ATRIAL FIBRILLATION AND ORAL ANTICOAGULATION: THE IMPORTANCE OF GUIDELINE-ADHERENCE AND CLARITY

by

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Abstract

Atrial fibrillation (AF) is the most prevalent arrhythmia, affecting 350,000 Canadians. AF can impact quality of life, mortality, and morbidity. The most serious complication of AF is thrombo-embolic stroke, and is responsible for 20 to 30% of all strokes. Oral anticoagulation (OAC) of AF can decrease the risk of stroke by 64%. Risk stratification tools have been developed and incorporated into guidelines to assist practitioners in providing the most appropriate OAC treatment for each individual patient. However, research has indicated that there is a lack of adherence by practitioners to guideline-based oral anticoagulation therapy. Until recently, warfarin was the anticoagulant of choice for nonvalvular AF. Warfarin is inexpensive, widely available, and also has the benefit of having widely available reversal agents. More recently, direct oral anticoagulants (DOACs) have been approved for the treatment of nonvalvular AF. In clinical trials DOACs have demonstrated to be as safe and effective in preventing strokes compared to warfarin if not more. They are also more convenient for patients as they have much fewer drug and food interactions and do not require rigorous routine blood monitoring. However, DOACs are more expensive than warfarin and previously did not have reversal agents available. Dabigatran (a DOAC), now has a reversal agent, and other reversal agents are being developed for the rest of the DOACs. In this paper, I will review three guidelines for oral anticoagulation treatment in nonvalvular AF. I will discuss potential reasons for practitioners' lack of adherence to these guidelines. And finally, I will explain the pocket guide that I will create to assist new practitioners in treating AF. By summarizing different guidelines into one pocket guide, I will assist new practitioners in having the richest source of information in one location, as opposed to having to consult different guidelines and potentially

becoming confused as to what is best practice. The ultimate goal of this project is to decrease the number of AF-induced strokes.

Atrial Fibrillation and Oral Anticoagulation:

The Importance of Guideline-Adherence and Clarity

Of all the cardiac dysrhythmias, atrial fibrillation (AF) is the most prevalent, affecting 350,000 Canadians (Heart and Stroke, n.d.). In the past 20 years there has been a 66% increase in the number of hospitalizations due to this arrhythmia (Patterson, Wolfe, & Bower, 2010). In 2010, Canadian hospitalization costs attributed to AF were estimated at $815 million annually (O'Reilly et al., 2013). AF when left untreated, has the potential to cause serious and even life threatening complications such as thrombo-embolic strokes, congestive heart failure and can even lead to death (Lewis et al., 2014). AF is the culprit for 20-30% of all strokes and increases the risk for death by 1.5 to 2-fold (ESC and EACTS, 2016). However, oral anticoagulation can decrease the risk of stroke by 64% and the risk of death by 26% in these patients (Piccini & Fonarow, 2016). Evidence suggests that guideline based medical therapy reduces AF related complications, however, practitioners adherence to these guidelines remains low (Lewis et al., 2014). The complexity of choosing the proper treatment for AF can be appreciated in this statement by Hart, Pearce, and Aguilar (2007): "the choice of antithrombotic prophylaxis is best individualized and should consider the patient's inherent stroke risk and the best estimate of the absolute benefits, as well as bleeding risk, access to high quality anticoagulation monitoring, and patient preferences" (p. 865). It is important to note that stroke prevention is just one portion of the complexity of treating AF, as treatments may include: rate or rhythm control therapy; cardioversion; and procedures such as catheter ablations; as well as medications for anticoagulation. However, the focus of this paper will be on oral anticoagulation for nonvalvular AF in primary care within the scope of a nurse practitioner (NP).

This paper will review the evidence that suggests that the number of AF patients receiving the appropriate oral anticoagulant therapy (OAC) in primary care settings as per guidelines is low, especially considering the large amount of research and number of clinical guidelines available to assist practitioners. To provide perspective on the complexity of treating AF, I will briefly discuss the topic of rate versus rhythm control, but it will be excluded from the pocket guide. This paper will also include: a discussion of the current recommended thrombo-embolic prophylaxis treatments and the problems associated with them by reviewing the Canadian, American, and European guidelines; a review of gaps in current OAC treatment practices, a discussion of the potential for improving stroke prevention practices; and ultimately an overview of a clinical resource I will create to help novice primary practitioners to improve their confidence and practice in regards to preventing strokes in patients with AF.

Classification of Atrial Fibrillation

AF has a number of different classifications based on duration of episodes. Reversible causes must first be ruled out, such as: thyroid disease, pericarditis, or pulmonary embolism (Spragg & Kumar, 2017). Some of the common risk factors for developing AF include: increasing age, hypertension, structural heart disease, and obstructive sleep apnea (Spragg & Kumar, 2017). The classification of AF is a continuum.

Paroxysmal AF (PAF) is defined as intermittent AF that lasts longer than 30 seconds and less than seven days as well as being self-limiting (Spragg & Kumar, 2017). Frequency of PAF is sometimes difficult to discern as episodes, even those lasting longer than 48 hours, can be asymptomatic (Spragg & Kumar, 2017). Because AF can be asymptomatic, patients may remain undiagnosed until later into the disease continuum. It has not been established if PAF carries the same risk for thrombo-embolism as permanent AF, therefore, PAF is treated in the same way as

permanent AF in regards to thrombo-prophylaxis (Manning & Singer, 2017). PAF progresses into persistent or permanent AF and the likelihood of this progression increases over time (Spragg & Kumar, 2017). At the five-year mark, there is a 25% chance of PAF progressing to permanent AF (Spragg & Kumar, 2017).

Persistent AF differs from PAF in that it persists for greater than seven days (NIH, 2014). This form of AF can be terminated either spontaneously or through medical intervention (NIH, 2014).

Long-standing AF is a relatively new term defined as AF that is sustained for more than one year (Cantillon, 2014). The longer the duration of AF the more challenging it becomes to treat and more persistent it becomes (Stopafib, 2014).

Permanent AF is when normal sinus rhythm cannot be maintained even with medical interventions (NIH, 2014). PAF and persistent AF can eventually lead to permanent AF (NIH, 2014).

Nonvalvular AF refers to AF that occurs when there is no associated rheumatic heart disease, mechanical or bioprosthetic valve, or mitral valve repair (January et al., 2014).

Description of the Problem

AF can lead to a variety of symptoms such as: palpitations, chest pain, shortness of breath, lightheadedness, fatigue, or weakness (Spragg & Kumar, 2017). Symptoms can range from mild to severe and often lead to a reduction in quality of life. The degree to which symptoms are experienced depends on factors such as: the patient's overall cardiac health, fitness level, age, the severity of the tachycardia, the degree of irregularity of the rhythm, and whether there are concomitant conditions such as heart failure (Spragg & Kumar, 2017). Symptoms such as shortness of breath and muscle fatigue are caused by the loss of atrial kick leading to a 30%

reduction in cardiac output. Tachycardia induced congestive heart failure is caused by the disorganized rapid ventricular rate associated with AF over long periods of time (Spragg & Kumar, 2017). This rapid ventricular rate can also lead to demand ischemia, which can ultimately lead to chest pain (angina) or other symptoms of ischemia (Spragg & Kumar, 2017).

For patients with AF, there are two different components of treatment that must be addressed: prophylactic treatment to prevent thrombo-embolic strokes (anticoagulation); and treatment of the dysrhythmia either by rhythm or rate control to avoid sequelae and improve symptoms and ultimately quality of life (Kumar, 2017). However, this paper will focus on the first pillar: thrombo-prophylaxis. There are several different approaches to thrombo-prophylaxis, including: anticoagulants and antiplatelets depending on the patient's risk profile. Hart, Pearce, and Aguilar (2007) note that antiplatelet therapy alone for AF decreases the risk of stroke by 20%, while adjusted-dose warfarin (an OAC) decreases the risk of stroke by 64% while limiting the risk of intracranial hemorrhage, a potential serious complication of anticoagulation.

Hsu et al., (2016b), identified that less than 50% of AF patients who were identified as being at high-risk for stroke were prescribed proper OAC. These authors suggest that such disregard for adhering to the treatment guidelines is a critical gap in current treatment practices for these patients. Verdino (2015) demonstrated that prescribing practitioners have poor understanding of the benefit to risk ratio of anticoagulation. One explanation for this is that current guidelines provide differing information, making it unclear for practitioners, which has the potential to lead to a low practitioner adherence rate (Preventing a stroke, 2011).

Addressing Atrial Fibrillation and Stroke

The next sections of this paper will address how to identify a patient's risk of stroke and also the potential pharmacological treatments.

Risk Stratification Tools

Each set of guidelines utilizes different risk stratification tools. These tools are used to assess the patient's risk for stroke and their risk for bleeding. From this equation, an appropriate antithrombotic treatment regimen is decided. Depending on the patient's risk, pharmaceutical treatment will involve either no medical treatment, monotherapy, or a combination of antithrombotics (Manning, Singer, & Lip, 2017). The different risk stratification tools evaluating stroke risk that will be discussed in this paper are: CHADS2, CHA2DS-VASc, and CHADS2 65.

On the opposite side of the spectrum, HAS-BLED assesses the patient's risk for bleeding (Lip & Lane, 2012). Compared to other bleeding risk tools, HAS-BLED provides a more specific prediction of bleeding and is also more user friendly (Lip & Lane, 2012). However, HAS-BLED alone should not disqualify patients from receiving OAC, but should be used as a tool to help treat other risks and co-morbidities that can be corrected, and also prompt more regular screening for patients who are at a higher risk for bleeding (Lip & Lane, 2012). The overarching goal of all these tools is to find the balance between treating patients with the proper OAC therapy without causing harm due to bleeding events.

CHADS2.

The CHADS2 risk stratification tool had previously been the most commonly used scheme recommended in guidelines (Gage et al., 2001). This tool assigns one point for each risk factor: congestive heart failure (CHF)/ left ventricular (LV) dysfunction, hypertension, age greater than 75, diabetes, and two points for any history of stroke or transient ischemic attack (TIA) (Gage et al., 2001). The more points a patient has, the higher their risk is for stroke. One important criticism of the CHADS2, is that it does not differentiate enough among those that have a low risk (score of 1) (Winkle, Mead, Engel, Kong, & Patrawala, 2013). These patients

then fall into a category of uncertainty as to whether they need aspirin or OAC (Winkle et al., 2013). Odum, Cochrane, Aistrope, and Snella (2012) also criticise the tool for neglecting to include critical risk factors, having a low predictive ability, and assigning too many patients to an ambiguous, intermediate-risk group.

CHA2DS2-VASc.

The CHA2DS2-VASc scoring system was developed to correct the gaps of the CHADS2 tool (Winkle et al., 2013). The updated tool was first accepted in 2010 by the European AF guidelines (Winkle et al., 2013). The difference between this newer tool and CHADS2 is that it incorporates different age categories, vascular disease, and female sex as risk factors. Overall, the goal of this newer system was to create more distinct levels of risk, increasing precision for decision-making regarding thrombo-embolic prophylaxis (Winkle et al., 2013). The CHA2DS2-VASc tool categorizes patients more often as higher risk than the CHADS2 tool, which results in more aggressive thrombo-prohylaxis (Winkle et al., 2013). The newer system places fewer patients in low and intermediate risk, and more patients in the higher risk categories (Winkle et al., 2013). A CHA2DS-VASc score equal to 2 or greater is better at predicting thrombo-embolic events than the original CHADS2 tool (Zhu, Xiong, & Hong, 2015). Ultimately the CHA2DS2-VASc is superior in recognizing truly low-risk and high-risk patients and leaving fewer patients in the ambiguous intermediate-risk category (Zhu et al., 2015). Interestingly, the incorporation of vascular disease has little impact on risk stratification as vascular disease is often due to diabetes, hypertension and age; which are already accounted for in the CHADS2 tool (Winkle et al., 2013). The vast majority of changes (increasing patients' risk stratification) are due to incorporating 1 point for female sex and age 65 to 75, and then 2 points for age 75 and older (Winkle et al., 2013). Other criticisms of CHADS2 that led to the development of CHA2DS2-

VASc, are that it does not take into account sex, vascular disease and then age range between 65 and 74 (Winkle et al., 2013). The controversies of the tools are obvious when looking at the categories of sex and age. The Canadian AF guidelines consider whether or not sex should be included, as multivariate analysis indicates female sex alone is not a risk factor for thrombo-embolism (Winkle et al., 2013). In the end the CCS did not include sex as a risk factor. Furthermore, the 2012 European Guidelines suggest bypassing sex when risk-stratifying if the patient is under the age of 65 and sex is the only point that would have been assigned (Winkle et al., 2013). CHA2DS2-VASc assigns a higher risk rate to women over the age of 65 and anyone over the age of 75. Interestingly these two factors, older age and female sex, are also risk factors for bleeding (Odum et al., 2012). Ultimately the CHA2DS2-VASc tool categorizes more patients as high risk, which points to a definite indication for OAC therapy (Winkle et al., 2013). CHA2DS2-VASc also has a greater tendency to assign patients to the low risk category that are actually at low-risk and do not require as aggressive pharmacotherapy (Odum et al., 2012).

CHADS2 65.

The Canadian Cardiovascular Society (CCS) guidelines previously used the CHADS2 stratification tool in their 2010 and 2012 recommendations. In 2014, the CCS guidelines used an amalgamation of CHADS2 and CHA2DS2-VASc (Verma, 2014). The CCS authors used the parts of CHA2DS2-VASc that they deemed were appropriate, namely, age greater than 65 (Verma, 2014). The guideline-writing committee agreed that age greater than 65 was a significant risk factor that needed to be incorporated, especially for patients that had a CHADS2 score of 0, to determine proper OAC therapy (Verma, 2014). This created the CHADS2 65 risk stratification tool utilized by the most current CCS guidelines.

HAS-BLED.

HAS-BLED, according to Pisters (2010), is an easy-to-use, practical bleeding-risk tool, to aid practitioners in their decision making for OAC therapy for patients with AF. This tool estimates the 1-year risk for major bleeding, defined as: intracranial hemorrhage, bleeding requiring hospitalization, hemoglobin decrease by 2g/L, and/or the need for blood transfusion (Pisters, 2010). HAS-BLED has been incorporated into the European and Canadian AF guidelines, further legitimizing its value (Roldan, 2013). The risk factors that HAS-BLED considers are: hypertension, renal and liver function, stroke, bleeding history, stability of INR, age, and drug or alcohol use. Each risk factor is assigned 1 point, and a total of 3 or more points indicates high increased risk for major bleeding events. This in turn suggests caution with OAC or closer follow up (Pisters, 2010). Pisters (2010), demonstrates the legitimacy of HAS-BLED with the following predictive values: overall C statistic = 0.72; bleeding risk with antiplatelet therapy C statistic = 0.91; with no OAC C statistic = 0.85. Pisters (2010) notes the difficulty clinicians have, as those with a higher risk for CVA are often those who are at a higher risk for bleeding. It has been estimated that HAS-BLED could have prevented more than 1/10 major bleeds in Euro Heart Survey (Pisters, 2010). The downside is that patients with a CHADS2 score of 1 or greater who did not suffer a major bleed would have been refused OAC for prophylaxis because the HAS-BLED score outweighed their CHADS2 score (Pisters, 2010). The HAS-BLED system is intended to bring to the attention of the practitioner patients who are at a high risk for bleeding, but it should not necessarily lead to withholding OAC therapy (Roldan, 2013).

Rate versus Rhythm Control

An irregular ventricular response and disorganized contraction of the atria due to AF can lead to unpleasant symptoms, unstable hemodynamic status, increased risk for thrombo-embolic

events, and chronic dysfunction of the left atrium and ventricle (Kumar & Manning, 2016). Due to these issues, a decision must be made to either control the ventricular rate (rate control) or convert the rhythm back to sinus (rhythm control). Both rate and rhythm control improve the symptoms associated with an accelerated ventricular response, however, there is no evidence that either option improves mortality compared to the other (Piccini & Fauchier, 2016). The AFFIRM trial investigated differences in outcomes between rate and rhythm control. The outcome of the trial indicated that there was no identified statistically significant difference between the groups in respect to cardiac death, death related to arrhythmias, death due to ischemic strokes, or hemorrhagic strokes. There was also no identified difference in quality of life between the groups (Kumar & Manning, 2016). It should be noted that if either option becomes ineffective at any time during therapy, then the second option must be considered (Kumar & Manning, 2016).

Rate control is achieved via medications that block or slow conduction through the atrioventricular (AV) node, such as beta blockers, calcium-channel blockers or digoxin (Kumar & Manning, 2016).

Some patients have superior improvements in quality of life with rhythm control over rate control (Kumar & Manning, 2016). Examples of these patients are: those that have failed rate control, younger and active patients, and those that are earlier in the continuum of AF (Kumar & Manning, 2016). There are several options for rhythm control including: pharmacological or electrical cardioversion, catheter ablation, and surgical procedures (Piccini & Fauchier, 2016). Prescribing rate and noncomplex anti-arrhythmic regimens falls within the scope of primary care providers, however, managing complex anti-arrhythmic therapy and

invasive interventions such as cardiac ablation require referral to a cardiologist for advanced assessment and treatment.

Successful rhythm control does not negate the need for thrombo-prophylaxis if the patient's risk profile indicates it (Piccini & Fauchier, 2016). There are several explanations as to why there is no reduction in the risk for thrombo-embolism in this situation. First, 35 to 60 percent of patients revert to AF after cardioversion or anti-arrhythmic therapy, whether paroxysmal or continuous, by one year (Kumar & Manning, 2016). As many as 90 percent of these cases are asymptomatic and therefore go unrecognized (Kumar & Manning, 2016). Nevertheless, episodes of AF lasting more than 48 hours are common, and this provides enough time for emboli to form in the left atrium (Piccini & Fauchier, 2016). Even more daunting is that brief bursts of AF can still increase the risk of stroke 6-fold (Kumar & Manning, 2016).

The second explanation is AF patients often have other co-morbidities and risk factors for forming emboli, even when they remain in sinus rhythm (Kumar & Manning, 2016). Examples of these risk factors are: hypertension leading to vascular disease and complex aortic plaque and left ventricular dysfunction (Violi, Pastori & Pignatelli, 2014).

Another explanation is that there may be asynchrony between the body of the left atrium and the left atrial appendage where the majority of emboli form (Violi, Pastori, & Pignatelli, 2014). The left atrium may have a normal sinus rhythm while the left atrial appendage specifically can be fibrillating (Kumar & Manning, 2016).

Oral Anticoagulants

Vitamin K antagonists.

Historically warfarin, which is a vitamin K antagonist (VKA), has been the anticoagulant of choice for patients with AF (Davis, 2013). Warfarin dramatically reduces thrombo-embolic

strokes by two-thirds while maintaining an acceptable risk of bleeding (Manning et al., 2017). However, as for any anticoagulant, there is the risk for bleeding with intracranial hemorrhage being the most severe and worrisome concern for increasing morbidity and mortality. Warfarin has a 0.2 to 0.4 percent risk per year of major bleeding (Manning et al., 2017). But when compared to the risk of ischemic stroke, the risk of bleeding is significantly lower, thus adding to the risk-to-benefit argument (Manning et al., 2013). However, warfarin has two significant issues: it is underutilized and it also has a narrow therapeutic window which the patient requires frequent blood work for as it is challenging to maintain an INR between 2 and 3 (Davis, 2013). Patients being treated with warfarin have the potential to have labile INRs. If the INR becomes sub-therapeutic, there is a risk for a stroke. If the INR becomes supra-therapeutic there is a risk for bleeding. Also warfarin's effectiveness depends on many things, such as other medications, co-morbidities, systemic illness, and diet (Hull & Garcia, 2017). Due to all of these potential interactions, patients can become sub- or supra-therapeutic even if their INR has been stable for months (Hull & Garcia, 2017).

Although warfarin does carry a risk for bleeding, it can be reversed if a patient has sustained a major bleed. Vitamin K, which is inexpensive and widely available, is used to completely reverse warfarin within 12-24 hours (Freeman, Aguilar, & Weitz, 2014). Warfarin can also be reversed with prothrombin complex concentrate, and fresh frozen plasma (Patel et al., 2017).

Direct oral anticoagulants.

Since 2010, four non-vitamin K anticoagulants referred to as direct oral anticoagulants (DOACs) have been approved by Health Canada for stroke prevention in patients with AF. A growing number of clinical trials have indicated that DOACs are a safe and effective alternative

to warfarin and in comparison, are associated with fewer major bleeding events and hemorrhagic strokes (Hicks, Stewart, & Eisinga, 2016). There are two different categories of DOACs: thrombin inhibitors and factor Xa inhibitors. They were first developed as an alternative to vitamin K antagonists as warfarin is challenging to maintain a therapeutic INR and is also inconvenient for patients (Patel, Pandya, & Goldberg, 2017). From a point of medication patient adherence and convenience, DOACs do not require regular blood monitoring and have much fewer drug and food interactions (Hicks et al., 2016). DOACs are dose-dependent, have predictable anticoagulant effects, and have a more rapid onset of action and termination (Hanley & Kowey, 2015).

However, DOACs are known to put patients at a higher risk for gastrointestinal bleeding than warfarin (Hanley & Kowey, 2015). As well, reversal agents for DOACs are still being investigated and developed, putting DOACs currently at a disadvantage to warfarin in that regard (Hanley & Kowey, 2015). DOACs are also excessively more expensive than warfarin. In the clinical trials performed, all DOACs proved to be comparable with each other, as no head-to-head trials have been conducted at this point (Patel et al., 2017).

Dabigatran.

Dabigatran is a direct thrombin inhibitor that is taken in a fixed dose without the need for laboratory monitoring (Connolly et al., 2009). Dabigatran was the first DOAC to be approved in Canada in 2010. In the most pivotal trial, the RE-LY trial, two dosages of dabigatran (110 mg and 150mg twice daily) were compared to adjusted –dose warfarin in patients with AF who were at risk of stroke. The 110mg dose showed similar rates of stroke and thrombo-embolism as warfarin. However, the study indicated that dabigatran had lower rates of major bleeding. In comparison, the 150mg dose indicated similar rates to warfarin for major bleeding but lower

rates of stroke and thrombo-embolism (patients receiving dabigatran had one-third the incidence of intracranial hemorrhages of warfarin). The authors of the trial stated that intracranial hemorrhage is the biggest concern with warfarin, so dabigatran having one-third the incidence of intracranial hemorrhages, while still having high efficacy in preventing ischemic strokes is highly favourable towards dabigatran. However, in a secondary analysis both doses of dabigatran were associated with higher rates of myocardial infarction than warfarin, and patients in the dabigatran 150mg arm had higher rates of gastrointestinal bleeding as well.

Factor Xa inhibitors.

Rivaroxaban.

The ROCKET AF trial was the definitive trial of Rivaroxaban (Patel et al., 2011). Rivaroxaban was the second DOAC developed and it directly inhibits clotting factor Xa. This DOAC has an optimal drug profile, in that it has a more consistent and predictable anticoagulation pattern compared to warfarin. The ROCKET AF trial compared once a day dosing of rivaroxaban to dose-adjusted warfarin for thrombo-embolic prevention in moderate- to high-risk nonvalvular AF patients. The study found no significant differences between the two medications in regards to major and minor bleeding. Fatal bleeding occurred more often in patients treated with warfarin, especially due to intracranial hemorrhage. Patients in the rivaroxaban arm had higher rates of gastrointestinal bleeding, as well as bleeding that required blood transfusion. The ultimate finding of this study indicated that rivaroxaban was non-inferior to warfarin in thrombo-embolic prophylaxis and safe in terms of major bleeding.

Apixaban.

Apixaban was the third DOAC created and was evaluated in the ARISTOTLE trial (Granger et al., 2011). Apixaban directly inhibits factor Xa and is rapidly absorbed. This

anticoagulant has a 12-hour half-life and 25% renal excretion. The primary end point of this trial was to compare apixaban to warfarin for the prophylaxis of stroke and systemic embolism in AF patients with at least one other stroke risk factor. The trial compared once daily dosing of apixaban to dose-adjusted warfarin. Other outcomes taken into consideration were major bleeding as per the International Society on Thrombosis and Haemostasis (ISTH) criteria. The study also evaluated death from any cause. The results of the study indicated that apixaban, in comparison to warfarin, significantly reduced the relative risk of ischemic stroke and systemic embolism by 21%, major bleeding by 31%, and any-cause death by 11%. The overall findings of the study were that apixaban was superior to warfarin in preventing thrombo-embolism, decreasing bleeding, as well as in all-cause mortality. The trial also indicated that, for patients with a creatinine clearance of 25-50ml/min, apixaban was marginally superior for preventing stroke and having fewer bleeding events.

Edoxaban.

Edoxaban is the most recently approved DOAC and is a direct factor Xa inhibitor that is indicated for ischemic stroke prophylaxis in nonvalvular AF patients (Giugliano, 2013). The authors on the definitive edoxaban trial, the ENGAGE trial, indicated that edoxaban reaches its maximum concentrations within one to two hours and has 50% renal excretion. Patients with moderate to severe kidney disease, low body weight or concomitant use of a P-glycoprotein inhibitor should reduce their edoxaban doses by half. The ENGAGE trial evaluated two doses of edoxaban (60mg and 30mg once daily) in comparison to warfarin for patients with AF at moderate- to high-risk of stroke. The outcomes measured were stroke and systemic embolism. Major bleeding was also evaluated as per the ISTH criteria. The results of the study indicated that neither of the edoxaban doses were inferior to warfarin for thrombo-embolic prophylaxis.

The higher dose of edoxaban was more efficacious than warfarin. Patients receiving the lower dose of edoxaban tended to have higher rates of ischemic stroke than those receiving warfarin. Both edoxaban regimens resulted in lower rates of hemorrhagic strokes and cardiovascular deaths than that of warfarin. The trial concluded that edoxaban is superior to warfarin for all types of bleeding complications, including major, minor and life-threatening bleeding. The lone exception to this was in regards to gastrointestinal bleedings which occurred at a higher rate with high-dose edoxaban but lower for low-dose edoxaban compared to warfarin. The ultimate conclusion from the ENGAGE trial was that edoxaban is a safe and efficacious drug, with no unexpected adverse drug events, fewer side effects than warfarin, and a favourable outcome in regards to stroke, systemic embolism, major bleeding events, and death from any cause.

Reversibility.

Warfarin reversal agents.

Warfarin, which historically has been the standard of care for anticoagulation in the population of interest, can be reversed in situations of major and minor bleeding (Hanley, 2004). As per the British Columbia guidelines, patients who are a high risk for bleeding with an INR >5 should be considered for anticoagulation reversal with oral vitamin K as well as interrupting the warfarin therapy (Government of BC, 2015). For patients with minor bleeding and an INR >9, a higher dose of vitamin K should be administered as well as temporarily holding the warfarin therapy (Garcia & Crowther, 2012). Patients who are experiencing major bleeding should have their anticoagulation reversed with intravenous vitamin K and prothrombin complex concentration (PCC) or fresh frozen plasma (FFP) (Makris et al., 2009). Oral vitamin K can correct an elevated INR in 24 hours (Makris et al., 2009). Intravenous vitamin K has the advantage of relatively rapid reversal, effecting significant decreases in INR within 6-8 hours

(Makris et al., 2009). The risk with vitamin K is that the anticoagulation effects are overcorrected, leaving the patient at risk for thrombo-embolism (Makris et al., 2009). Administration of FFP poses challenges such as: fluid overload as most patients require more than one litre of this treatment, prolonged administration time when urgent reversal is required, and the ethical ramifications of administering a blood product (Makris et al., 2009). The concern with PCC is the risk of thrombosis once supra-therapeutic INR levels are corrected (Makris et al., 2009).

Idarucizumab.

Prior to 2016 there was no reversal agent for dabigatran or any other DOAC. Then in 2016 Health Canada approved the antidote for dabigatran. Idarucizumab is a monoclonal antibody fragment that binds to dabigatran 350 times more than thrombin does. The RE-VERSE AD trial was performed to determine the safety and efficacy of this medication for situations of serious bleeding, or in patients with life threatening bleeding or requiring immediate surgical or procedural interventions (Pollack et al., 2015). One of the more important evaluation end points was the return of hemostasis. The study revealed that idarucizumab completely reversed dabigatran and its anticoagulation properties within minutes in 88-98% of the patients. The clinical trial reported a total of five thrombotic events that occurred within 72 hours of idarucizumab administration. None of the five patients were currently receiving antithrombotic therapy when these events occurred. The downside of idarucizumab is that a single treatment is nearly $3500 USD, therefore, reserving the treatment for severe situations (Buchheit, Reddy, & Connors, 2016).

Andexanet.

The ANNEXA-A and ANNEXA-R trials were conducted because a large limitation of apixaban and rivaroxaban is the lack of a reversal antidote for the anticoagulation effects (Siegal et al., 2015). Andexanet is a specific reversal medication created to neutralize the anticoagulation properties of direct and indirect factor Xa inhibitors. The purpose of these two trials was to evaluate the safety and efficacy of andexanet in reversing the anticoagulation of apixaban and rivaroxaban in (otherwise) healthy older adults. The findings of both trials were that andexanet did, in fact, reverse the two factor Xa inhibitors safely and rapidly. Andexanet is a reversal agent for both direct and indirect factor Xa inhibitors, therefore, can be used to reverse apixaban, rivaroxaban, edoxaban, and enoxaparin.

At this time andexanet has not been approved by Health Canada (Tangedal et al., 2016). Although andexanet has been shown to be an effective reversal agent in healthy participants, its effectiveness has not yet been examined in seriously ill patients (Macle et al., 2016). An open-label, phase III trial is underway, evaluating the efficacy and safety in patients who present to emergency services with major or intracranial bleeding who are on factor Xa inhibitors (Macle et al., 2016).

Special Populations: Renal Failure

In this section the terms chronic kidney disease (CKD) and renal insufficiency will be used interchangeably to indicate patients with all levels of kidney impairment (eGFR below 60ml/min). Patients with renal insufficiency who are on oral anticoagulation for AF have increased risk for both thrombo-embolism and bleeding (Jennings, 2016). The relevance is that every one of the DOACs is eliminated to some degree by the kidneys, and thus, require renal dosing adjustments (Jennings, 2016). The latest evidence however, indicates that DOACs are equally good as, if not superior to warfarin for patients with CKD who maintain an eGFR of

greater than 30 (Jennings, 2016). However, at this time there has not been enough research to indicate if DOACs are safe for patients with an eGFR less than 30 (Jennings, 2016).

Warfarin also carries with it the risk of complications in patients with CKD, since the risk of bleeding while on warfarin significantly increases as kidney disease progresses (Di Lullo, 2017). However, Di Lullo explains there is still minimal data on the safety and efficacy of warfarin in patients with CKD. Furthermore, patients with an eGFR of less than 30 have a 4.9-fold increase in bleeding risk. However, warfarin has less than 1% renal excretion as the majority of warfarin is cleared via hepatic metabolism. Although warfarin only has minimal renal excretion, CKD has shown to affect non-renal clearance. Specifically, CKD can cause significant down-regulation of the hepatic cytochrome P-450, a major metabolic enzyme of warfarin. Because of this non-direct influence CKD has on warfarin metabolism, patient's with CKD often have increased lability of INRs which leads to the increase in significant bleeding risk.

Due to the limitations of available data, the 2014 ACC/AHA/HRS clinical practice guidelines recommend warfarin as the anticoagulant of choice for patients with advanced CKD or end-stage renal disease (ESRD), defined as an eGFR <15, or requiring hemodialysis (January et al., 2014). Di Lullo (2017) states the reason for warfarin being the drug of choice in this population is its low cost and availability of multiple reversal agents. In 2013, Thrombosis Canada recommended that patients with mild kidney disease (eGFR > 50ml/min) do not require dose reduction of apixaban (Thrombosis Canada, 2013). Patients with moderate kidney disease (eGFR 25-50ml/min) can also be treated with the full dose of apixaban, unless they also have two of the three following criteria: serum creatinine above 133 μmol/L; age 80 years or greater; or body weight equal to or less than 60 kg (Thrombosis Canada, 2013). Rivaroxaban is currently

not recommended for patients with ESRD (Turpie, Purdham, & Ciaccia, 2017). Dabigatran has been approved by Health Canada at its lower dose (110mg twice daily) in patients with a CrCl between 30 and 50ml/min (Turpie, Purdham, & Ciaccia, 2017). The risk-benefit ratio of OAC in CKD patients with AF has not been established, but according to the ACC/AHA/HRS guidelines, warfarin is the drug of choice for CKD stages 4, 5, and for dialysis patients, because all the DOACs rely on significant renal clearance (January et al., 2014). The ESC guidelines have indicated that DOACs are appropriate for patients with a CrCl between 30 and 40ml/min (Kirchhof, 2016).

Current Guidelines for Antithrombotic Therapy

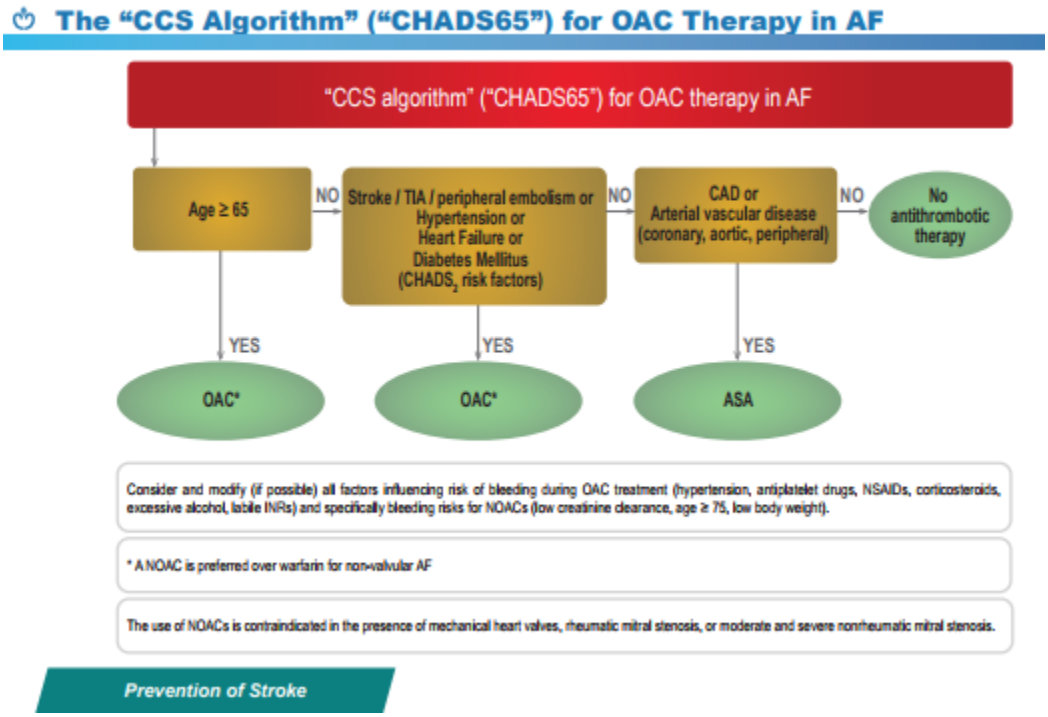
See Table 1 for a summary of the ESC, ACC/AHA/HRS, and CCS guidelines.

See Table 2 for a summary of the ESC, ACC/AHA/HRS, and CCS recommendations for treatment in AF with concomitant CKD.

The Canadian Cardiovascular Society (CCS) Guidelines

The CCS 2016 guidelines recommend the use of the CHADS2 65 which is a modified CHADS2 tool to assess for the need for anticoagulation. In this modified tool, they incorporate age greater than 65, all of the CHADS2 risk factors, and CAD or arterial vascular disease as risk factors for thrombo-embolism (Macle et al., 2016). The risk factors attributable to the patient determine OAC, aspirin, or no antithrombotic treatment. The CCS writing group states that DOACs are preferred to warfarin for nonvalvular AF. CCS guidelines also recommend the consideration of the HAS-BLED tool to assess for the risk of major bleeding events, and trying to reduce these risks (such as controlling hypertension) as well as possible. The guidelines mention that they allow for consideration of the CHA2DS2-VASc risk factors with the exception

of female sex, as this remains controversial. The guidelines recommend that patients 65 or older, with a CHADS2 score of 1 or greater, should be placed on OAC.



The guidelines give a thorough overview of the OAC to be considered in patients with renal dysfunction including recommendations for which OAC is appropriate for various levels of renal dysfunction (Macle et al., 2016). This section provides clarity, as it states that any patient with a CHADS2 score of 1 or greater should be taking an OAC.

However, the CCS guidelines have some ambiguity throughout. They lack clarity, making it difficult to navigate through the guidelines. The purpose of guidelines are to help direct the practitioner to choose the most appropriate and evidence-based treatment for their patient. However, I do not believe the CCS guidelines have simplified this process for practitioners. The algorithm shows that if a patient has concomitant CAD and AF they should receive a DOAC (Macle et al., 2016). However, they also state that some pundits prefer combination therapy of a DOAC and aspirin for those who are at a higher risk of a coronary

event. The guidelines also indicate if a patient is less than 65 years of age and has any of the CHADS2 risk factors, they should be placed on OAC. Essentially the CCS guidelines recommend most of the CHA2DS2-VASc elements, minus female sex, as they incorporate vascular disease and the age group between 65 and 74 into the algorithm. So for the most part they have used CHA2DS2-VASc. However, they have not indicated that and have also not implemented their risk stratification tools in a linear fashion that makes it easy to identify the patient's level of risk. It should be mentioned that this algorithm is not clear as to whether prior stroke/TIA affords 1 or 2 points. Although this will not change the treatment for the patient, as a score of 1 or greater will both require OAC, the total score does indicate the level of risk. For example, a CHA2DS2-VASc score of 1 carries an annual 1.3% risk of stroke, compared to a score of 4 which carries an annual 4.0% risk of stroke (Lip et al., 2010). The algorithm also mentions the CHADS2 risk factors, listing all of them except for age 75 years and up. In summary, the CCS algorithm has drawn on both CHADS2 and CHA2DS2-VASc, but has included some of the risk factors, removed others, and has not been clear on defining a point structure, instead just recommending OAC if even one risk factor is met. Essentially the CCS has created their own risk stratification tool by amalgamating already established tools, accompanied by an algorithm that is not-user friendly, due to these ambiguities.

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) Guidelines

The most recent ACC/AHA/HRS guidelines endorse the CHA2DS2-VASc risk stratification tool (January et al., 2014). The guidelines recommend that patients with a prior stroke/TIA or a CHA2DS2-VASc score of 2 or greater should receive thrombo-embolic prophylaxis with warfarin, dabigatran, rivaroxaban, or apixaban. The guidelines further

recommend that it is a viable option to provide no thrombo-prophylaxis for a CHA2DS2-VASc score of 0.

These guidelines are clear and concise as to which stratification tool they recommend and how to use it (January et al., 2014). The ACC/AHA/HRS guidelines do not indicate a preference between vitamin K antagonists (warfarin) or DOACs. The only exception to this is if patients continue to have labile INRs on warfarin, in which case they should be changed to a DOAC. Also, they do not mention edoxaban as a viable option, as it was only approved in 2015. The guidelines do mention that renal function should to be assessed before initiating a DOAC, and provide specific guidelines in regards to which OACs are appropriate for which level of renal dysfunction. For a CHA2DS2-VASc score of 1 they recommend either no treatment, OAC treatment, or treatment with aspirin alone, which leaves a lot of room for clinical discretion. Furthermore, the ACC/AHA/HRS guidelines mention the HAS-BLED tool, indicating its use for identifying patients at higher risk for bleeding, but devalue its clinical efficacy.

European Society of Cardiology (ESC) Guidelines

The latest update to the ESC AF guidelines are from 2016 (Kirchhof, 2016). The ESC guidelines recommend the need for OAC for most patients with AF, except those of low risk, which is defined as a CHA2DS2-VASc score of zero. The authors explain that patients are often under-treated or have premature discontinuation of their OAC, which they attribute to the perceived high risk of bleeding with OAC and the difficulty of monitoring and titrating VKAs. The ESC guidelines explain that the risk for stroke most often is greater than the bleeding risk even in those patients who are deemed at high risk for bleeding. To further their argument of the need for OACs, the authors explain that the risk for bleeding is equal with aspirin, VKAs, and DOACs, but aspirin does not have as great of efficacy in thrombo-prophylaxis.

The ESC guidelines have recommended use of the CHADS2-VASc risk stratification tool since 2010 (Kirchhof, 2016). As per the ESC guidelines, men with a CHADS2-VASc score of 1 and greater, and women with a score of 2 or greater will most likely benefit from OAC therapy. This appears to be a way of using the CHA2DS2-VASc but nullifying female sex as a risk factor, as it remains controversial at this time. The guidelines refer to HAS-BLED as well as several other bleeding risk stratification tools. The ESC guidelines recommends using these tools to identify risk factors for bleeding, so that modifiable risk factors can be treated, but not to encourage withholding OAC. These guidelines suggest that VKAs and DOACs are effective treatments.

As opposed to other guidelines, the ESC uses the entire CHADS2-VASc guidelines including female sex (Kirchhof, 2016). The guidelines do not take a position on whether DOACs or VKAs are preferred, but do include renal dose adjustments for DOACs and include edoxaban. However, the graph they provide for renal dysfunction adjustments is not user friendly. For example, the graph shows that dabigatran can be dosed at either 150mg or 110mg, but they do not mention considering a lower dose for a CrCl between 30-49.

Nurse Practitioners' Role in Atrial Fibrillation Management

Due to the anticipated trajectory of a decreasing number of physicians, and the increasing scope and implementation of NPs, the role of NPs is ever expanding; NPs are being utilized more throughout all areas of healthcare (Abbot & Homoud, 2016). Current estimates indicate that there will be a severe inability for physicians alone to meet the ever increasing health care demands in Canada (Smigorowsky, Norris, McMurty, & Tsuyuki, 2017). The demand for cardiac services is steadily increasing (Abbott & Homoud, 2016). The current Canadian

healthcare system is deemed to be unsustainable, and poorly controlled AF is one example of the increasing health care costs (Smigorowsky et al., 2017).

NPs are often the primary care provider for those with AF, which includes diagnosis and management of AF (Abbott & Homoud, 2016). It is important that NPs treat AF as per current guidelines, so as to improve mortality and morbidity (Leslie, 2013). For those at risk of thrombo-embolism, NPs should conduct risk stratification to determine the most appropriate treatment (Leslie, 2013). It is also within the scope of NPs to assess whether warfarin or a DOAC is appropriate for each individual patient (Leslie, 2013). As well, it is important that NPs educate their patients on the importance of medication adherence, lifestyle modification, and warning signs of side effects and other untoward events (Leslie, 2013).

Patients often find greater satisfaction with NP-led care versus physician-led care, as indicated by the study by Smigorowsky et al. (2017) which found that patients consistently provided higher satisfaction ratings for NP-led care. This could be due to NPs spending more face-to-face time with patients and creating individualized care plans, educating, and counselling (Smigorowsky et al., 2017). Due to these facts, patient adherence to treatment regimens may be increased, which will lead to better patient outcomes and overall healthcare savings (Smigorowsky et al., 2017). Several studies have been conducted indicating benefits of NP-led, and it can be assumed that this would continue into AF care (Richardson, Derouin, Vorderstrasse, Hipkens, & Thompson, 2014; Smigorowsky et al., 2017; Spencer & Hanania, 2013).

Practitioners' Lack of Adherence to Current Guidelines

Mazurek et al. (2017) conducted research to evaluate the impact of guideline-adherent antithrombotic treatment in AF on stroke and mortality rates compared to non-adherent

treatment. The conclusion of their study indicated that guideline-adherent oral anticoagulation in AF significantly reduces the risk of stroke and improves mortality. The study showed that only half of AF patients are currently being treated with appropriate guideline-based OAC therapy. Furthermore, approximately one-third of AF patients who are deemed at risk for stroke are not treated with any OAC or with antiplatelet monotherapy, and approximately 50% who do not have any risk factors are prescribed OAC inappropriately. The authors contended that lack of guideline adherence by practitioners can be categorized as either overtreatment or under-treatment. This is most concerning, as mentioned previously but of significant importance, because guideline-based treatment drastically reduces stroke rates and increases survival rates. Mazurek and colleagues added that strict guideline-adherence is even more important for those at high risk for stroke. The research team demonstrated the importance of guideline-directed treatment, as neither overtreatment or under-treatment is beneficial for these patients, and in fact caused a 2-fold increase in all-cause mortality. Several studies suggest guideline adherence improves morbidity, mortality, and reduces hospitalizations (Gorin et al., 2011; Hendricks et al., 2012; Mazurek et al., 2017). Clearly there is a great opportunity for improving adherence to guidelines and ultimately increasing patients' survival rates.

Due to the alarming rates of improper treatment for AF patients, the AHA initiated the "Get With the Guidelines (GWTG) AF" program, which increased guideline-based adherence rates (Lewis et al., 2014). The authors of this paper indicate potential reasons for practitioners' low adherence rates are due to variable familiarity and experience with the current guidelines.

Reasons for Practitioners' Lack of Adherence

It is quite clear that guideline-based AF treatment provides the greatest outcomes to patients. Improved risk stratification tools have been created to help practitioners rate the level

of patients' risk for thrombo-embolism, and current guidelines outline how to treat each patient, depending on their overall risk. So why is there still such low adherence rates?

One systematic review by Pugh, Pugh, and Mead (2011), included studies that surveyed physicians in regards to their attitudes' toward OAC. The findings were that physicians were hesitant to prescribe OAC to the elderly, those with a history of falls, and a history of bleeding. This indicates that physicians had a greater fear of causing harm from bleeding associated with OAC rather than fear of strokes in these patients.

Van Doorn et al. (2015) conducted a study to examine causes for practitioner non-adherence to guidelines. The main findings were: some physicians believed the patients had been in sinus rhythm for more than a year; and over a quarter surveyed could not recall the reason, but believed the assigned cardiologist was responsible for this treatment. In regards to practitioners believing their patients had remained in sinus rhythm for a year or longer, Holter studies showed almost all patients still had PAF, including asymptomatic episodes that would go undetected. As mentioned previously, PAF treatment guidelines are the same for permanent and persistent AF. Interestingly, physicians rarely mentioned contraindications for anticoagulation, drug interactions, or patient preference as their rationale for not adhering to the guidelines.

Practitioners' Hesitancy Towards Anticoagulation

Verdino (2015), suggests practitioners' lack of confidence may lead them to underestimate the risk for stroke and overestimate the risk for bleeding. Verdino also notes that patients can be resistant to receiving OAC therapy, which may affect the practitioners' decision-making. This may partly be a reflection of the practitioner's ability to explain the pathophysiology of AF and the risks and benefits of anticoagulants. Verdino also suggests that some practitioners may have difficulty identifying which patients are appropriate candidates and

therefore, overestimate their overall risk for bleeding. This further strengthens the need for simplified, user-friendly guidelines.

Sen and Dahlberg (2014) reviewed studies evaluating physicians' fears due to associating anticoagulation with death from bleeding. These authors cite that 2003 and 2004 death certificate data ranked anticoagulants as the number one category of drugs causing death due to their adverse effects. They found that physicians also had fears around gastrointestinal bleeds due to anticoagulants and intracranial hemorrhages from falls or uncontrolled hypertension.

Many practitioners are fearful of prescribing OAC to elderly patients who are at risk for falls (Calderon, 2012). However, evidence suggests that the benefits of OAC in these patients outweigh the risks. Calderon suggests that a patient over 65 with a CHADS2 score of 2 or greater on OAC would need to fall 295 times in a year for the risks of fall-related subdural hemorrhages to outweigh the benefits.

Description of the Project

The purpose of creating a pocket guide for new practitioners is to simplify the different published guidelines on OAC for nonvalvular AF in the adult population, with an added focus on CKD. This pocket guide is an amalgamation of the three guidelines that have been critiqued earlier in this paper into one easy-to-read algorithmic chart. By amalgamating the three highly credible guidelines, and using each of their strengths, this pocket guide takes an evidence-based approach to simplifying the risk stratification tools into one user-friendly resource. Instead of practitioners having to search for guidelines, decide which one they will use, make sense of the guideline and deduce how to use it appropriately, the pocket guide I have created has already done that for the practitioner. This way the practitioner will have easy access to a tool that results from evaluation of the guidelines and makes the implementation of them much simpler.

My hope is that this will increase the confidence of new practitioners in assessing the need for and selecting anticoagulant agents in AF. The overall goal is to increase the rates of guideline-directed OAC in AF, and thus improve overall mortality and morbidity.

The pocket guide is one page, back and front, ideally laminated. The idea is to have all the information simplified as to not overwhelm the practitioner with an abundance of information. Through the review of literature and evaluation of the three guidelines I have conducted, I have incorporated the most up-to-date and evidence-based aspects of the three guidelines into a one-page pocket guide. I will use an algorithmic approach in the pocket guide.

Although I will not be evaluating the outcome of the use of the pocket guide, this should be done before the guide becomes widely adopted into clinical practice. I would suggest doing a quantitative quasi-experimental study using a pre-test post-test design. This would allow the researcher to gather data before implementing the pocket guide, gleaning what the rates of practitioner adherence to guidelines are in the local region. From there, the pocket guide would be distributed within the same jurisdiction and a pre-determined amount of time would be allowed to elapse, to promote the implementation and uptake of the guide. Once that time elapses, the post-test data would be collected to evaluate if there was any change in practitioner guideline-adherence. If this hypothetical study showed that the pocket guide did improve guideline-adherence rates, it could be speculated that the previous lower rates were due to a lack of clarity on which guideline to use and how to use that specific guideline.

For my pocket guide I have used the CHA2DS2-VASc risk stratification tool. As mentioned previously, the ESC guidelines require women to have an extra risk factor, which ultimately nullifies sex as a risk factor. Further research should be done to determine if female sex is a true risk factor. In a study performed by Mikkelsen et al. (2012), the authors concluded

that female sex was only a risk factor for stroke in those 75 years of age or greater, and that sex alone should not be automatically considered as an independent risk factor; and should not necessarily be a part of the CHA2DS2-VASc risk stratification tool (Mikkelsen et al., 2012). The ESC guidelines also state that female sex alone does not appear to increase the risk of stroke, if other risk factors are not present (Kirchhoff, 2016). Because of this ambiguity, the algorithm I created does differentiate between sexes and requires females to have a score of two to warrant DOAC treatment.

All three of the guidelines agree that a score of zero does not warrant OAC treatment. Therefore, this guideline does not recommend any OAC for a score of zero. If the patient does have coronary artery disease (CAD) or other vascular disease, they will require aspirin (however, they would then have a score of one [this is addressed below]). All three guidelines also agree that a score of two (regardless of the risk stratification implemented) does warrant OAC. Therefore, this algorithm recommends OAC for a score of 2 but includes an asterisk, indicating that the guidelines should be referred to if the patient has CAD or other vascular disease, to determine if antiplatelet therapy is appropriate.

There is some variation of which family of OACs should be used. The CCS and ESC guidelines recommend DOACs, whereas the ACC/AHA/HRS guidelines suggest warfarin. Therefore, this pocket guide recommends DOACs when OAC treatment is appropriate. The greatest area of confusion in the guidelines is around a risk stratification score of one. The CCS guidelines recommend DOAC treatment with a score of one. The ACC/AHA/HRS guidelines do not take a strong position as they recommend either aspirin, no OAC, or treatment with an OAC. However, this recommendation has only been given Level of Evidence: C, and therefore is a weaker recommendation based on the current research. The ESC guidelines suggest considering

a DOAC with a score of one, this is mostly because of the ambiguity of female sex being a risk factor. The ESC guidelines go on to recommend a DOAC for men with a score of one and for women with a score of two. Because of these recommendations, this pocket guide recommends DOAC treatment with a risk stratification score of one for males who do not have CAD/vascular disease, but not females. Males with a score of one who are less than 65 years of age and have CAD/vascular disease should be prescribed aspirin.

All three guidelines incorporate the HAS-BLED risk stratification tool. None of them recommend withholding OAC treatment based on HAS-BLED; however, there is a recommendation of treating any treatable HAS-BLED conditions, to reduce the risk for major bleeding. Therefore, this pocket guide incorporates HAS-BLED as a prompt for the practitioner to evaluate the patient's risk for bleeding, and treat any treatable conditions that increase the patient's risk.

The pocket guide also includes a chart on the back pertaining to CKD in AF. I have created a chart outlining the recommendations of each guideline for treating thrombo-prophylaxis in AF with the various degrees of CKD. There is also a chart outlining the risk percentage of stroke per year in relation to the CHA2DS2-VASc score.

Summary and Conclusions

In this paper I have reviewed AF's pathophysiology, presentation, and the clinical ramifications it can have. I have detailed how current OAC treatment practices are failing those with AF. The practitioner should be versed in how to appropriately treat their patients with AF, based on their risk stratification, to minimize the risk of thrombo-embolism. Unfortunately, studies have shown that the number of patients being treated appropriately is significantly lower

than it should be. Practitioners often over- or under-estimate their patients' risk for stroke, and therefore, do not prescribe the optimal treatment for them.

I have reviewed the risk stratification tools that are used and how they have evolved. The CHA2DS2-VASc tool is beneficial as it includes age 65 and greater as well as arterial disease as being risk factors. Although it does include female sex as a risk factor, the most recent research indicates that female sex was overemphasized and is not a significant risk factor. We see the evidence of this, as the ESC guidelines require females to have an extra risk factor than men, to negate the sex risk factor. I hope that future evolution of risk stratification tools will modify this to make the tools simpler to use. Also, bleeding risk stratification tools such as HAS-BLED are often referred to in guidelines but do not have as much of a practical implementation. At this point it appears that HAS-BLED helps identify risk factors for bleeding so practitioners can try to remedy them. Perhaps in the future, bleeding risk stratification tools will be integrated with stroke risk stratification tools.

I have reviewed the DOACs which have been a monumental development for AF treatment, and many of the guidelines agree that DOACs are superior to warfarin for the majority of patients. Of course each patient is unique, and each patient must be evaluated individually. There is still a lack of evidence on treatment regimens for CKD and OAC. Even though warfarin is recognized as being the standard OAC for CKD, it is still unclear about its safety and efficacy in ESRD. But at this time certain DOACs have been approved for specific degrees of CKD, and hopefully as more trials are conducted DOACs will prove safe and effective for all levels of CKD.

I have evaluated the ESC, ACC/AHA/HRS, and CCS guidelines, examining their advantages and disadvantages. None of the guidelines are exactly the same and each have pros

and cons that the others do not. It is my argument that this inconsistency is one of the factors that has led to a lack of guideline-based treatment. The inconsistencies can cause confusion for the practitioner, when they are looking for straight forward guidance on how to treat their patient. The guidelines differ on the risk stratification tools and the OACs to use.

I propose that it would be helpful to have a simplified, user-friendly pocket guide to assist new practitioners with treating AF in nonvalvular patients. It is my goal to remove as much uncertainty and fear from the guidelines as possible, to increase the rates of guideline adherence and decrease the rates of mortality and morbidity due to AF induced thrombo-embolism.

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Table 1. *Summary of ESC, ACC/AHA/HRS, and CCS OAC guidelines*

Guideline	Recommended OAC	Risk Tool		OAC Recommendation, by Risk Score			Advantages	Disadvantages
		Bleeding	Stroke	0	1	>/= 2		
ESC	DOAC	HAS-BLED, HEMORR2HAGES, ATRIA, ORBIT, ABC	CHA2DS2-VASc	No tx	Consider DOAC	DOAC	-Includes edoxaban	-Women require 1 extra risk factor -States men w/ a score of 1 and women w/ a score of 2 are likely to benefit from OAC -different risk factors weighted differently but no clarification for clinical decision-making -No clear guidelines on concomitant AF and CKD
ACC/AHA/HRS	Warfarin or DOAC	HAS-BLED	CHA2DS2-VASc	Reasonable to omit tx	Consider no tx	OAC (warfarin or DOAC)	-Recommend DOAC if INR labile w/ warfarin -Includes recommendations for CKD -Clear & concise guidelines	-Edoxaban excluded -Ambiguity if CHA2DS2-VASc = 1
CCS	DOAC	HAS-BLED	CHADS65	->/=65 yrs: DOAC -<65 w/arterial disease: ASA -<65 w/ no arterial disease: no tx	DOAC	DOAC	Excludes edoxaban	Not user-friendly. Ambiguity re: implementing CHADS65

Note. OAC, oral anticoagulant; DOAC, direct oral anticoagulant; CKD, chronic kidney disease; Tx, treatment; w/, with; INR, international normalized ratio; AF, atrial fibrillation; ASA, aspirin

Table 2. *ESC, ACC/AHA/HRS, and CCS recommendations for OAC treatment in AF with concomitant CKD*

Guideline	Renal Function			
	CrCl>50ml/min	**CrCl 30-49ml/min**	**CrCl 15-29ml/min**	**ESRD or Dialysis - Dependent**
ESC	OAC can be safely used w/ moderate or moderate-to-severe CKD Monitor renal function regularly and adjust DOAC dose as needed			
ACC/AHA/HRS	-Warfarin (dose-adjusted) -Dabigatran 150mg BID -Rivaroxaban 20mg OD -Apixaban 5 or 2.5mg BID	-Warfarin (dose-adjusted) -Dabigatran 150mg BID -Rivaroxaban 15mg OD -Apixaban 5 or 2.5 mg BID	-Warfarin (dose-adjusted) -Dabigatran 75mg BID -Rivaroxaban 15mg OD	-Warfarin (dose-adjusted)
CCS	-Warfarin (dose-adjusted) -Dabigatran 150mg BID -Rivaroxaban 20mg OD -Apixaban 5mg BID	-Warfarin (dose-adjusted) -Dabigatran consider 110mg BID -Rivaroxaban 15mg OD -Apixaban consider 2.5mg BID	-Dose-adjusted warfarin has been used, but data regarding safety and efficacy are conflicting	-Dose-adjusted warfarin has been used, but conflicting data regarding safety and efficacy – possibly causes harm

Note. OAC, oral anticoagulant; DOAC, direct oral anticoagulant; CKD, chronic kidney disease; w/, with; ESRD, end stage renal disease; CrCl, creatinine clearance; OD, once daily; BID, twice daily