65 to 74 years, and the risk of patients ≥ 65 years old vs < 65 years of age could not be considered. The CHA<sub>2</sub>DS<sub>2</sub>-VASc schema was developed and validated in databases of patients aged ≥ 20 years.<sup>18</sup> Accordingly, the increased risk of patients ≥ 65 years old was identified and incorporated.

**Diabetes.** The definition of diabetes mellitus in the SPAF trials, the AFI publication, and the CHADS<sub>2</sub> index was simply a history of, or ongoing pharmacological treatment for diabetes mellitus. Diabetes mellitus was more rigorously defined in the CHA<sub>2</sub>DS<sub>2</sub>-VASc schema<sup>18</sup> as fasting plasma glucose concentration ≥ 7.0 mmol/L, or treatment with oral hypoglycemic agents and/or insulin. This definition has since remained unchanged.

**Stroke.** The inconsistent definition of previous stroke has the potential to contribute substantially to variability among the risk schemas. The SPAF trials included previous ischemic stroke and/or systemic thromboembolism, but not transient ischemic attack (TIA).<sup>16</sup> In the AFI publication the definition included previous ischemic stroke or TIA, but not previous systemic embolism.<sup>15</sup> When the results of the SPAF and AFI analyses were integrated into CHADS<sub>2</sub>, the definition included previous ischemic stroke or TIA.<sup>17</sup> The original CHA<sub>2</sub>DS<sub>2</sub>-VASc schema defined “stroke” as the composite of ischemic stroke, TIA, peripheral embolism, and pulmonary embolism.<sup>18</sup> Publications by Lip and colleagues emphasize the uncertainties caused by variable definitions of thromboembolism as a risk factor and as an outcome.<sup>11,12</sup>

Variations among risk schemas in the definitions of their component risk factors over time are not likely to result in major differences in the categorization of patients into low, medium, and high risk for stroke. However, they might be important in the calculation of the annual stroke risk, and to influence specific anticoagulation recommendations for patients at relatively low risk of stroke (0.5%-2% per year).



**Figure 1.** The simplified "CCS algorithm" ("CHADS65") for deciding which patients with atrial fibrillation (AF) or atrial flutter (AFL) should receive oral anticoagulation (OAC) therapy. It recommends OAC for most patients  $\geq 65$  years and for younger patients with a CHADS<sub>2</sub> score  $\geq 1$ ; aspirin (ASA) for patients  $< 65$  years with CHADS<sub>2</sub> score = 0 with arterial vascular disease (coronary, aortic, or peripheral); and no antithrombotic therapy for patients  $< 65$  years with a CHADS<sub>2</sub> score = 0 and no arterial vascular disease. Bleeding risks should be modified whenever possible. A non-vitamin K antagonist oral anticoagulant (NOAC) is recommended in preference to warfarin for OAC therapy in non-valvular AF patients.

### Validation of Risk Prediction Schema

The CHADS<sub>2</sub> index was validated in a cohort of 1733 US Medicare recipients aged 65-95 years, who had nonrheumatic AF documented during an index hospitalization, and who were not prescribed warfarin at hospital discharge.<sup>17</sup> Patients were followed for a median of 1 year for the outcome of hospitalization for ischemic stroke or TIA.

Subsequently, the CHADS<sub>2</sub> index and CHA<sub>2</sub>DS<sub>2</sub>-VASc schema have been validated in a cohort of patients in the EuroHeart Survey aged  $\geq 18$  years, who were free of mitral stenosis or previous heart valve surgery, had AF on ECG or Holter monitor during a qualifying hospital admission or consultation, were not receiving a vitamin K antagonist (VKA) or heparin at the qualifying visit, and whose survival and thromboembolism outcome status was known after 1

year.<sup>18</sup> Patients were followed for 1 year for thromboembolism, defined as any one of ischemic stroke (focal neurological deficit of sudden onset diagnosed by a neurologist, lasting > 24 hours and caused by ischemia), peripheral embolism (thromboembolism outside of the brain, eyes, heart, and lungs), or pulmonary embolism (defined by the responsible physician). Additionally, they have been validated in a cohort of 7329 patients randomized to ximelagatran or warfarin in the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) 3 and 5 trials, and in a large Danish national registry.<sup>19,22</sup> This cohort of 73,538 patients had a hospital discharge diagnosis of AF or atrial flutter, no previous diagnosis of mitral or aortic valve disease, no previous mitral or aortic valve surgery, and no VKA or heparin therapy from 180 days before discharge to 7 days after discharge.<sup>22</sup> Patients were followed for up to 10 years for hospitalization or death due to ischemic stroke, peripheral artery embolism, or pulmonary embolism. The receiver operating characteristic of these risk schemas vary somewhat, with the CHA<sub>2</sub>DS<sub>2</sub>-VASc providing marginally better risk prediction (c-statistics) and capacity to discriminate within low risk patient groups (eg, patients with a CHADS<sub>2</sub> score of 0 or 1).

A 2012 Swedish cohort, including 90,490 patients from the national patient registry followed until 2008 for the occurrence of either ischemic stroke or the composite of ischemic stroke, unspecified stroke, TIA, or systemic embolism compared the predictive value of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc for stroke prediction and the Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly (>65 Years), Drugs/Alcohol Concomitantly (HAS BLED) and Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older (Age > 75 Years), Reduced Platelet Count or Function, Rebleeding Risk, Hypertension (Uncontrolled), Anemia, Genetic Factors, Excessive Fall Risk, and Stroke (HEMORR<sub>2</sub>HAGES) schemas for bleeding risk.<sup>26</sup> A subsequent 2014 Swedish cohort included 140,420 patients, with documented NVAF at the time of a visit to a hospital or a hospital-affiliated open clinic between 2005 and 2010 who had not been exposed to a VKA at any time during follow-up and were followed until 2010 for the occurrence of ischemic stroke, systemic embolism, pulmonary embolism, or TIA.<sup>27</sup> The principal goal of this study was to relate rates of ischemic stroke to CHA<sub>2</sub>DS<sub>2</sub>-VASc score and the effect on outcome rates of the progressive addition of unspecified stroke plus systemic embolism, then pulmonary embolism, and then TIA. The addition of unspecified stroke and systemic and pulmonary embolism increased the event rate by 25% and the further addition of TIAs increased the event rate by a cumulative 44%. The annual rate of ischemic stroke for patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc = 1 was only 0.5%, compared with the rate of thromboembolism of 1.5% in the Danish study.<sup>22</sup> The differences are due in part to the exclusion by the Swedish group of nonspecific stroke, systemic embolism, and pulmonary embolism.

Finally, a Taipei cohort included 186,570 patients aged ≥ 20 years with AF (hospital discharge diagnosis or confirmed more than twice as an outpatient between 1996 and 2011) who were followed to the end of 2011 for the occurrence of ischemic stroke (confirmed using computed tomography or magnetic resonance imaging).<sup>28</sup> In men with a CHA<sub>2</sub>DS<sub>2</sub>-VASc of 0 or 1 and women with a score of 1 or 2, the rates of stroke in each of the risk categories were generally higher than in the Danish and Swedish validation cohorts.

**Table 1. Definitions of stroke risk factors in the Canadian Cardiovascular Society Atrial Fibrillation Guidelines update**

<b>Factor</b>	<b>Definition</b>
<b>Congestive Heart Failure</b>	Documented moderate to severe systolic dysfunction; signs and symptoms of heart failure with reduced ejection fraction; or recent decompensated heart failure that required hospitalization irrespective of ejection fraction
<b>Hypertension</b>	Resting blood pressure > 140 mm Hg systolic and/or > 90 mm Hg diastolic on at least 2 occasions or current antihypertensive pharmacological treatment
<b>Age 65</b>	Age ≥ 65 years
<b>Diabetes mellitus</b>	Fasting plasma glucose concentration ≥ 7.0 mmol/L (126 mg/dL) or treatment with oral hypoglycemic agents and/or insulin
<b>Stroke/transient ischemic attack /peripheral embolism</b>	Ischemic stroke: focal neurologic deficit of sudden onset diagnosed by a neurologist, lasting > 24 hours, and caused by ischemia; Transient ischemic attack: focal neurological deficit of sudden onset diagnosed by a neurologist, lasting < 24 hours; Peripheral embolism: thromboembolism outside the brain, heart, eyes, and lungs, or pulmonary embolism (defined by the responsible physician)
<b>Vascular Disease</b>	Coronary artery disease, peripheral artery disease, or aortic plaque

### What Are the Definitions of Stroke Risk Factors in the CCS Atrial Fibrillation Guidelines Update?

The 2014 CCS Atrial Fibrillation Guidelines update used the CHADS<sub>2</sub> index with the evolved definitions of its component risk factors for stroke (termed the CCS Algorithm).<sup>3</sup> The evolved definitions were not explicitly stated in the CCS Atrial Fibrillation Guideline update and are now detailed in [Table 1](#). Female sex was not considered to be an independent risk factor, in agreement with the ESC 2012 guidelines.<sup>21</sup>

The estimates for annual risks of the outcome of “stroke” used in the 2014 CCS update were taken from the 5-year follow-up data of the Danish validation cohort<sup>22</sup> as follows: age 65-74 years (2.13%), age ≥75 years (4.37%), CHF (2.35%), hypertension (1.60%), diabetes (2.28%), previous stroke (7.87%), vascular disease (1.40%), and female sex (0.86%). These are summarized in [Table 2](#). The 2014 CCS panel concluded that oral anticoagulant therapy was justified when the annual risk of the outcome of “stroke” (using the event of thromboembolism precipitating hospitalization or death as defined in the Danish cohort) exceeded 1.5%. Accordingly, the CCS Algorithm ([Fig. 1](#)) recommended oral anticoagulation for patients aged ≥ 65 (even without any other criteria) and for younger patients with any of CHF, hypertension, diabetes, or stroke as defined in [Table 1](#). Acetylsalicylic acid was recommended for patients with vascular disease as the only risk factor. No antithrombotic therapy was recommended for patients with none of these criteria.

## AF and Valvular Heart Disease

### What is the current definition of NVAf?

The term “nonvalvular AF” has been used for at least 35 years<sup>29</sup> but has never been satisfactorily defined. In the 1950s, observational reports suggested that AF was associated with a very high risk of thromboembolic events in patients with rheumatic mitral stenosis, the most common form of chronic valvular heart disease (VHD) at the time. Further reports suggested that this risk could be reduced with the use of a VKA.<sup>30,31</sup> In the late 1970s and early 1980s it was recognized that AF was independently associated with stroke, even in the absence of rheumatic mitral stenosis, and such patients came to be referred to as having “nonrheumatic AF” or “NVAf.”<sup>29</sup>

Because patients with rheumatic mitral stenosis or a mechanical prosthetic valve were considered to require VKA therapy, they were excluded from the randomized trials of antithrombotic therapy for stroke prevention in patients with AF.

However, although these trial subjects were referred to collectively as having either “nonrheumatic” or “nonvalvular” AF, some patients with valvular disease other than mitral stenosis or with a bioprosthetic valve were enrolled. These uncertainties translate into varying definitions of “NVAf.” Although the increased risk of stroke in patients with AF associated with “valvular heart disease” is well recognized (relative risk of thromboembolic events, 3.2; 95% CI, 2.6-3.8, and death 2.5; 95% CI, 2.2-2.7),<sup>32</sup> the precise distinction between “valvular” and “nonvalvular” AF varies among the trials of oral anticoagulation therapy (Table 3), and among the AF guidelines of major societies.

The present CCS Atrial Fibrillation Guidelines define valvular AF as that occurring in a patient with “rheumatic mitral stenosis, mitral valve repair, mechanical or bioprosthetic heart valve.”<sup>3</sup> This definition is the same as the definition used in the 2014 American College of Cardiology/ American Heart Association/Heart Rhythm Society guidelines.<sup>23</sup> However, the CCS Atrial Fibrillation Guidelines definition differs slightly from that used by the ESC AF guidelines of 2012, which defines valvular AF as that occurring in a patient with “rheumatic valvular disease (predominantly mitral stenosis) and prosthetic heart valves.”<sup>21</sup> Previous iterations of the ESC AF guidelines included clinically significant mitral regurgitation (MR) as part of the definition but this entity was not specifically included in the 2012 ESC AF guidelines update.<sup>38</sup>

**Table 2. Event rates (95% CI) and hazard ratios for hospital admission and death due to thromboembolism according to components of CHA<sub>2</sub>DS<sub>2</sub>-VASc score at 5-years follow-up**

Risk Factor	Annual Risk (95% CI)	Hazard Ratio (95% CI)	P
CHA <sub>2</sub> DS <sub>2</sub> -VASc = 0	0.69 (0.59-0.81)	1.0	
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc = 1</b>			
- Heart failure	2.35 (1.30-4.24)	3.39 (1.84-6.26)	< 0.0001
- Diabetes mellitus	2.28 (1.42-3.66)	3.31 (2.00-5.46)	< 0.0001
- Hypertension	1.60 (1.26-2.01)	2.32 (1.75-3.07)	< 0.0001
- Age 65-74	2.13 (1.85-2.46)	3.07 (2.48-3.80)	< 0.0001
- Vascular disease	1.40 (0.91-2.15)	2.04 (1.29-3.22)	0.002
- Female sex	0.86 (0.70-1.06)	1.25 (0.96-1.63)	0.10

CHA<sub>2</sub>DS<sub>2</sub>-VASc, Congestive Heart Failure, Hypertension, Age (≥75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age (65-74 years), Sex (Female); CI, confidence interval. Modified from Olesen et al.<sup>22</sup> with permission from BMJ Publishing Group Ltd.

### Which types of valvular AF presently exclude the use of a NOAC?

Irrespective of the presence of AF, patients with mechanical heart valves are at increased risk for thromboembolism. In the absence of anticoagulation, patients with mechanical heart valves but no AF have an annual estimated rate of stroke or systemic thromboembolism of 4.0%, which is similar to that reported in AF patients without valvular disease.<sup>39</sup> Although this risk is modulated by several factors such as age, comorbidity, prosthetic valve type, prosthetic valve location, and number of prosthetic valves, the risk of thromboembolism increases substantially in patients with mechanical heart valves and coexistent AF.<sup>40</sup> The sites for thromboembolism in patients with AF and a mechanical prosthetic valve are multiple, and include the prosthesis (sewing ring, struts, or leaflets), the body of the left atrium, and the left atrial appendage.

In the absence of AF, VKA therapy decreases the risk of prosthetic valve thromboembolism from 4% per year to <1% per year.<sup>39</sup> The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxilate in Patients After Heart Valve Replacement (REALIGN) study randomized patients with mechanical heart valves 1:2 to warfarin or dabigatran (150 mg, 220 mg, or 300 mg twice daily [bid], based on renal function).<sup>41</sup> The trial was terminated early because of an excess of thromboembolic and bleeding events in the dabigatran treatment group: in the dabigatran group, stroke and major bleeding occurred in 9 (5%) and 7 (4%) patients respectively, vs 0 (0%) and 2 (2%) of warfarin-treated patients. It was postulated that thrombin generation triggered by exposure of blood to the artificial surface of the valve might have overwhelmed the local effects of dabigatran. Thus, a VKA remains the treatment of choice for AF patients with mechanical heart valves.

### Mitral stenosis

Rheumatic mitral stenosis is the form of native VHD that, when accompanied by AF, is associated with the highest risk of stroke and systemic embolism. In the preanticoagulant era it was estimated that 22% of patients with rheumatic mitral stenosis died from thromboembolic complications.<sup>42,43</sup> Many of these embolic events occurred early (one-third within 1 month of AF onset, and two-thirds within 1 year), and with a high risk of recurrence.<sup>42,43</sup> Unfortunately, embolism can be the first manifestation of mitral stenosis, even when it is mild.<sup>44</sup>

AF that occurs in patients with mitral annular calcification has also been associated with a fivefold increase in the adjusted relative risk of stroke, whereas the risk of stroke is doubled by either AF or annular calcification alone.<sup>45</sup>

There have been no randomized trials of anticoagulation for prevention of thromboembolic events in patients with mitral stenosis, but retrospective studies have suggested a 4- to 15-fold decrease in the incidence of embolic events with anticoagulation.<sup>46</sup> Accordingly, mitral stenosis remains a clear indication for anticoagulation. Because such patients were excluded from the pivotal randomized trials of NOACs for stroke prevention, VKAs remain the standard of care in this patient population until further evidence emerges.

### Do other types of valvular AF confer an increased risk of stroke?

Unfortunately, beyond rheumatic mitral stenosis and of mechanical heart valves, there is substantial uncertainty regarding the risk of AF-related thromboembolism with other forms of VHD.

**Native VHD.** Other forms of native VHDs, such as nonrheumatic MR (due to mitral valve prolapse, chordal or papillary muscle dysfunction, and mitral annular dilatation), aortic stenosis or insufficiency, and tricuspid insufficiency have not been associated with increased risks of thromboembolism beyond that expected of the AF itself.<sup>47,48</sup> In the case of MR it is thought that the mitral regurgitant jet might provide some protective effect as it increases flow throughout the left atrium (“washing effect”).<sup>49</sup>

**Bioprosthetic heart valves.** The presence of a bioprosthetic heart valve or a history of valve repair is not an indication for long-term anticoagulation in the absence of other risk factors. However, it is estimated that the risk of thromboembolism in patients with a bioprosthetic heart valve and AF is approximately 5% per year, which is similar to that of an age-matched AF population with traditional stroke risk factors.<sup>50</sup> Whether treatment with a NOAC would be as effective as treatment with a VKA is unknown.

### Can NOACs be used for patients with some types of valvular AF?

Patients with moderate to severe mitral stenosis and with mechanical prosthetic valves were excluded from the pivotal trials of NOAC therapy in patients with AF, in part based on uncertainty that the increased risk of stroke and adverse outcomes were based on thrombogenic mechanisms similar to those of patients with “nonvalvular” AF.

Beyond the exclusion of these 2 populations, the definitions of NVAf in the pivotal trials of NOAC therapy for thromboembolic event prevention varied (Table 3).<sup>33-37</sup> Because of this variability, post hoc analyses have been performed to evaluate the efficacy of these agents in patients with VHD. These are summarized in Table 4.

In the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, which evaluated dabigatran, 3950 patients (21.8% of the trial population) had concomitant VHD (3101 patients with MR, 1179 patients with tricuspid regurgitation, 817 patients with aortic regurgitation, 471 patients with aortic stenosis, and 193 patients with mitral stenosis).<sup>51</sup> Patients with VHD had comparable risks of stroke and systemic embolism, but were at higher risk of death and of major bleeding ( $P \leq 0.002$ ), compared with patients without VHD. However, patients with VHD benefitted similarly from dabigatran therapy compared with warfarin with respect to the primary efficacy outcome of stroke or systemic thromboembolism, and showed a similar trend toward less major bleeding.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which evaluated apixaban, 4808 patients (26.4%) had concomitant VHD (3526 with MR, 2124 with tricuspid regurgitation, 887 with aortic regurgitation, 384 with aortic stenosis, 131 with mitral stenosis, and 251 with previous valve surgery).<sup>52</sup> The efficacy and safety of apixaban in patients with VHD were no different from those of patients without VHD. The favourable profile of apixaban vs warfarin was preserved with respect to the primary efficacy outcome of stroke or systemic thromboembolism and with respect to the primary safety outcome of major bleeding.

In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial, which evaluated rivaroxaban, 1992 patients (14.1%) had VHD (89.6% MR with or without aortic stenosis or regurgitation).<sup>53</sup> There were no differences in the efficacy of rivaroxaban between patients with VHD and patients without VHD for stroke and systemic embolism. However, the rates of clinically relevant bleeding were higher in patients with VHD, and were relatively higher with

rivaroxaban vs warfarin. These data suggest that the effects of warfarin and rivaroxaban on thromboembolic outcomes are similar among AF patients with and without significant VHD, whereas bleeding rates might differ.

**Table 3. Summary of definitions of valvular heart disease from the major trials of stroke prevention that used a novel direct oral anticoagulant**

Study	Exclusion Criteria
<b>RE-LY (dabigatran)<sup>33</sup></b>	History of heart valve disorders (ie, prosthetic valve or hemodynamically relevant valve disease)
<b>ROCKET-AF (rivaroxaban)<sup>34</sup></b>	Hemodynamically significant mitral stenosis or prosthetic heart valve Subjects with annuloplasty with or without prosthetic ring, commissurotomy, and/or valvuloplasty, as well as native valve disorders other than mitral stenosis could be included
<b>ARISTOTLE (apixaban)<sup>35</sup></b>	Moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation (eg, a prosthetic heart valve)
<b>AVERROES (apixaban)<sup>36</sup></b>	Valvular disease requiring surgery. Prosthetic mechanical heart valve. Conditions other than atrial fibrillation that required chronic anticoagulation
<b>ENGAGE AF-TIMI 48 (edoxaban)<sup>37</sup></b>	Moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve Subjects with bioprosthetic heart valves and/or valve repair could be included

ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ENGAGE AF-TIMI 48, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; RE-LY, Randomized Evaluation of Long-term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

**Table 4. Efficacy and safety of NOACs vs warfarin in patients with and without significant VHD**

	VHD	No VHD	Interaction <i>P</i>
<b>Stroke or systemic embolism</b>			
- Dabigatran 150 mg vs warfarin	HR, 0.59; 95% CI, 0.37-0.93	HR, 0.67; 95% CI, 0.52-0.86	0.63
- Dabigatran 110 mg vs warfarin	HR, 0.97; 95% CI, 0.65-1.45	HR, 0.88; 95% CI, 0.70-1.10	0.65
- Apixaban vs warfarin	HR, 0.70; 95% CI, 0.51-0.97	HR, 0.84; 95% CI, 0.67-1.04	0.38
- Rivaroxaban vs warfarin	HR, 0.83; 95% CI, 0.55-1.27	HR, 0.89; 95% CI, 0.75-1.07	0.76
<b>Major Bleeding</b>			
- Dabigatran 150 mg vs warfarin	HR, 0.89; 95% CI, 0.68-1.16	HR, 0.99; 95% CI, 0.83-1.17	0.24
- Dabigatran 110 mg vs warfarin	HR, 0.72; 95% CI, 0.54-0.96	HR, 0.85; 95% CI, 0.71-1.02	0.38
- Apixaban vs warfarin	HR, 0.79; 95% CI, 0.61-1.04	HR, 0.65; 95% CI, 0.55-0.77	0.23
- Rivaroxaban vs warfarin	HR, 1.25; 95% CI, 1.05-1.49	HR, 1.01; 95% CI, 0.94-1.10	0.034

CI, confidence interval; HR, hazard ratio; NOAC, novel non-vitamin K antagonist; VHD, valvular heart disease.

#### How do the members of our panel handle the use of NOACs with various forms of VHD?

In the absence of clear evidence, expert opinion was obtained by surveying the 33 members of the primary and secondary panels of the CCS Atrial Fibrillation Guidelines with respect to their advisability of NOAC use in patients with various forms of VHD. These results are presented in [Table 5](#). A strong majority of respondents would avoid NOACs in AF patients with mechanical heart valves or moderate to severe mitral stenosis, and would use them in patients with bioprosthetic valves, postmitral annuloplasty, mitral or tricuspid regurgitation, aortic stenosis and/or regurgitation, and mild nonrheumatic mitral stenosis.

**Table 5. Expert opinion survey regarding the clinical use of a NOAC in relation to the following commonly encountered scenarios: Would you consider NOAC use to be: (1) contraindicated or (2) not contraindicated (ie, reasonable to use) with the following valvular disorders?**

<b>NOAC use is contraindicated</b>	<b>NOAC use is reasonable</b>
<b>Mechanical heart valves</b> <ul style="list-style-type: none"> <li>In any position (100% agreement)</li> </ul>	<b>Bioprosthetic heart valve</b> <ul style="list-style-type: none"> <li>Aortic position (82% agreement)</li> <li>Mitral position (73% agreement)</li> </ul>
<b>Rheumatic mitral stenosis</b> <ul style="list-style-type: none"> <li>Mild (47% agreement)</li> <li>Moderate-severe (88% agreement)</li> <li>After commissurotomy (42% agreement)</li> </ul>	<b>Mitral annuloplasty</b> <ul style="list-style-type: none"> <li>With or without prosthetic ring (88% agreement)</li> </ul> <b>Nonrheumatic mitral stenosis</b> <ul style="list-style-type: none"> <li>Mild (97% agreement)</li> </ul> <b>Mitral regurgitation</b> <ul style="list-style-type: none"> <li>Mild (97% agreement)</li> <li>Moderate-severe (&gt;90% agreement)</li> </ul> <b>Tricuspid regurgitation</b> <ul style="list-style-type: none"> <li>Any severity (98% agreement)</li> </ul>
<b>Non-rheumatic mitral stenosis</b> <ul style="list-style-type: none"> <li>Moderate or severe (69% agreement)</li> </ul>	<b>Aortic stenosis or regurgitation</b> <ul style="list-style-type: none"> <li>Mild (98% agreement)</li> <li>Moderate to severe (80% agreement)</li> </ul>

NOAC, novel non-vitamin K antagonist.

## How Do We Manage NOACs in Patients With Compromised Renal Function?

### How should we measure renal function?

The serum concentration of creatinine, a by-product of the metabolism of creatine and phosphocreatine in skeletal muscle is, in steady state, a fairly reliable indicator of kidney function. Unfortunately, the use of serum creatinine level is limited by its indirect relationship to glomerular filtration. The production of serum creatinine is proportional to muscle mass (which is modified by factors such as sex, age, muscle mass, race, and nutrition), and the clearance of creatinine is influenced not only by glomerular filtration (ie, renal function) but also factors that influence the active secretion of creatinine in the proximal tubule (such as drugs like amiodarone and dronedarone).

Multiple formulae have been developed to correct for creatinine production (ie, muscle mass), and provide a more accurate estimate of overall renal function. The most commonly applied formulae use estimated creatinine clearance (eCrCl; using the Cockcroft-Gault formula), or filtration of creatinine by the glomerulus (estimated glomerular filtration rate [GFR] or eGFR) using either the Modification of Diet in Renal Disease (MDRD) formula or the Chronic Kidney Disease (CKD) Epidemiology Collaboration (CKDEPI) formula.

However, it is important to remember that altered glomerular filtration is not the only factor that can affect drug clearance in the presence of renal dysfunction. Changes in tubular function, and the volume of distribution, albumin concentration, and organic acid accumulation might all influence the risk of drug toxicity. Nevertheless, GFR remains the most appropriate tool for making drug dose adjustment decisions.

### Should we use creatinine clearance or GFR?

The eCrCl and the eGFR measure slightly different things. The eGFR equations (MDRD and CKD-EPI) are more accurate estimates of renal function than is the Cockcroft-Gault eCrCl, which suffers from several limitations. First, it was derived in a limited number of patients (249; 96% male) in 1976 using nonstandardized creatinine assays. The introduction of standardized creatinine assays has resulted in a decline in the measured creatinine level. Although the original creatinine assay is no longer available for direct comparison, it is estimated that the use of values from standardized creatinine assays causes the Cockcroft-Gault formula to overestimate renal function by approximately 5%.

The MDRD equation was derived from 1628 patients with impaired renal function, in a comparison of nonstandardized serum creatinine levels against 125I-iothalamate clearance.<sup>54</sup> Because the MDRD was developed in patients with impaired renal function, it loses precision in patients with normal renal function and might falsely suggest CKD. Similarly, the performance of MDRD is reduced in pregnant patients, patients at the extremes of age, and patients with unusual muscle mass, body habitus, or weight. In distinction to the Cockcroft-Gault formula, the MDRD formula was modified to provide a more accurate estimate of eGFR with the use of standardized creatinine measurements.<sup>55</sup> This updated version of the MDRD formula is the most commonly used eGFR calculation formula in use in Canada.

The CKD-EPI formula was subsequently designed to be as accurate as the MDRD equation at lower renal function, but to have better precision in patients with normal renal function.<sup>56</sup> The CKD-EPI formula was derived from 5504 patients with and without CKD using methodology similar to the MDRD derivation. Given the inclusion of patients with normal renal function the CKD-EPI is more accurate in this population, and classifies fewer patients with normal renal function into the CKD range and provides more accurate categorization of the risks of mortality and end-stage renal disease.<sup>57</sup> Similar accuracy improvements were observed with subpopulations defined according to sex, race, diabetes status, transplant status, age, and body mass index.<sup>58</sup> Some jurisdictions have recently switched from the MDRD to the CKDEPI formula, with a Canada-wide plan for substitution in place.

However, despite the improved accuracy and precision of these newer equations, drug manufacturers have typically used the older Cockcroft-Gault eCrCl method when recommending medication dosage adjustments for patients with renal dysfunction. This preference is a reflection of a key difference between the formulae. Specifically, the eCrCl as measured using Cockcroft-Gault is more of an estimate of the “raw GFR” (ie, the volume of fluid that passes through the glomeruli per unit time), whereas the MDRD and CKD-EPI equations include a body surface area normalization. This differentiating factor is important for drugs that are renally cleared, because their removal will be proportional to the raw GFR rather than the normalized version. Thus, the use of normalized eGFR (MDRD or CKD-EPI) will underestimate drug removal in large people, and overestimate it in smaller people. As a result, the National Kidney Disease Education Program and the Food and Drug Administration have recommended the eGFR estimates (MDRD/CKD-EPI) for evaluation of the progression of renal disease, and reserve the Cockcroft-Gault eCrCl for medication dose adjustments.

### How often should we measure renal function?

Renal function, hemoglobin, and hepatic function should be assessed on an annual basis for stable patients with preserved renal function.

For patients with renal dysfunction, kidney function should be measured every 3 months for patients with an eGFR of 15-30 mL/min, and every 6 months for those with an eGFR of 30-60 mL/min.

In addition, renal function should be monitored during the course of any intercurrent illness that might affect volume or renal status (eg, gastroenteritis, influenza, after surgery); or with the initiation of medications that have the potential to affect renal function (eg, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, mineralocorticoid receptor antagonists, or nonsteroidal anti-inflammatory drug therapy).

### **Should we use lower NOAC doses for patients with an eCrCl of 30-50 mL/min?**

Because a parallel relationship generally exists between NOAC plasma exposure and anticoagulation effects, the extent of renal excretion becomes an important factor to consider. Specifically, up to 80% of circulating dabigatran, 33% of rivaroxaban, and 25% of apixaban is excreted renally, which results in differential accumulation in the drug concentration.<sup>59</sup> As a result, the use of each of the agents in moderate renal dysfunction must be carefully considered.

The only NOAC that was prospectively studied with a reduced dose for patients with moderate renal impairment (eCrCl of 30-50 mL/min) was rivaroxaban.<sup>34</sup> In ROCKETAF 2950 patients (21%) had renal insufficiency. Of those, 1474 were randomized to rivaroxaban 15 mg daily and the remainder were randomized to warfarin. Compared with warfarin, rivaroxaban therapy was associated with a nonsignificant reduction in stroke or systemic embolism with a HR of 0.84 (95% CI, 0.57-1.23). Subgroup analyses did not demonstrate any difference in efficacy or safety outcomes between those with preserved renal function (eCrCl > 50 mL/min) who received the higher rivaroxaban dose (20 mg daily), and those with moderate renal impairment who received the lower rivaroxaban dose (15 mg daily).<sup>60</sup> This observation validated previous pharmacokinetic analyses that suggested that a dose adjustment to 15 mg daily would compensate for the increase in rivaroxaban exposure because of the decreased renal function (from > 50 mL/min to 30-50 mL/min).

In the ARISTOTLE study (which evaluated apixaban) patients were excluded if their eCrCl was < 25 mL/min; however, the criteria for dose reduction relied on an age criterion (>80 years), a weight criterion (<60 kg), and a renal function criterion (serum creatinine > 133 mmol/L). If 2 of the 3 criteria were met, the dosage of apixaban was reduced from 5 mg bid to 2.5 mg bid. Most patients with moderate renal impairment (eCrCl 30-50 mL/min) continued to receive the higher (5 mg bid; 1063 patients) rather than the lower dose (2.5 mg bid; 294 patients). Apixaban was superior to warfarin in reducing stroke or systemic embolism, major bleeding, and mortality irrespective of kidney function.<sup>35</sup> Apixaban therapy was associated with less major bleeding vs warfarin across all categories of renal function and the reduction was significantly greater in patients with an eCrCl ≤50 mL/min.

The RE-LY study (which evaluated dabigatran) excluded patients with an eCrCl < 30 mL/min. Patients with moderate renal impairment (eCrCl of 30-50 mL/min) could be randomized to either dabigatran 110 mg bid or dabigatran 150 mg bid. Although the dominant route of elimination of dabigatran is renal (approximately 80%), the RE-LY study did not note any statistically significant interaction between treatment effect and baseline eCrCl.

Accordingly, it is our opinion that patients with moderate renal impairment (ie, eCrCl of 30-50 mL/min) should receive NOACs with dose adjustment as performed in the original pivotal randomized trials (Table 6).

**Table 6. Recommendations for dosage of oral anticoagulants based on renal function**

CrCl	Warfarin	Dabigatran	Rivaroxaban	Apixaban
CrCl > 50 mL/min	Dose adjusted for INR 2.0-3.0	150 mg bid*	20 mg daily	5 mg bid
CrCl 30-49 mL/min	Dose adjusted for INR 2.0-3.0	Consider 110 mg bid in preference to 150 mg bid	15 mg daily	5 mg bid (consider 2.5 mg bid) <sup>§</sup>
CrCl 15-29 mL/min	No RCT data <sup>  </sup>	No RCT data	No RCT data	Very limited RCT data <sup>†</sup>
CrCl < 15 mL/min (or the patient is dialysis-dependent)	No RCT data <sup>Δ</sup>	No RCT data <sup>†</sup>	No RCT data <sup>†</sup>	No RCT data <sup>†</sup>

ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; bid, twice daily; CrCl, creatinine clearance; INR, international normalized ratio; RCT, randomized clinical trial.

\*Consider dabigatran 110 mg oral bid if age > 75 years.

§Consider apixaban 2.5 mg oral bid if 2 of the 3 following criteria are present: (1) age > 80 years; (2) body weight < 60 kg; or (3) serum creatinine > 133 mmol/L.

||Dose-adjusted warfarin has been used, but data regarding safety and efficacy are conflicting.

†The ARISTOTLE trial did include patients with a CrCl as low as 25 mL/min, but this was a very small number of patients (1.5% of patients in the trial).

ΔDose-adjusted warfarin has been used, but data regarding safety and efficacy are conflicting and might lean toward causing harm.

† 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.

### Can we use NOACs for patients with creatinine clearance < 30 mL/min?

European and American dosing recommendations state that apixaban and rivaroxaban can be administered to patients with an eCrCl > 15 mL/min. However, the evidence for this recommendation comes from pharmacokinetic studies in a limited number of patients.

Because of the limited experience with NOACs at this level of renal dysfunction, it is our opinion that VKAs are generally the preferred agent for patients with an eCrCl of 15-30 mL/min. The systematic use of any oral anticoagulant or acetylsalicylic acid has not been demonstrated to be beneficial for AF patients who are hemodialysis-dependent.<sup>61</sup> In particular, warfarin use has not demonstrated clinical benefit, and might actually increase the risk.<sup>62</sup>

## Conclusions

There are clearly many major practical questions about the application of AF guidelines that remain unanswered. We have attempted to provide expert guidance wherever possible, but on some issues

(notably the duration of AF paroxysms at which anticoagulation should be instituted), only future research will provide adequate guidance.

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## Supplementary Material

To access the supplementary material accompanying this article, visit the Canadian Cardiovascular Society at [www.ccs.ca](http://www.ccs.ca).