CARDIOLOGY

PROPER USE OF ANTICOAGULANTS FOR STROKE PREVENTION IN ATRIAL FIBRILLATION

Stroke Prevention in Atrial Fibrillation: The Guidelines

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Chapter 1: STROKE PREVENTION IN ATRIAL FIBRILLATION: THE GUIDELINES

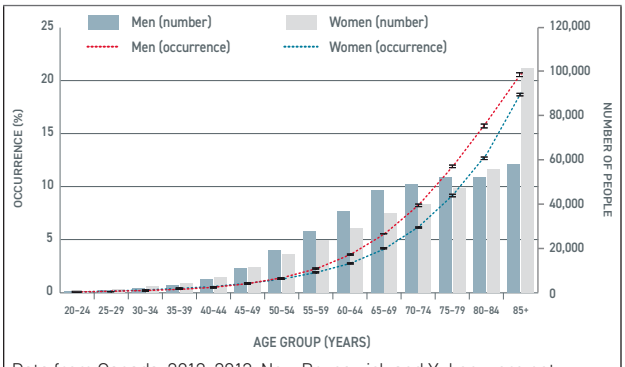
In the setting of atrial fibrillation (AF), anticoagulation significantly reduces the risk of stroke. Yet, studies have shown repeatedly that AF patients have not received appropriate anticoagulation whether the goal is primary or secondary prevention. The problems have included failure to place AF patients on any anticoagulation, failure to employ a therapeutic dose, and failure of patients to adhere to their prescription. Understanding the reasons for the disappointing adherence to guidelines provides an opportunity to reverse an ongoing source of preventable mortality and morbidity. The goal of this program will be to emphasize the risk of stroke in patients with AF and clarify the evidence-based strategies for the proper management of AF patients whether preventing a first stroke or recurrent strokes. With greater adherence to proper use of anticoagulation, a substantial reduction in preventable morbidity and stroke-related death can be anticipated.

Epidemiology of Stroke in Atrial Fibrillation

Atrial fibrillation (AF) is an important but readily modifiable risk factor for stroke.[1] Patients with AF have a five-times greater risk of stroke than those without AF.[2] Of ischemic strokes, which account for approximately 80% of all strokes,[3] 20% to 30% are attributed to AF, but the proportion grows in aging patients, exceeding 35% in those older than 80 years of age.[4] In Canada, where stroke is the third most common cause of death and tenth largest cause of disability,[5,6] strategies to reduce risk of stroke in AF patients represents a major target of avoidable morbidity and mortality. In AF patients who have experienced an initial stroke, the age-adjusted risk for a recurrent stroke in the absence of anticoagulation is increased by more than two-fold.[7]

Whether strokes are ischemic or hemorrhagic, risk increases with age.[3] Calculated from the age of 25, the lifetime risk of stroke is 25%,[8] but events track with the prevalence of modifiable risk factors for vascular disease, including hypertension, diabetes mellitus, dyslipidemia, and obesity.[3] As a result, stroke incidence in Canada, as elsewhere, remains low until late middle age when the consequences of poor lifestyle choices, such as sedentary behavior and an unhealthy diet, contribute to vascular diseases, including stroke (Figure 1).

FIGURE 1 | Stroke Occurrence and Number of People, by Age Group and Sex



Data from Canada, 2012–2013; New Brunswick and Yukon were not available. NOTES: The 95% confidence interval shows an estimated range of values which is likely to include the true value 19 times out of 20.

Public Health Agency of Canada, using Canadian Chronic Disease Surveillance System data files contributed by provinces and territories, May 2016.

In Canada, about 10% of adults aged 65 years or older have experienced a stroke, and more than 400,000 individuals are living following a stroke.[9] The stroke incidence is modestly higher in men than women, but women represent a greater proportion of survivors 80 years of age or older. From 2003 to 2012, there was a decline in the incidence and mortality attributed to stroke in Canada, due possibly to better and more prompt treatments, but the absolute number of stroke survivors is rising due both to population growth and the aging of the Canadian population.[9]

AF, the most common type of cardiac arrhythmia, is also age-related. With a lifetime risk of approximately 25%, the prevalence of AF doubles with every decade of life.[10] Due to the increased life expectancy and demographic shift that is increasing the proportion of individuals aged 65 or older in Canada and many other countries, an epidemic of AF that is already underway is expected to persist for the next two decades.[11] In addition to age, many risk factors for ischemic stroke, including hypertension, obesity, diabetes mellitus, and coronary artery disease, are shared with AF.[12] By itself, AF is associated with a two-fold increase in all-cause mortality in women and a 50% increase in men.[13] Stroke is only one contributor. Nearly one-third of patients have left ventricular dysfunction by the time they develop AF.[12] Disseminated vascular disease is implicated in the high rates of deaths due to myocardial infarction and other heart-related causes in patients with AF as well as in the subclinical ischemia that is now understood to be the cause of neurological deficits in AF patients even in the absence of stroke.[14,15]

Furthermore, stroke patients with AF are more likely to have a higher disability and mortality. For example, a study from Ontario, Canada comprising over 12,000 patients with an acute ischemic stroke showed 30% lower likelihood of being independent at 30 days among patients with AF compared to those without AF.[16] In this study, stroke patients with AF also had higher risk of death at 30 days (22.3% versus 10.2%; $P<0.0001$), 1 year (37.1% versus 19.5%; $P<0.0001$) and death or disability at discharge (69.7% versus 54.7%; $P<0.0001$) compared with non-AF patients. In addition, patients with AF were less likely to recover from intravenous thrombolysis compared to those without AF. Other studies have found similar results.[4,17] In patients with a first stroke, a new diagnosis of AF is associated with an increased risk of recurrent stroke even relative to patients with known AF.[18]

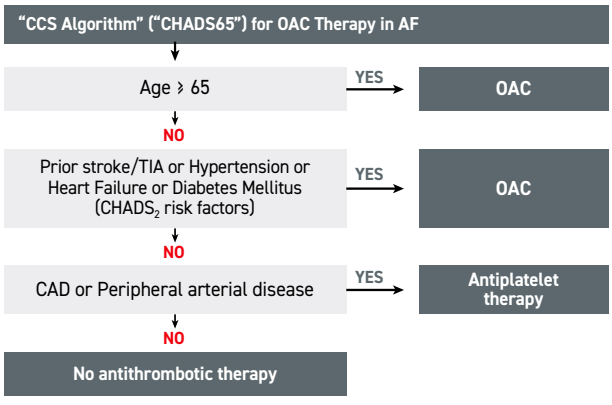
As a consequence, both primary and secondary stroke prevention among patients with AF are critical. In patients with AF, there is a near universal benefit from stroke prophylaxis with anticoagulation therapy, according to multiple evidence-based guidelines.[12,19-21] This is due to very high rates of death and disability that preserve a favourable benefit-to-risk ratio for primary or secondary prevention in the vast majority of individuals with AF. Relative to individuals who develop stroke in the absence of AF, AF patients are significantly more likely to be chronically disabled following stroke ($P<0.0005$) and nearly twice as likely to die within six months ($P<0.001$).[4,17] AF patients with even minor strokes or transient ischemic attacks (TIAs) are at increased risk of cardiovascular events as well as recurrent strokes.[21] Consequently, risk classification is critical for stroke prevention among patients with AF. For example, a previous study on nearly 100 opinion leaders revealed risk classification errors in 50% of simulated AF scenarios and therapeutic inertia, defined as lack of initiation of oral anticoagulation, in 60%.[22]

The Solution: Managing Stroke Risk in Patients with AF

Each of the major guidelines for the management of AF, including those written for Canada,[19] the United States,[20] and Europe,[12] recommend oral anticoagulation for primary stroke prevention, identifying candidates with risk scoring systems. In Canada, guidelines for secondary prevention of stroke emphasize the importance of screening for AF and implementing anticoagulation as well as vascular risk modification in such patients.[21]

The European and U.S. guidelines both identify candidates for anticoagulation with CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular Disease, Age and Sex), which is an updated version of $CHADS_2$, which did not consider vascular disease or gender.[23] The Canadian Cardiovascular Society (CCS) guidelines employ CHADS-65, a simplified version of $CHADS_2$.[19] According to the CHADS-65 algorithm, oral anticoagulation should be routinely considered in any AF patients more than 65 years of age (Figure 2). It is also recommended for younger patients with any of the risk factors identified in $CHADS_2$, which includes prior stroke, hypertension, heart failure, or diabetes mellitus. Due to the frequency with which AF occurs in patients over the age of 65 years or in those with common cardiovascular risk factors, such as hypertension, most patients with AF are likely to be candidates for non-vitamin K antagonist oral anticoagulants (NOACs) for primary stroke prevention.

FIGURE 2 | The CCS Guidelines Recommend NOACs in Preference to Warfarin for Most Patients with AF



CCS: Canadian Cardiovascular Society; NOAC: non-vitamin K antagonist oral anticoagulant; CAD, coronary artery disease

Andrade JG et al. *Can J Cardiol* 2018;34:1371-92.

Although based on CHA_2DS_2-VASc, the European guidelines for primary stroke prevention are similar.[12] Oral anticoagulation is recommended for any man with a score of one or greater and any woman with a score of two or greater. A score of one is obtained for anyone of 65 years or greater and anyone with a history of vascular disease, defined as history of myocardial infarction, peripheral artery disease, or aortic plaque. An age of 75 years or older is given a score of two. The U.S. guidelines call for two risk factors in men and three in women irrespective of age,[20] but, again, exemptions on this basis would be expected to be limited among patients in the age range where AF typically occurs.

The Canadian Stroke Best Practice Recommendations (CSBPR) for secondary stroke prevention calls for routine screening for AF.[21] In those with AF, the same protection from the high rates of disability and mortality are anticipated from preventing a second stroke as from preventing the first.[24,25] In long-term management, NOACs are the preferred treatment option for most patients with AF and recurrent stroke. Patients with a mechanical heart valve are an exception. In those taking warfarin, dosing within target international normalized ratio (INR) is essential for optimizing benefit. These climb from a range of 2.0 to 3.0 in the absence of a mechanical heart valve to 2.5 to 3.5 in those with a valve. For those taking NOACs, patients should be informed of the danger of missed doses and monitored routinely for adherence. To adjust NOAC doses appropriately, renal function should be assessed annually or more often in those at risk of altered renal function.

All of the major guidelines now recommend NOACs over the vitamin K antagonist warfarin, which had once been a standard.[12,19,20] There are four agents in this class approved in Canada. Although warfarin remains an acceptable alternative in each of the guidelines, the NOACs are preferred on the basis of clinical trials showing similar or greater efficacy with similar or lower rates of the intracranial haemorrhage, the most feared type of bleeding. In addition, NOACs are easier to use. Unlike warfarin, they do not require INR monitoring and dose adjustments to ensure adequate anticoagulant effect.

In general, AF patients at increased or high risk of bleeding are not contraindicated for oral anticoagulation. The European guidelines, for example, recommend identifying and treating modifiable risk factors for bleeding but conclude that oral anticoagulation should not generally be withheld due to an elevated bleeding risk.[12] The CCS guidelines for prevention of stroke in patients with AF also acknowledge bleeding risk factors without specific limitations on anticoagulant prophylaxis.[19]

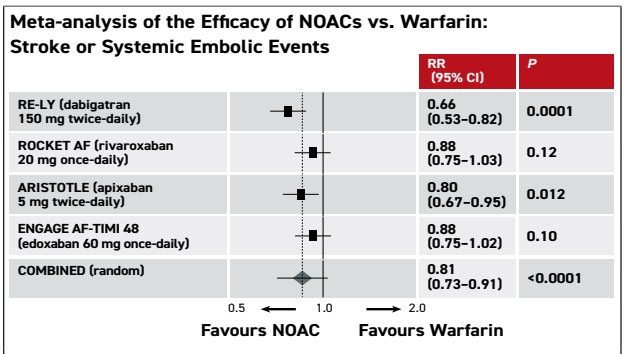
Pivotal Trials: NOACs as Standard for Stroke Prevention

Warfarin is highly effective for stroke prevention in AF patients,[26] but the preference for NOACs in current guidelines is evidence-based. NOACs are not interchangeable for important characteristics, such as safety in patients with compromised kidney function, but pivotal trials with each of these agents showed each to be at least as effective and safe as warfarin. The four

NOACs available in Canada are the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, and dabigatran, a direct thrombin inhibitor.

The pivotal NOAC trials had similar designs. In each, the NOAC was tested for non-inferiority to warfarin for the primary outcome of stroke or embolism. All NOACs were associated with at least a numerically lower risk of the primary outcome relative to warfarin with the difference reaching significance in the RE-LY trial with dabigatran. In a meta-analysis of these trials, the 19% reduction for NOACs versus warfarin was highly significant (*P*<0.0001)[27] (Figure 3).

FIGURE 3 | NOACs are as Effective as Warfarin for Stroke Prevention

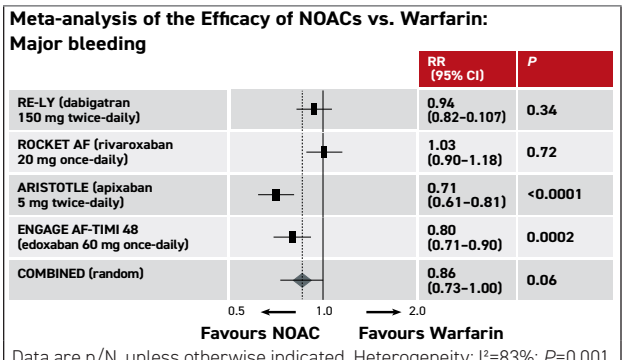


Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; *P*=0.13. NOAC: non-vitamin K antagonist oral anticoagulant; RR=risk ratio.

Ruff CT et al. *Lancet* 2014;383(9921):955-62.

When compared for bleeding events, the pivotal trials indicated that risk of bleeding was no greater on NOACs than warfarin. In two of the trials, ARISTOLE with apixaban (*P*<0.0001) and ENGAGE AF-TIMI 48 trial with edoxaban (*P*=0.0002), there was a significant advantage for the NOAC over warfarin. In the meta-analysis of these pivotal NOAC trials, the reduction in the bleeding risk for NOACs approached statistical significance (*P*=0.06) (Figure 4).

FIGURE 4 | NOACs are as Safe as Warfarin for Relative Risk of Bleeding



Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; *P*=0.001. NOAC: non-vitamin K antagonist oral anticoagulant. RR=risk ratio.

Ruff CT et al. *Lancet* 2014;383(9921):955-62.

In ROCKET-AF,[28] rivaroxaban was non-inferior to warfarin for the primary endpoint on an intention-to-treat analysis but statistically superior on the per-protocol analysis. Rivaroxaban was associated with an increase in some non-fatal bleeding events, but a significant reduction in hemorrhagic stroke and intracranial bleeding. No mortality advantage was observed.

In the ARISTOTLE trial,[29] apixaban was associated with a significant 21% reduction in the primary outcome, a 31% reduction in major bleeding, and an 11% reduction in all-cause mortality. In a further breakdown of secondary endpoints, apixaban was associated with a significant reduction in hemorrhagic stroke and intracranial bleeding relative to warfarin, but ischemic stroke was not significantly reduced.

In the ENGAGE AF-TIMI 48 trial,[30] the 60 mg dose of edoxaban was associated with a 21% reduction in the primary endpoint relative to warfarin (*P*<0.001) along with a 20% reduction in risk of major bleeding (*P*<0.001). The 60 mg dose of edoxaban, which is the standard, was also associated with a relative 14% reduction (*P*=0.013) in cardiovascular death and 10% reduction (*P*=0.02) in a composite secondary endpoint of stroke, systemic embolic event, or death.

In the RE-LY trial, the 150 mg dose of dabigatran was associated with a 35% reduction in the primary endpoint relative to warfarin. Ischemic stroke was reduced by 24% and vascular mortality was reduced by 15%. A 12% reduction in death from any cause narrowly missed statistical significance (*P*=0.051). The 150 mg dose of dabigatran was associated with increased risk of gastrointestinal bleeding but not in major bleeding. It was associated with a 60% reduction in intracranial bleeding.

It is not possible to compare NOACs across trials, but the NOACs are collectively considered to have a favorable benefit-to-risk ratio relative to warfarin. In a meta-analysis of the more than 70,000 patients enrolled in these four trials, NOACs were associated with a 19% reduction (*P*<0.0001) in stroke or systemic embolic events and a 10% reduction (*P*=0.0003) in all-cause mortality.[27] The meta-analysis also associated NOACs with a 51% reduction (*P*<0.0001) in intracranial hemorrhage.

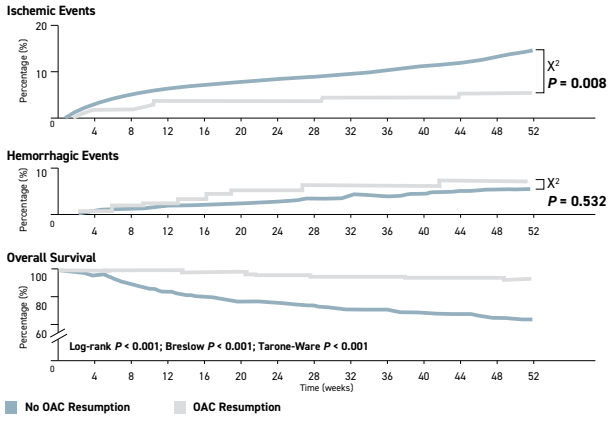
In this meta-analysis, gastrointestinal bleeding was 25% higher (*P*=0.04) on NOACs relative to warfarin, but there was significant heterogeneity (*P*=0.001) among the NOACs for the category of major bleeding.[27] The combined data associated NOACs with a 14% reduction in this outcome relative to warfarin, which did not reach significance, but the 29% reduction in risk of bleeding associated with 5 mg apixaban (*P*<0.0001) and the 20% reduction (*P*=0.0002)

associated with edoxaban were both significant. The 6% reduction associated with 20 mg rivaroxaban was not, and major bleeding was increased by a non-significant 3% for 150 mg of dabigatran relative to warfarin.

Despite variability in the efficacy and safety outcomes, the NOACs as a group offer a favourable risk-to-benefit ratio relative to warfarin, according to the authors of this meta-analysis.[27] In addition, the favourable efficacy and safety was characterized as consistent across a wide range of patients. Differences between NOACs might be relevant in some patient groups, such as the elderly,[32] but these data support NOACs as a guideline-directed preferred therapy.[10,12,20]

The relative advantages of NOACs over warfarin extend to patients with recurrent stroke, according to the CSBPR,[21] but the timing of resumption of anticoagulation remains controversial. Although a mortality benefit from restoring anticoagulation has been observed even in stroke patients who have had a prior intracerebral hemorrhage (ICH)[33] (Figure 5), there is concern that resumption too soon after a first ischemic stroke might increase risk of ICH whereas resumption too late might leave patients vulnerable for recurrent stroke. The data from published studies, most of which are small or retrospective, have been inconsistent.[34] Although the European Society of Cardiology advocates a 1-3-6-12 rule of thumb,[35] which calls for resumption of anticoagulation one day after a transient ischemic attack, three days after a non-disabling stroke, six days after a moderate stroke, and 12 days after a major stroke, guidelines in the United Kingdom and Germany conclude that there is insufficient data to judge safety and efficacy at a start day anytime within 14 days of a stroke.[34]

FIGURE 5 | Resumption of OAC Following OAC-associated ICH Associated with Reduced Ischemic Events and Improved Survival



OAC: oral anticoagulation; ICH: intracerebral hemorrhage

Kuramatsu JB et al. *JAMA* 2015;313(8):824-36.

Ongoing Trials Hope to Determine Optimal Timing for Treatment Initiation

The question of the optimal timing for resumption or new start of an oral anticoagulant might be settled by four large randomized multicenter trials that are now ongoing (Figure 6). Ranging in size from 1000 to nearly 4000 patients, three of the trials, TIMING, START, and ELAN, are scheduled for completion in 2021. A fourth trial will be completed in 2022. Each is comparing an early to some later resumption of a NOAC after an ischemic stroke in AF patients. Designs differ, but an early start is generally defined as within four days. The delayed starts range from five days to more than 14 days after stroke. In each of the trials, patients are permitted to take any of the four currently approved NOACs. These four trials hope to provide further insight into whether early NOAC treatment has the same degree of safety and efficacy as late treatment initiation. Trial results in favour of early treatment would likely impact patient convenience via early hospital discharge as well as clinical practice in regards to improved compliance and continuation of anticoagulant medication started in hospital.

FIGURE 6 | NOAC Studies Ongoing to Evaluate Best Timing of Post-stroke Initiation

Study Name	Population	Interventions & timing	Anticipated completion
TIMING[1]	3,000 patients with AIS and AF	Any NOAC starting on Days 1-4 or Days 5-10 post-stroke	May 2021
START[2]	~1,000 patients with AIS and AF	Any NOAC starting at one of four times post-stroke: 60 hours (Day 3); 132 hours (Day 6); 228 hours (Day 10); or 324 hours (Day 14)	Aug. 2021
ELAN[3]	~2,000 patients with AIS and AF	NOAC (apixaban, dabigatran, edoxaban or rivaroxaban) administered early (<48 hours) or late (as per current recommendations) post-stroke	Oct. 2021
OPTIMAS[4]	3,478 with AIS and AF	Any NOAC administered early (<96 hours) or late (7-14 days)	Sept. 2022

AIS: acute ischemic stroke; AF: atrial fibrillation

Clinicaltrials.gov Identifiers: 1. NCT02961348; 2. NCT03021928; 3. NCT03148457; 4. NCT03759938.

Oral Anticoagulation in the Emergency Department Upon AF Diagnosis

Upon diagnosis of AF in an emergency department, new evidence shows that patients are more likely to fill a prescription for oral anticoagulation if it is provided prior to discharge.[36] In this cohort study involving 15 Canadian hospitals, the absolute risk of not filling a prescription for oral anticoagulation at six months was increased by 30.6%. At 12 months, it was increased by 23.2%. The numbers needed to treat at these time intervals were three and four, respectively. The disparities in adherence point to one source for the therapeutic gap in stroke prevention.

Summary

Oral anticoagulation is a proven strategy for reducing the high clinical toll imposed by primary and secondary stroke in AF patients. According to major guidelines, including those issued in Canada, the evidence base for major risk reductions with oral anticoagulation in general and NOACs specifically is compelling. The guidelines for both primary and secondary prevention are simple. All patients without a clear contraindication should receive a NOAC, typically administered in standard doses. In the CCS guidelines, only those under the age of 65 years without history of heart failure, hypertension, diabetes mellitus, prior thromboembolism, or cerebrovascular attack are exempted from primary stroke prevention.[19] For secondary stroke prevention, the CSBPR indicate that all AF patients should be considered candidates for oral anticoagulation. Adherence to current guidelines offers an opportunity to reduce an important source of morbidity and mortality in Canada. ●

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Chapter 2: STROKES IN AN ERA OF EFFECTIVE PREVENTION

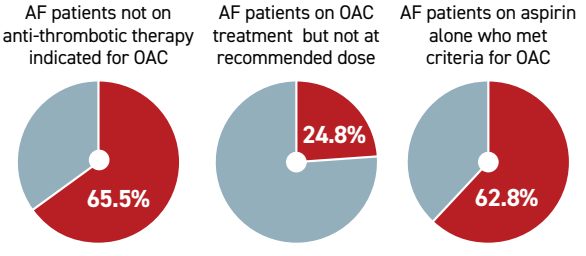
In Canada, about one fifth of ischemic strokes are attributed to atrial fibrillation (AF). Of stroke causes, AF-associated stroke is considered one of the most preventable. The benefit of the vitamin K antagonist warfarin has been clearly established in multiple large clinical trials and subsequent trials with non-vitamin K antagonist oral anticoagulants (NOACs) have shown a similar benefit associated with a lower risk of bleeding. The problem is that these drugs are underutilized at least in part due to fear of inducing bleeding. The guidelines for use of oral anticoagulants are relatively simple and evidence-based, but studies show that these agents are frequently withheld or NOACs are used in reduced dosages to avoid risk of bleeding. Modified dosing is appropriate in a few well-defined subgroups, but due to the devastating consequences of major strokes, the benefit-to-risk ratio favors full doses of NOACs in the majority of AF patients who are candidates for stroke prevention.

The Persistent Problem of No or Inadequate Anticoagulation

In randomized trials, oral anticoagulation in patients with AF reduces the risk of stroke by up to 85% relative to no treatment and by 50% relative to aspirin alone.[1-3] The benefit-to-risk ratio of stroke prevention favors oral anticoagulation in almost all patients because the risk of serious debilitating and life-threatening strokes is high, typically overwhelming the relatively modest risk of clinically significant bleeding, according to the evidence-based guidelines.[4-6] In a population-based net-benefit calculation of 182,678 subjects in Sweden, it was estimated that only 3.9% of AF patients would not benefit.[7] These were AF patients at lowest risk, defined as a score of 0 on the CHA_2DS_2-VASc calculator. Such patients are already excluded from oral anticoagulation in current guidelines.

In recommending routine stroke prevention with oral anticoagulation in all AF patients, except those younger than 65 years of age with no vascular risk factors, such as hypertension or diabetes, the major guidelines are consistent.[5,6,8] Yet, there are numerous sets of data suggesting that a substantial proportion of AF candidates for oral anticoagulation are being undertreated. In a national chart review of more than 7000 patients with nonvalvular AF undertaken in Canada, 65.5% of those not taking any oral anticoagulant were candidates by guideline criteria, while 24.8% of those receiving oral anticoagulation were not on the recommended dose[9] (Figure 1).

FIGURE 1 | National Chart Audit of 7,019 Patients with Atrial Fibrillation in Canada

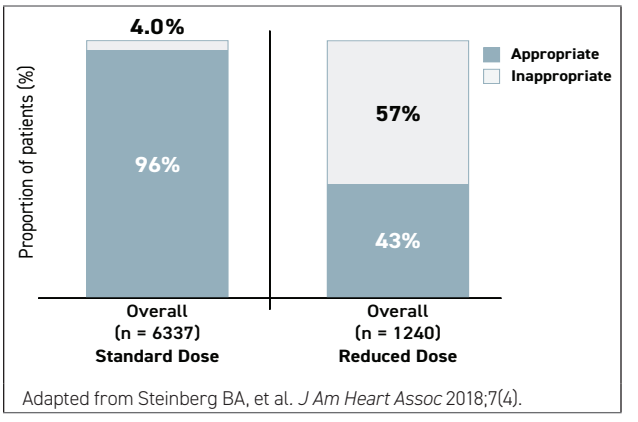


Adapted from Bell AD, Gross P, Heffernan M, et al. *Am J Cardiol* 2016;117:1107-11.

In AF patients on oral anticoagulation who have a stroke, inadequate dosing has been documented repeatedly. In one study of 60 patients on a NOAC, more than one third (34.1%) were prescribed a subtherapeutic dose and 25% were not adherent to their treatment.[10] In a study undertaken in Canada, an analysis of 24 patients who had an ischemic stroke while on a NOAC found that only 10 (42%) were taking an appropriate dose.[11] Of the remaining, seven were on long-term therapy with a lower-than-recommended dose and six did not receive recommended NOAC treatment when undergoing surgery.

When inappropriate doses of oral anticoagulation are prescribed, the problem by far is too little therapy rather than too much. In the ORBIT-II trial, which evaluated NOAC use in nearly 8000 patients, 57% of those taking a reduced dose were undertreated by guideline criteria.[12] Of those on standard doses, just 4% were overdosed (Figure 2). When compared, those on a reduced dose had a 50% increased likelihood of a thromboembolic event (HR 1.56) and a more than two-fold increased likelihood of death (HR 2.61) relative to those on a standard dose. After risk adjustment, these risks were no longer significant, but the authors maintained that this does not negate the finding that most patients on reduced doses of NOACs are not being treated according to product monograph recommendations.

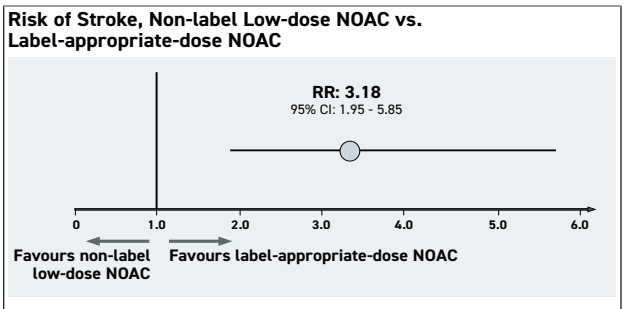
FIGURE 2 | Frequency of Inappropriate NOAC Dosing in a Large U.S. Cohort (ORBIT-II)



Adapted from Steinberg BA, et al. *J Am Heart Assoc* 2018;7(4).

In a multinational case-control study that compared 713 consecutive AF patients with an ischemic stroke to 700 consecutive AF patients without a cerebrovascular event, low doses of NOACs were associated with a more than three-fold increased odds ratio (OR 3.18; 95% CI, 1.95 – 5.85) of ischemic events on a multivariate analysis.[13] This increase was statistically significant (Figure 3). Many patients on low doses of NOACs had a history of bleeding or were on concomitant antiplatelet therapy, which were cited as reasons for a fear of bleeding and the justification for a low-dose regimen.

FIGURE 3 | 3-Fold Higher Risk of Stroke among AF Patients Treated with Subtherapeutic NOAC Dose



Case-control study at 37 stroke units across Europe, North America and Asia, between January 2016 and June 2018. **Cases**: 713 consecutive patients with AF who had acute cerebrovascular ischemic events during NOAC treatment. **Controls**: 700 consecutive patients with AF who did not have cerebrovascular events during NOAC treatment.
Adapted from Paciaroni M, et al. *Stroke* 2019; 50(8):2168-74.

Presumably, many patients are prescribed reduced doses of NOACs in an effort to lower bleeding risk, but this practice is not consistent with guideline recommendations. In a study of 14,865 AF patients, 1,473 (9.9%) were on a reduced NOAC dose due to renal dysfunction. However, 13.3% of the remaining 13,392 were also on a lower dose with no clear indication although advanced age was associated with underdosing.[14] In these patients, the risk of stroke was increased almost five-fold (HR 4.87; 95% CI, 1.30 – 18.26). Yet, the lower dose was not associated with significant protection from major bleeding. In a trial that showed significantly greater adherence to once-daily NOAC than twice-daily NOAC therapy, there was no significant increase in minor or major bleeding in the group on once-daily therapy.[15]

Many of the risk factors for AF and stroke associated with AF, such as advancing age, are also risk factors for bleeding. The guidelines recommend full doses of oral anticoagulation even in patients with risk factors for bleeding on the basis of benefit-to-risk calculations that favor stroke prophylaxis when these competing risks are calculated together. Although many guidelines recommend bleeding risk assessment with the goal of correcting those that are modifiable, low risk of stroke rather than high risk of bleeding is the major reason for exempting patients from long-term oral anticoagulation.

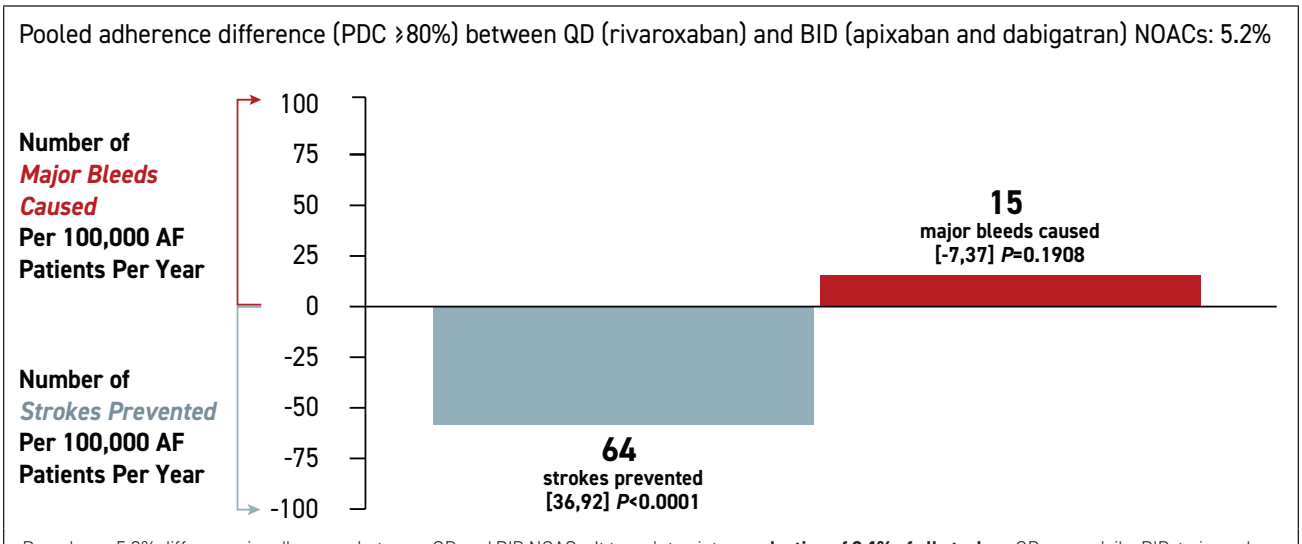
The Health and Financial Cost of Non-Adherence

When compared to vitamin K antagonists, NOACs have several advantages that have led them to be granted preferred status in major guidelines. In one large analysis of randomized trials, NOACs were at least as effective as warfarin for prevention of stroke but were associated with a significantly lower risk of hemorrhagic strokes and other major bleeding events.[16] In addition, NOACs provide an antithrombotic effect on the first day, accelerating the time to protection when compared to the two to four days typically required after initiation of warfarin to reach therapeutic levels. NOACs, by circumventing the need for therapeutic monitoring, are also easier to administer. In one study of AF patients admitted for ischemic stroke while taking an oral anticoagulant, the dose at admission was subtherapeutic in 91.7% of those on a vitamin K antagonist (international normalized ratio [INR] <2.0) versus 43% of those on a NOAC.[10]

Of the obstacles to stroke prevention with oral anticoagulation in patients with AF, none are likely to be more important than adherence. In a recent population-based cohort study, more than 40% of AF patients initiating oral anticoagulation were not fully adherent whether receiving warfarin or a NOAC 12 months after initiating therapy.[17] For a group of therapies with a low risk of side effects, intolerance is an unlikely explanation for diminishing adherence over time. Rather, simple regimens that are easy to remember and to take appear to improve adherence to oral anticoagulants as they have for other conditions requiring chronic therapy, such as chronic obstructive pulmonary disease (COPD) or hypertension.[18,19]

In one multicenter cross-sectional study of 2214 AF patients taking NOACs for at least three months, a once-daily NOAC increased the likelihood of adherence by more than 10% (P=0.001).[15] Speculation that twice daily dosing might better compensate for missed doses is not supported by a study that addressed this question. When AF patients with suboptimal adherence to once- versus twice-daily oral anticoagulation were compared, stroke rates were nearly identical.[20] In another study assessing once- versus twice-daily dosing, a substantially improved benefit-to-risk ratio was identified in real-world data. In a claims database of more than 50,000 patients, a non-significant increase of 15 major bleeds (P<0.191) among those taking once- versus twice-daily NOAC was counterbalanced by 64 fewer strokes (P<0.001)[21] (Figure 4). The reduction in strokes was associated with a large cost saving.

FIGURE 4 | Better Adherence with QD vs BID NOACs Leads to a Significant Number of Strokes Prevented, with no Significant Difference in Major Bleeding



Based on a 5.2% difference in adherence between QD and BID NOACs. It translates into a **reduction of 2.1% of all strokes.** QD: once-daily; BID: twice a day
Adapted from McHorney CA, et al. *Curr Med Res Opin*, 2019, 35(4), 653-660.

Sustaining Benefits of Anticoagulation

Due to the important protection afforded by oral anticoagulation against stroke in patients with AF, strategies to sustain optimal protection have been developed for specific situations in which the benefit-to-risk of this therapy might be altered. This includes those undergoing a surgical procedure, those who have a first ischemic stroke, and those who have had a hemorrhagic stroke. In a retrospective study conducted at McGill, six of 14 strokes in AF patients attributed to inappropriate NOAC use involved inappropriate discontinuation or an unnecessarily prolonged discontinuation of the anticoagulant for a surgical procedure.[11]

For perioperative risk management, Thrombosis Canada offers specific although similar recommendations for each of the available NOACs: dabigatran, rivaroxaban, apixaban, and edoxaban.[22] In all cases, discontinuation of oral anticoagulants, whether NOACs or warfarin, is not recommended for minor surgery, such as root canals, cataract procedures, coronary angiography, or pacemaker insertion. For surgery associated with moderate risk of bleeding, such as orthopedic, vascular, or laparoscopic surgery, discontinuation of the NOAC two days before the surgery is recommended for those with normal renal function but three days prior in those with impaired renal function taking dabigatran. Withholding NOACs three days prior to surgery is also recommended for high-risk procedures, such as neurosurgery, major cardiac surgery, or extensive cancer resections. The exception is for those on dabigatran with renal impairment in which drug discontinuation is recommended five days in advance (Table 1).

Following surgery with moderate bleeding risk, all of the oral anticoagulants should be resumed the day after the procedure. Following surgery with a high bleeding risk, resumption should take place 48 to 72 hours after surgery, although an earlier prophylactic dose can be considered.

For episodes of bleeding unrelated to surgery, oral anticoagulants should be continued if bleeding is expected to be self-limited, such as bruising, according to Thrombosis Canada.[23] For major bleeding requiring medical attention, it is reasonable to consider withholding oral anticoagulation until the bleeding has stopped. This decision should be made within the context of bleeding severity and the expected duration of anticoagulant effect, which relates to such factors as timing of the last dose and drug half-life. If the risk posed by uncontrolled bleeding is considered to exceed the risk of a thromboembolism, additional steps, such as the introduction of an anticoagulation drug reversal agent, if available, might be appropriate. Oral anticoagulation should be resumed as quickly as possible after bleeding has been controlled and the risk of rebleeding is low.

In AF patients who have had a stroke, oral anticoagulation should be started or resumed as quickly as possible for secondary prevention. In this case, as in primary prevention, NOACs are preferred.[24] The exceptions are those who have a mechanical heart valve, for whom warfarin with tight INR monitoring is preferred. All patients with a stroke should be screened for the presence of AF and placed on oral anticoagulation for secondary prevention if this arrhythmia is found.

In AF patients who have had a cerebrovascular event, the optimal timing for resuming oral anticoagulation is not evidence-based. According to one expert consensus, starting or resuming treatment on the same day or within one day of a transient ischemic attack, three days of a mild stroke, six days of a moderate stroke, and 12 days of a severe stroke is reasonable.[24] Several large randomized trials evaluating early and late start of NOACs to prevent recurrent stroke are in progress, three of which will yield data before the end of 2021.

TABLE 1 | Thrombosis Canada Recommendations for Pre-Operative Management of NOAC Therapy

Drug	Renal function	$t_{1/2}$ (hrs)	Moderate bleeding risk procedure (12-25% residual anticoagulant effect at time of surgery acceptable)	High bleeding risk procedure (<10% residual anticoagulant effect at time of surgery acceptable)
Apixaban (b.i.d.)	CrCl ›30mL/min	8-12	Last dose 2 days before surgery/ procedure (i.e., skip 2 doses)	Last dose 3 days before surgery/ procedure (i.e., skip 4 doses)
Dabigatran (b.i.d.)	CrCl ›50mL/min	7-17	Last dose 2 days before surgery/ procedure (i.e., skip 2 doses)	Last dose 3 days before surgery/ procedure (i.e., skip 4 doses)
	CrCl 30-49 mL/min	7-20	Last dose 3 days before surgery/ procedure (i.e., skip 4 doses)	Last dose 5 days before surgery/ procedure (i.e., skip 8 doses)
Edoxaban (q.d.)	CrCl ›30mL/min	10-14	Last dose 2 days before surgery/ procedure (i.e., skip 1 dose)	Last dose 3 days before surgery/ procedure (i.e., skip 2 doses)
Rivaroxaban (q.d.)	CrCl ›30mL/min	7-11	Last dose 2 days before surgery/ procedure (i.e., skip 1 dose)	Last dose 3 days before surgery/ procedure (i.e., skip 2 doses)

Adapted from Thrombosis Canada. Clinical Guides: NOACs/DOACs: Perioperative Management. http://thrombosiscanada.ca/clinicalguides/

Similarly, the optimal time to resume oral anticoagulation in AF patients following an intracranial hemorrhage is unknown.[25] In a review, modifiable risks were identified for stroke and recurrent intracerebral hemorrhage. The authors counseled individualizing the decision to resume anticoagulation based on both. More guidance is expected from the ongoing trial that will randomize patients at different time intervals following intracranial hemorrhage to a low- or high-dose NOAC regimen.[26] Outcomes will be compared at 24 months.

Summary

Appropriate use of oral anticoagulation presents a major opportunity to reduce the risk of mortality and morbidity associated with stroke. Approximately one in five strokes are associated with AF, patients with AF are five times more likely to have a stroke than matched patients without AF, and AF-associated strokes are more likely to lead to disability than strokes of other types.[27] Based on data that support the premise that most strokes related to AF can be prevented with oral anticoagulation, it is essential for clinicians to screen aging patients for AF and to initiate oral anticoagulation in all but those under the age of 65 without other stroke risk factors, such as vascular disease or congestive heart failure.

The frequency with which patients with known AF are not receiving oral anticoagulation or are receiving subtherapeutic doses emphasizes a need to reevaluate obstacles. For providers, concern about bleeding in patients who are elderly, have a history of bleeding, or are considered to be at high risk of bleeding has been identified as a source of hesitation or uncertainty regarding full-dose therapy. Similarly, failure to resume anticoagulation after surgery, after a significant bleeding event, or after a first stroke, might represent missed opportunities for stroke prevention. Guidelines outline evidence-based strategies for most of these scenarios. All of the obstacles to stroke prevention in AF patients, including inadequate adherence, are readily addressed by a more rigorous and systematic approach. ●

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Chapter 3: PRACTICAL CONSIDERATIONS FOR ORAL ANTICOAGULANTS IN STROKE PREVENTION

Non-vitamin K antagonist oral anticoagulants (NOACs) are often not employed in recommended or adequate doses for stroke prevention in patients with atrial fibrillation (AF). Largely attributed to fear among clinicians of inducing bleeding events, this suggests there is an incomplete understanding of the major opportunity these agents provide for risk reduction. In almost all patients, benefit-to-risk ratio from stroke prevention is favorable. When compared to warfarin, the four available NOACs have demonstrated similar or superior efficacy in pivotal trials. The modest differences amongst the NOACs in safety relative to warfarin and in pharmacokinetics relative to each other are relevant to dosing or choice of NOAC in some patients. Recognizing the importance of anticoagulation in AF patients and the principles of appropriate therapy provides an important opportunity to reduce an important source of morbidity and mortality in Canada.

Simplifying Choices of NOACs in Stroke Prevention

Anticoagulation is an effective means of reducing the risk posed by AF for stroke and other thromboembolic events, but clot inhibition raises the risk of bleeding. For individuals with AF where anticoagulation is indicated for stroke prevention, the benefit of reducing potentially disabling or lethal ischemic strokes typically exceeds the risk of intracranial hemorrhage (ICH) or major bleeding by a significant margin. Clinicians must weigh these competing outcomes to avoid permitting fear of an iatrogenic ICH or a serious bleed to obscure the more important opportunity for preventing stroke with appropriate doses of anticoagulation.

In calculating these risks, a focus solely on bleeding scores such as the HAS-BLED or HEMORR$_2$HAGES scales provides an incomplete picture, as these scales tend to be co-linear with thromboembolic risk scores (CHADS$_2$ or CHA$_2$DS$_2$-VASc) and the absolute risk of ischemic events. Typically, the margins of benefit from anticoagulation outweigh the absolute increased risk of hemorrhagic events in patients deemed at high risk for bleeding. Regrettably, national registries continue to show alarming rates of anticoagulation under usage. In the PINNACLE registry, a quality initiative sponsored by the American College of Cardiology, only 45% of patients with AF without apparent contraindications to anticoagulation were receiving appropriate anticoagulation.[1]

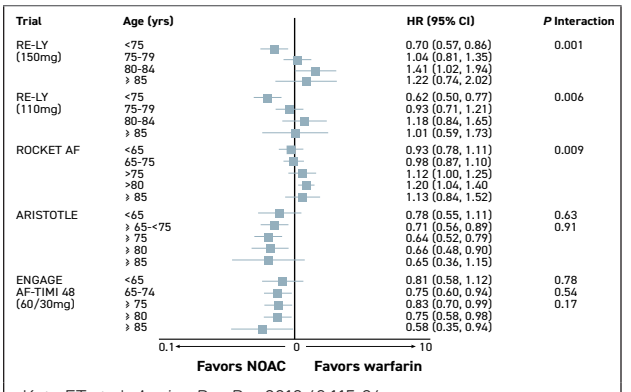
The risk of strokes associated with AF, like risk of AF itself, increases with advancing age.[2,3] Although the risk of major bleeding, including ICH, also increases with age, stroke prevention retains a favorable benefit-to-risk ratio in AF patients across age groups.[4] In a retrospective study that looked specifically at AF patients 90 years or older, there was a net clinical benefit whether the oral anticoagulant warfarin was compared to no treatment or to aspirin.[5] When NOACs were compared to warfarin in this age group, the newer agents were associated with a lower risk of ICH, resulting in an increased net clinical advantage in this very elderly population.

The major guidelines do not impose any age restrictions on stroke prevention in AF patients. Yet, there are multiple sets of data indicating that oral anticoagulation is either withheld or provided at inappropriately low doses in older individuals otherwise indicated for this therapy.[6,7] In one study, the proportion of AF patients receiving an oral anticoagulant at discharge fell incrementally with each decade of age, declining from 75% among those less than 70 years of age to 24% among those 90 years of age or older.[8] When prescribing clinicians were asked why anticoagulation was withheld, risk of hemorrhage was prominent among cited justifications.

Yet, due to greater risk posed by AF-related stroke relative to major bleeding for disability and mortality, the relative advantage of oral anticoagulation is at least as great or greater in older relative to younger individuals.[9] In the major clinical trials of oral anticoagulation for AF patients, the net benefit, which is the reduction in stroke after accounting for any increased risk of bleeding, is derived from full therapeutic doses.[10] With only a limited number of exceptions, such as in patients with severely impaired renal function who were not eligible for the pivotal AF randomized trials, the guideline-recommended doses are appropriate in all patients at risk of AF-associated stroke.

Warfarin is an acceptable oral anticoagulant for stroke prevention in patients with AF, but NOACS are the preferred oral agents in major guidelines on the basis of greater convenience, similar or superior stroke prevention, a halving of ICH risk, and similar or lower risk of major bleeding.[11-13] There is evidence that the potential safety advantage of NOACs increases with advancing age. In the ARISTOTLE trial with apixaban and the ENGAGE AF-TIMI 48 trial with edoxaban,[14,15] bleeding rates trended lower with NOACs relative to warfarin with each 5-year increment of patient age[10] (Figure 1). In a prespecified analysis of the ENGAGE AF-TIMI 48 trial that explored this relationship, the reduction in risk of major bleeding translated into a greater net clinical benefit for those 75 years and older relative to those younger.[16]

FIGURE 1 | Risk of Major Bleeding with NOACs vs. Warfarin by Age Subgroups in Major NOAC Trials

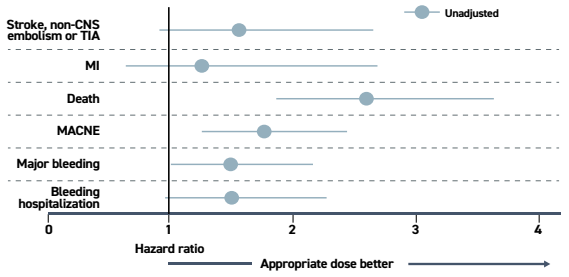


Kato ET et al. *Ageing Res Rev* 2019;49:115-24.

The evidence that older AF patients typically derive greater net clinical benefit from oral anticoagulants relative to younger patients does not negate efforts to minimize bleeding risk at any age. It is, for example, appropriate to consider and address modifiable risk factors, such as, inadequately controlled hypertension, excess alcohol consumption, propensity toward falling, and unnecessary use of medications associated with increased bleeding risk, as well as identifying and treating sources of anemia.[13] However, the presence of risk factors for bleeding, like older age, should not preclude full dose oral anticoagulation in AF patients who are candidates for stroke prevention. In ORBIT-II, 1289 (16%) of 7,925 patients evaluated received NOAC doses judged to be inappropriately reduced.[17] When

this group was compared to those receiving standard doses, the risk of death was highly significantly increased (Figure 2).

FIGURE 2 | Trends towards Higher Thromboembolic Risk and Overall Mortality among Those Taking Inappropriately Reduced NOAC Doses



CNS: Central Nervous System, TIA: Transient Ischemic Attack, MI: Myocardial Infarction, MACNE: Major Adverse Cardiovascular and Neurological Events
Adapted from Steinberg BA, et al. *J Am Heart Assoc* 2018;7(4).

The misperception that age and vulnerability to bleeding should alter strategies for stroke prevention is common. Numerous observational studies have documented high rates of no or inadequate oral anticoagulation in AF patients who are older, have comorbidities, or are otherwise thought to be at increased risk of bleeding.[18] In GARFIELD-AF, history of bleeding was a predictor of inadequate anticoagulation in AF patients.[19] The data from the GARFIELD-AF registry are among those that support the guidelines. In those who were candidates for anticoagulation, the risk of major bleeding was lower rather than higher when anticoagulation was withheld (0.5% vs. 0.8%; $P<0.001$; perhaps due to confounding by indication rather than a treatment effect), while the risk of stroke (1.6% vs. 1.1%; $P<0.001$) and risk of all-cause mortality (5.3% vs. 3.9%; $P<0.001$) were significantly greater. In a case-control multicenter study inappropriately and off label reduced dosing of NOACs was one of the most potent risk factors for stroke, leading to an adjusted ~3.5-fold increased risk.[20] Inappropriately reduced dosing of NOACs seems to only increase the risk of thromboembolic events, without any benefits in reducing hemorrhagic events.[21]

Similarly, there have been concerns regarding anticoagulation in AF patients with ischemic stroke who are noted to have evidence of occult microbleeds, defined as round intraparenchymal lesions of hemosiderin staining that are <10 mm in diameter, on blood sensitive magnetic resonance imaging sequences. Microbleeds are most often markers of age-related cerebral small vessel disease in AF patients, notably either hypertensive arteriopathy or cerebral amyloid angiopathy. Microbleeds are associated with a heightened risk of future incident ICH in this context, but also are at heightened risk for ischemic stroke.[22] Consistent with the theme however, the absolute rates of ischemic stroke far overshadow that of ICH in ischemic stroke patients with microbleeds on MRI, irrespective of microbleed severity, and anticoagulant therapy should not be withheld in these patients when indicated.[22,23]

Among AF patients over the age of 65 with an additional risk factor for stroke, such as hypertension or diabetes, there are only a few situations in which benefit remains unclear. One is a history of ICH, as these patients have been excluded from AF anticoagulation randomized trials. Even within this high-risk subgroup, meta-analyses of observational data suggest reduced all-cause mortality and net benefit with anticoagulation, including in patients with lobar intracerebral hemorrhage that have the highest rate of long-term ICH recurrence.[24,25] Interestingly, the risk of ischemic stroke is reported to be as high as 10 to 13% per year in patients with previous intracerebral hemorrhage who do not receive anticoagulation.[26,27]

In an algorithm proposed by a recent review, NOACs were recommended four or more weeks after imaging has confirmed resolution of ICH despite the absence of a phase 3 randomized trial.[28] In the Canadian-led NASPAF-ICH trial (unpublished), which randomized 30 AF patients with previous intracerebral hemorrhage to standard dosing NOAC therapy or aspirin 81 mg daily, there was only one ischemic stroke over mean follow-up of 1.53 years that occurred in an aspirin-assigned participant. There was no recurrent intracerebral hemorrhage in either arm of the study. All participants had close home blood pressure monitoring to ensure target <130/80 mm Hg, which is an essential prerequisite—that can halve the risk of intracerebral hemorrhage recurrence—when considering anticoagulation (re-)initiation in this population.

These preliminary results are being investigated further in ongoing randomized trials. The largest, ENRICH-AF, is a global phase 3 randomized trial, where AF patients with a CHA_2DS_2-VASc ≥2 who have had a previous ICH will be randomized to edoxaban or a control strategy.[30] Controls will receive no antithrombotic therapy or antiplatelet monotherapy at the discretion of the local investigator. The study dose of edoxaban is 60 mg, but a dose of 30 mg will be used in those meeting criteria for the lower dose, consistent with the ENGAGE AF-TIMI 48 and current on-label dosing criteria. The co-primary endpoints of ischemic stroke, hemorrhagic and undetermined stroke will be evaluated once 123 primary events have accrued. A composite of ischemic events, including myocardial infarction and all-cause death, are among secondary endpoints. The study, which will also monitor ICH and major hemorrhage, is intended to determine whether NOAC for stroke prevention provides a net clinical benefit in this high-risk AF population.

Not All NOACs Are Alike: Differentiating Characteristics

In current guidelines, including those in Canada, the four NOACs approved for prevention of stroke in patients with AF are recommended without preference.[11-13]

In pivotal phase 3 trials, each has demonstrated comparable or greater efficacy than warfarin in stroke prevention and similar or lower risk of bleeding.[14,15,31,32] Relative to warfarin, all are considered more convenient in major guidelines because they can be administered in a fixed dose without therapeutic monitoring.[12,13,33] The specific pharmacokinetic properties of NOACs, although similar, range to a degree that might be clinically relevant for some patients (Table 1).[34]

TABLE 1 | NOACs: Similarities and Relevant Differences

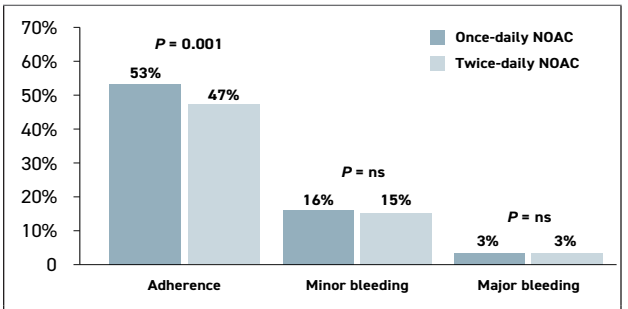
	APIXABAN	DABIGATRAN	EDOXABAN	RIVAROXABAN
Mechanism of action	Direct Factor Xa inhibitor	Direct thrombin inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
Oral bioavailability	~50%	~6.5%	62%	80-100%
Food effect	No	No	No	Yes (needs to be taken with food)
Pro-drug	No	Yes	No	No
Mean half-life ($t_{1/2}$)	~12 h	11-17 h	10-14 h	5-13 h
T_{max}	3-4 h	0,5-2 h	1-2 h	2-4 h
Recommended daily dose	5 mg BID	150 mg BID	60 mg QD	20 mg QD

Pradaxa Product Monograph. Boehringer Ingelheim Canada Ltd., May 23, 2020; Xarelto Product Monograph. Bayer Inc., September 20, 2019; Eliquis Product Monograph. Pfizer Canada ULC and Bristol-Myers Squibb Canada Co., October 7, 2019; Lixiana Product Monograph. Servier Canada Inc., February 12, 2020

Of these differences, frequency of dosing, relative risk of drug-drug interactions, risk of a food effect on drug metabolism, and dependence on renal clearance are among characteristics most likely to be clinically relevant for clinicians or patients attempting to select among the available NOACs. Dosing frequency might be relevant to patient preference and to long-term efficacy. Not all patients might perceive a once-daily dose more convenient, but there is evidence that the simpler daily regimen provides a modest but significant improvement in adherence (Figure 3).

Only one NOAC, rivaroxaban, is associated with a food effect. According to prescribing guidelines, the once-daily rivaroxaban—at doses greater than 10 mg daily that are used in AF—should be taken with a meal in order to achieve optimal bioavailability.[35] Pharmacokinetics (PK) analyses drawn from studies in patients and healthy volunteers suggest that adequate drug concentrations over a 24-hour period are achieved whether once-daily rivaroxaban is taken with the evening or the morning meals, but it is important to take the drug at the same meal each day to sustain 24-hour protection. All the NOACs, apart for dabigatran, which is supplied as a capsule containing tartaric acid that is essential for its gastrointestinal absorption, can be crushed for oral use in patients with dysphagia or administration via feeding tubes.

FIGURE 3 | Adherence to Once-daily NOAC Significantly Better than Twice-daily, With No Difference in Bleeding Risk



Multicenter, cross-sectional study of 2214 patients with AF taking NOACs for ≥3 months (once-daily: N=1000; twice-daily: N=1214). Adherence assessed by 8-item Morisky Medication Adherence Scale (MMAS-8). Emren SV et al. *Bosn J Basic Med Sci* 2018;18(2):185-90.

None of the NOACs are free of the risk of a drug-drug interaction, but the risks differ. Apixaban and rivaroxaban compete with drugs or foods that are metabolized by the hepatic cytochrome P450 3A4 isoenzyme. Examples include some antifungal agents, some tyrosine kinase inhibitors, and grapefruit juice.

TABLE 2 | NOACs and Drug Interactions

Potential ↑ in Apixaban		Potential ↓ in Apixaban	
Ketoconazole, Itraconazole, Voriconazole, Posaconazole= azole-antimycotics	Strong inhibitors of both P-gp and CYP 3A4	Carbamazepine	Phenobarbital
Ritonavir (all HIV protease inhibitors)	Diltiazem	Phenytoin	Rifampin
	Naproxen	St. John's Wort	Strong inducers of both P-glycoprotein and CYP-3A4

Potential ↑ in Dabigatran			Potential ↓ in Dabigatran	
Strong P-gp inhibitors	Cyclosporine	Verapamil*	Strong P-gp inducers	Proton Pump Inhibitors
Ketoconazole	Itraconazole		Carbamazepine	Atorvastatin
Dronedarone	Nelfinavir		Phenytoin	Antacids*
Ticagrelor	Posaconazole		Rifampin	
Tipranavir	Quinidine*		St. John's Wort	
Amiodarone	Ritonavir		Tenofovir	
Clarithromycin	Saquinavir			
	Tacrolimus			

*Recommend to give 2 hours after dabigatran

Potential ↑ in Edoxaban		Potential ↓ in Edoxaban	
Protease Inhibitors	Cyclosporine	Carbamazepine	Atorvastatin
Amiodarone	Dronedarone	Phenobarbital	Esomeprazole
Digoxin	Erythromycin	Phenytoin	
Verapamil	Ketoconazole	Rifampicin	
	Quinidine		

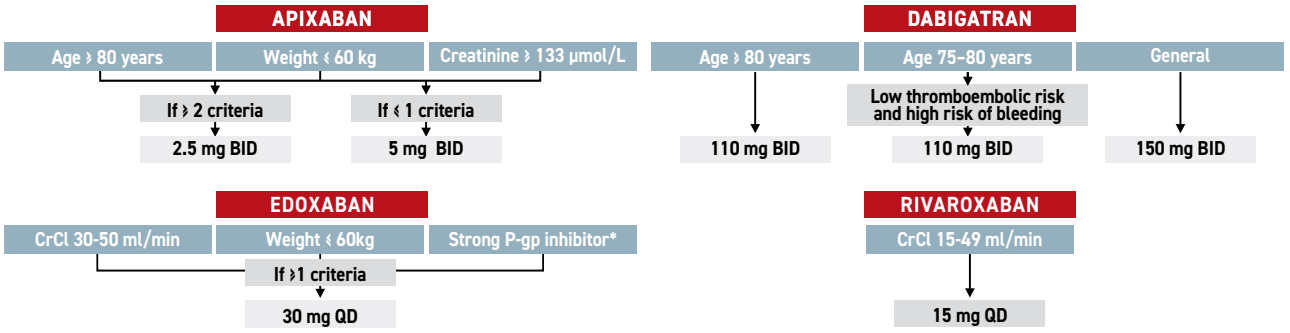
Potential ↑ in Rivaroxaban		Potential ↓ in Rivaroxaban	
Ketoconazole	Clarithromycin	Carbamazepine	Strong inducers of both P-gp and CYP 3A4
Posaconazole	Erythromycin	Phenobarbital	
Ritonavir	Fluconazole	Phenytoin	
Strong inhibitors of both P-gp and CYP 3A4	Nelfinavir	Rifampin	
	Posaconazole	St. John's Wort	

Contraindicated
Caution advised if co-administering; should be avoided
No empiric dosage adjustment required; however, use with caution
No dose adjustment is required
Reduce dose of edoxaban to 30 mg daily

Note that drug interaction data with the NOACs is limited and this table reflects currently available data. Interactions include, but are not limited to these examples. Consider Pharmacist consult as needed. Dabigatran etexilate and edoxaban are substrates for the P-glycoprotein (P-gp) and as such any strong inhibitors or inducers should be avoided. Rivaroxaban and apixaban are eliminated by both P-gp and cytochrome P-450 3A4 (CYP-450 3A4). As such the concomitant use of strong inhibitors/inducers of both P-gp and 3A4 should be avoided.

Thrombosis Canada. DOAC Follow-up Tool. Online at www.thrombosiscanada.ca. Accessed February 2020.

FIGURE 4 | Canadian Dose Reduction Criteria



CrCl: creatinine clearance; P-gp: P-glycoprotein - *Except verapamil and amiodarone

Pradaxa Product Monograph. Boehringer Ingelheim Canada Ltd., May 23, 2020; Xarelto Product Monograph. Bayer Inc., September 20, 2019; Eliquis Product Monograph. Pfizer Canada ULC and Bristol-Myers Squibb Canada Co., October 7, 2019; Lixiana Product Monograph. Servier Canada Inc., February 12, 2020.

These two NOACs, which are moderately dependent on liver metabolism for elimination, should therefore be used cautiously in patients taking CYP 3A4 inhibitors or inducers. Dabigatran and edoxaban are not dependent or have minimal dependence on liver metabolism.

All four drugs employ the P-glycoprotein (P-gp) transport system, creating the potential for drug-drug interactions with strong P-gp inhibitors or inducers, such as cyclosporine, digoxin or certain antiepileptic medications, particularly in patients with impaired renal clearance where the P-gp system is most active. However, labeling restrictions are based largely on pivotal trial designs. Earlier NOAC trials (apixaban, rivaroxaban and dabigatran) excluded concomitant use of strong P-gp inhibitors, producing a relative contraindication for these drugs in the presence of such medications (Table 2). However, in the ENGAGE AF-TIMI 48 trial the use of a strong P-gp inhibitor was listed as an indication for edoxaban dose adjustment, rather than an exclusion criterion. This trial was accordingly able to demonstrate the safety of the lower 30 mg edoxaban dose among patients on a strong P-gp inhibitor, and current drug labeling allows its use in this context.

In most patients with renal impairment, NOACs remain a preferred option to warfarin if doses are adjusted appropriately.[36] In the labeling, these adjustments are variably recommended by creatinine clearance, creatinine level, by weight, and by age, which is an important risk factor for impaired renal function in AF[37] (Figure 4). Dabigatran, at 85%, has the highest dependence of renal clearance. Apixaban, at approximately 27%, has the lowest. Edoxaban (50%) and rivaroxaban (36%) have a moderate dependence.

Evidence-Based Approach to AF-Associated Stroke Prevention

The major guidelines for prevention of stroke in patients with AF are relatively consistent, but there is evidence that more education of healthcare providers is needed. In a survey of healthcare providers in Canada, only 60% reported that they were comfortable prescribing oral anticoagulants.[38] Although the majority of respondents recognized that dose adjustments based on renal function and age are appropriate, only about 25% recognized that rivaroxaban had a food effect. Studies that have shown high rates of inappropriately withheld anticoagulants or anticoagulants prescribed as suboptimal doses in AF patients who meet guideline-recommended criteria for stroke prevention reinforce the persistent knowledge gaps for an important approach to reduction of preventable stroke-related morbidity and mortality.[10,39]

The guidelines for primary or secondary stroke prevention in AF patients are not complicated. With few exceptions, most AF patients over the age of 65 years and many AF patients who are younger with additional vascular risk factors are candidates for oral anticoagulation. If all AF patients with an indication for oral anticoagulation were treated, and at appropriate doses, most AF-associated strokes would be prevented.[20]

In the guidelines, the appropriate use of oral anticoagulants for those with renal impairment, those schedule for surgery, and those recovering from a first stroke are detailed but straightforward. Although dose reductions are required in selected cases to maintain an optimal benefit-to-risk ratio, the prevalent inappropriate use of off-label lower doses of NOACs is emerging as a significant modifiable risk factor for AF-related stroke in current practice.

Summary

A more rigorous and uniform application of oral anticoagulation therapies in AF patients will reduce mortality and morbidity in Canada. All of the NOACs, although not necessarily interchangeable, have shown efficacy that is as good or superior to warfarin in clinical trials. The risk of ICH was halved and other forms of major bleeding were the same or lower. These therapies are relatively simple to employ. While it is important to recognize when dose adjustments are appropriate, the vast majority of AF patients who are candidates for stroke prevention should be on these treatments indefinitely at dosages proven to be therapeutic that are on label and adjusted appropriately to patient individual characteristics. ●

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