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Review Article

The Role of Novel Oral Anti-Coagulants in Stroke Prevention in Non-Valvualr Atrial Fibrillation

Michael A Ward*

Department of Community and Family Medicine, University of Toronto, Canada

***Corresponding author**
Michael A Ward, Department of Community and Family Medicine, University of Toronto, Canada, Email: mikeward2226@rogers.com

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Abstract

Atrial Fibrillation (AF) is the most common dysrhythmia seen in primary care. Thromboembolic stroke remains one of the most feared complications of this rhythm disturbance. Five landmark trials have demonstrated the efficacy of warfarin and aspirin in reducing this risk. Warfarin use is known to be labor intensive for patients and concerns regarding multiple drug interactions and bleed risk have limited it use in some high-risk populations. Novel oral anti-coagulants come with the promise to lower serious/fatal bleed risk and reduce drug-drug interactions. The new anti-coagulants have fewer drug interactions and do not require regular laboratory monitoring. Here we review trials demonstrating the efficacy of four new oral anticoagulants and summarize their stroke and bleed risk relative to warfarin as a gold standard.

INTRODUCTION

Non-valvular atrial fibrillation (AF) is the most common arrhythmia managed by primary care practitioners [1]. It is estimated that 15.9 million people in the USA will be diagnosed with AF by 2050 [1]. The British SAFE [2] study reported an age-related increase in the prevalence of AF from 7.2% in patients aged 65 years and older to 10.3% in those over age 75. Of chief concern is the risk of stroke in these patients. It is well known that stroke associated with AF carries a higher risk of morbidity and mortality than strokes unrelated to AF [3] and thus their consequences can be substantial. Gage and colleagues have demonstrated annualized risks of stroke ranging from 1.9% to greater than 18.2% in this patient population [4,5].

Prior to 2009, Warfarin had been considered the cornerstone of anticoagulation therapy for stroke-prevention in non-valvular AF. Five landmark trials published from 1989 to 1992 [6-11] established both the efficacy and safety of warfarin (compared to aspirin [ASA] and placebo) in reducing stroke in AF. A recent meta-analysis [12,13] of stroke prevention in non-valvular AF showed a 22% relative risk reduction (RRR) with use of ASA versus placebo (absolute risk reduction [ARR] of 0.8% per year in primary prevention and 2.5% per year for secondary prevention) and a 64% RRR in favour of warfarin versus placebo (ARR 2.7% per year in primary prevention and 8.4% per year in secondary prevention). Warfarin was associated with a significant ARR in all-cause mortality of 1.6% per year.

When trials of ASA versus warfarin are compared, warfarin offers a 38% RRR for stroke over and above that reduction conferred by ASA. This reduction translates into an ARR for stroke of 0.7% per year in primary prevention and 7.0% for secondary prevention [13]. Indeed, international guidelines have endorsed the use of warfarin for stroke prevention but often cite a well-known care gap relating to the under-utilization of warfarin in this regard [14-18].

The introduction of novel oral anti-coagulants [NOACs] in 2009, has changed the face of anticoagulation and stroke prevention in both primary and speciality practice; primary care physicians may be challenged to keep pace with the rapidly evolving environment of stroke prevention in non-valvular AF. A review of the diagnosis and management of atrial fibrillation has recently been published [19]. Here the presently accepted standards, landmark trials, and efficacy of anticoagulants, indicated for stroke-prevention in non-valvular AF, will be reviewed in the context of primary care.

International guidelines exist to help guide the management of stroke prevention in non-valvular AF [14-18]. The decision to pursue anticoagulation is made largely on an assessment of the patient's $CHADS_2$ score (Figure 1) with 1 point each assigned for congestive heart failure (CHF), diabetes mellitus (DM), hypertension (HTN), age of 75 or greater, and with 2 points added for a previous stroke/TIA. A maximum $CHADS_2$ score of 6 carries with it a annualized stroke risk of 18.2% (Figure 1). This score has been validated in multiple cohorts [5]. A slightly more

detailed version of this score has emerged from the Euro Heart Study on Atrial Fibrillation and is known as the CHA_2DS_2-VASc score [20]. This measure adds 1 point for female gender, 1 point for known vascular disease (myocardial infarction, peripheral vascular disease, or aortic plaque), 2 points for age 75 or greater and 1 point for age 65 to 74 Figure 2.

Current guidelines [17,18] support the use of ASA in patients with a $CHADS_2$ score of 0 and anticoagulation with a $CHADS_2$ score of 2 or more. Management of a patient with a $CHADS_2$ score of 1 is perhaps more controversial – it may be prudent to assess a CHA_2DS_2-VASc score in these individuals to better stratify their risk. A patient with a CHA2DS2-VASc score of 1 may be offered ASA or anticoagulation, while those patients scoring 2 or more can be managed with anticoagulation [17,18].

The decision to offer anticoagulation for stroke prevention should be balanced with an individual's risk for clinically significant bleeding. To this end, the HAS-BLED score [21] has emerged as a practical and simplified tool for stratifying bleed risk (Figure 3). HAS-BLED has a maximum score of 9 and a score of 5 is associated with an annual bleed risk of 12.5% (the score and bleed risk are readily accessible on the Web). Each patient will harbor unique stroke and bleed risks and these must be balanced on an individual basis while considering the significant morbidity and mortality that accompanies a thrombotic stroke. If anticoagulation therapy is considered, the clinician must next provide his/her patient with a clear understanding of the relative risks and benefits of warfarin and the novel oral anticioagulants so that they might make an informed decision regarding their choice of anticoagulation/stroke-prevention.

The clinical use of warfarin is recognized as resource-intensive, requiring regular monitoring and dose adjustments, coupled with the ongoing concerns of multiple drug interactions and risk for serious bleeding. Centralized anti-coagulation services can be effective at maintaining therapeutic INR levels but these services are not widely available and achieve the therapeutic range less than 70% of the time, even in contemporary trials [22-25]. This suggests that most community patients spend upwards of at least one third of the time either over- or under-anti-coagulated. Despite these shortcomings and others, warfarin has remained the standard to which other therapies have been measured, until just recently.

$CHADS_2$ Acronym	$CHADS_2$ Calculation
Congestive Heart Failure	1 point
Hypertension	1 point
Age >/= 75 years	1 point
Diabetes Mellitus	1 point
Stroke/TIA	2 points
Maximum Score	6 points
$CHADS_2$ Score	**Stroke Risk***
0	1.90%
1	2.80%
2	4.00%
3	5.90%
4	8.50%
5	12.50%
6	18.20%

Figure 1 CHADS2 Score and Annualized Stroke Risk*.

CHA_2DS_2-VASc Acronym	CHA_2DS_2-VASc Calculation
Congestive Heart Failure	1 point
Hypertension	1 point
Age >/= 75 years	2 points
Diabetes Mellitus	1 point
Stroke/TIA	2 points
Vascular Disease (MI, PAD, Aortic plaque)	1 point
Age 65 - 74 years	1 point
Sex - Female	1 point
Maximum Score	9 points
CHA_2DS_2-VASc Score	**Stroke Risk***
0	0%
1	1.30%
2	2.20%
3	3.20%
4	4.00%
5	6.70%
6	9.80%
7	9.60%
8	6.70%
9	15.20%

Figure 2 CHA2DS2-VASc Score and Annualized Stroke Risk*.

HAS-BLED Acronym	HAS-BLED Calculation
Hypertension	1 point
Abnormal Renal or Liver function	1 point each
Stroke	1 point
Bleeding	1 point
Labile INR values	1 point
Elderly (>65 years)	1 point
Drugs or Alcohol	1 point each
Maximum Score	9 points
HAS-BLED Score	Annualized Bleed Risk
0	1.13%
1	1.02%
2	1.88%
3	3.74%
4	8.70%
5	12.50%
6	NA
7	NA
8	NA
9	NA

Figure 3 HAS-BLED Score and Annualized Risk for Major Bleeding.

The NOACs constitute a group of new anticoagulant agents shown to have similar efficacy and safety [22-25]. in non-valvular AF and do not require laboratory monitoring. The publication of The Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) trial in 2009 marked a change in the landscape of stroke risk management for both primary and specialty practice [22]. This landmark trial demonstrated superior efficacy of the novel direct thrombin inhibitor dabigatran in stroke reduction, with a concomitant reduction in serious bleeding. Subsequently, trials showcasing three novel factor Xa inhibitors have been published. The remainder of this review will present a snapshot of each of the four published trials and offer some insights as to where each NOAC may find its niche in primary care.

The RE-LY [22] trial was a randomized open-label study of warfarin versus dabigatran (2 doses daily, allocated in a blinded fashion) with primary endpoints of stroke or systemic embolism. A total of 18,113 patients were followed for a median of 2 years with a completion rate of 99.9% (20 lost to follow-up). The average CHADS score was 2.1 and INR values were maintained within the therapeutic range 64% of the time. All events were adjudicated in a blinded, independent fashion. Clinical outcomes are summarized in Table 1.

The RE-LY trial concluded that dabigatran at 150 mg bid was better (superior) than warfarin at reducing stroke/systemic embolism; the 110 mg bid dose was equivalent (non-inferior). The risk of intracranial hemorrhage (ICH) was lower with both dosages of dabigatran versus warfarin, while the risk of major bleeding was lower with the 110 mg dose only. Gastrointestinal (GI) bleed risk was equivalent to warfarin at dabigatran 110 mg bid, but was elevated with the 150 mg bid dose of dabigatran versus warfarin. Of note, a small but significant increase in the rate of myocardial infarction was seen at the dabigatran 150 mg dose relative to warfarin; the authors have subsequently published data looking at new Q waves on ECGs (i.e. indication of silent infarction) of study participants [26] and suggest that the risk of infarction is the same across all three arms of the trial. A recent study of dabigatran for the extended treatment of DVT [27] in a much younger population has reported a similar increase in the risk of acute coronary syndrome (ACS) and a previous meta-analysis has confirmed this finding [28]. There was a trend to a decrease in all-cause mortality in the RE-LY study but this did not meet significance. Thus, dabigatran showed efficacy in stroke prevention with dose-related equal, or lesser, risk of bleed compared to warfarin. The exception being an increased GI bleed risk with dabigatran at 150 mg bid. Compiled, but somewhat conflicting, data suggests increased risk of ACS with use of dabigatran.

Rivaroxaban is an oral factor Xa inhibitor used previously to prophylax against DVT in patients post total knee and total hip arthroplasty . The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) [23] was a double-blinded, double-dummy trial design comparing the efficacy of rivaroxaban (20 mg once daily) and warfarin with primary endpoints of stroke/systemic embolism. It included 14,264 patients followed for a mean of 1.9 years with 32 patients lost to follow up (completion rate of 99.8%). The average CHADS score was 3.5 and INR values were maintained within the therapeutic range 55% of the time. All endpoints were adjudicated in a blinded, independent fashion.Clinical outcomes are summarized in Table 2. In this more complex group of patients (mean CHADS score 3.5), rivaroxaban was found to be as effective as warfarin (non-inferior) at reducing the primary endpoint of stroke/systemic embolism. The risks of intracranial hemorrhage and GI bleeding were significantly lower with rivaroxaban while the risk of major bleeding remained the same versus warfarin. A higher CHADS score is often correlated with increased HAS-BLED bleeding risk as both scores share similar characteristics; thus the demonstrated safety of this agent in a population of complex patients with higher bleeding risks becomes a significant issue when aiming to prevent stroke in these 'sicker' patients. There was no change in myocardial infarction or all-cause mortality comparing rivaroxaban and warfarin. Rivaroxaban has been shown to be effective in both ACS and the treatment of pulmonary embolism and deep vein thrombosis [29,30,31]. In summary, rivaroxaban demonstrated similar efficacy in stroke prevention compared to warfarin, with lower risk of ICH and GI bleed and equivalent risk of major bleeding, ACS, and all-cause mortality.

Apixaban, another factor Xa inhibitor, was studied in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial [24]. This too was

Table 1: RE-LY Trial Summary.

	Warfarin	Dabigatran	Dabigatran	Dabigatran		Dabigatran	
		110 mg bid	150 mg bid	110 mg bid		150 mg bid	
				vs. Warfarin		vs. Warfarin	
				Relative Risk	P value	Relative Risk	P value
	%/yr	%/yr	%/yr	(95% CI)		(95% CI)	
Stroke/	1.69	1.53	1.11	0.91 (0.74- 1.11)		0.66 (0.53 - 0.82)	
Systemic					**<0.001 Non**		**< 0.001 Non**
Embolism					0.34 Sup		**<0.001 Sup**
ICH	0.74	0.23	0.3	0.31 (0.20 - 0.47)		0.40 (0.27 - 0.60)	
					<0.001		**<0.001**
Major	3.36	2.71	3.11	0.80 (0.69 - 0.93)		0.93 (0.81 - 1.07)	
Bleeding					**0.003**		0.31
GI Bleed	1.02	1.12	1.51	1.10 (0.86 - 1.41)		1.50 (1.19 - 1.89)	
					0.43		**<0.001**
Myocardial	0.74	0.23	0.3	0.31 (0.20 - 0.47)		0.40 (0.27 - 0.60)	
Infarction					**<0.001**		**<0.001**
All-cause	4.13	3.75	3.64	0.91 (0.80 - 1.03)		0.88 (0.77 - 1.00)	
Mortality					0.13		0.051

a double-blinded, double-dummy trial examining the efficacy of apixaban (5 mg bid) versus warfarin. The primary endpoint was stroke/systemic embolism. A total of 18,201 patients were followed for a mean of 1.8 years; 34 and 35 patients were lost to follow up in each arm respectively (completion rate of 99.2%). The average CHADS2 score was 2.1 and INR values were maintained in the therapeutic range 62.2% of the time. All endpoints were adjudicated in a blinded, independent fashion.

Clinical outcomes are summarized in Table 3. This group of patients was qualitatively similar to those in the RE-LY study when looking at mean CHADS2 scores, making it more comparable when examining trial outcomes directly. Apixaban was found to be more effective (superior) than warfarin at reducing the risk of the primary outcome of stroke/systemic embolism. The risks of intracranial bleeding and major hemorrhage were significantly reduced while GI bleeding remained the same. There was no observed increase in myocardial infarction risk. There was a significant decrease in all-cause mortality in the apixaban arm compared to warfarin. Thus apixaban showed greater efficacy in stroke prevention and reduced all-cause mortality compared to warfarin, with lower risk of ICH and major bleeding and equivalent risk of GI bleeding and ACS.

Edoxaban, the newest factor Xa inhibitor, was studied in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48 (ENGAGE AF -TIMI 48) trial – the most recent and largest NOAC trial to date [25]. This double-blinded, double-dummy trial compared edoxaban (30 mg once daily or 60 mg once daily) and warfarin, with a primary endpoint of stroke/systemic embolism. It included 21,105 patients followed for a mean of 2.8 years; 244 patients withdrew consent (completion rate of 99.5%). The average CHADS2 score was 2.8 and INRs were maintained in the therapeutic range 64.9% of the time. All endpoints were adjudicated in a blinded fashion.

Clinical outcomes are summarized in Table 4. Edoxaban was found to be equivalent (non-inferior) at both doses compared to warfarin in reducing the primary endpoint of stroke/systemic embolism. The risks of major bleeding and ICH were decreased

Table 2: ROCKET AF Trial Summary.

	Warfarin	Rivaroxaban	Rivaroxaban	
			vs. Warfarin	
			Relative Risk	P value
	%/yr	%/yr	(95% CI)	
Stroke/	2.4	2.1	0.88 (0.75 - 1.03)	**<0.001 Non**
Systemic				
Embolism				
ICH	0.7	0.5	0.67 (0.47 - 0.93)	**0.02**
Major Bleeding	3.4	3.6	1.04 (0.90 - 1.20)	0.58
GI Bleed	2.2	3.2	not stated	**<0.001**
Myocardial	1.1	0.9	0.81 (0.63 - 1.06)	0.12
Infarction				
All-cause	2.2	1.9	0.85 (0.70 - 1.02)	0.07
Mortality				

Table 3: ARISTOTLE Trial Summary.

	Warfarin	Apixaban	Apixaban	
			vs. Warfarin	
			Relative Risk	P value
	%/yr	%/yr	(95% CI)	
Stroke/	1.6	1.27	0.79 (0.66 - 0.95)	**0.01**
Systemic				
Embolism				
ICH	0.8	0.33	0.42 (0.30 - 0.58)	**<0.001**
Major Bleeding	3.09	2.13	0.69 (0.60 - 0.80)	**<0.001**
GI Bleed	0.86	0.76	0.89 (0.70 - 1.15)	0.37
Myocardial	0.61	0.53	0.88 (0.66 - 1.17)	0.37
Infarction				
All-cause	3.94	3.52	0.89 (0.80 - 0.99)	**0.047**
Mortality				

with edoxaban relative to warfarin; however high dose edoxaban increased GI bleeding while low dose edoxaban decreased GI bleeding relative to warfarin. There was no increase in myocardial infarction observed. All-cause mortality was decreased relative to warfarin in the low dose arm (30 mg) but this benefit was not seen in the higher dose (60 mg) arm. Thus, edoxaban showed efficacy in stroke prevention with lesser risk of ICH and major bleed compared to warfarin, with the exception of dose-related increased and decreased GI bleed risks with edoxaban. Data also suggested decreased all-cause mortality with low-dose edoxaban. At the time of writing, edoxaban had not received approval for stroke prevention in non-valvular AF .

Although NOACs represent a major leap forward in patient management and convenience, the most concerning issue with their wide-spread use at this time is our ability or lack thereof, to manage those few patients that present with serious bleeding [32]. Currently none of the new medications have direct reversibility; trials are ongoing to develop and test candidate agents but none has emerged as of yet. Both apixaban and edoxaban have demonstrated reductions in all-cause mortality compared to warfarin and this does lend a certain comfort to their use. Fortunately, there seems to be a sense of urgency surrounding this issue and hopefully a more definitive answer will present itself soon.

Novel anticoagulants will undoubtedly play a major role in stroke prevention in the context of non-valvular AF [33,34]. However, NOACs may not replace warfarin in its entirity. A recent trial comparing dabigatran and warfarin for stroke prophylaxis in mechanical heart valves was terminated due to an increased risk of thromboembolic events and bleeding [35]. Thus, without any new registered clinical trials involving Factor Xa inhibitors and stroke prevention in mechanical heart valve patients currently on the horizon [36], warfarin still has its place in the world of anticoagulants – we may all continue to manage the trials and tribulations of warfarin in some patients.

In those patients and conditions in which NOACs are indicated, it is safe to assume that these agents will quick enter into primary

Table 4: ENGAGE AF-TIMI 48 Trial Summary.

	Warfarin	Edoxaban	Edoxaban	Exodaban LD		Edoxaban HD	
		Low-Dose	High-Dose	vs. Warfarin		vs. Warfarin	
				Relative Risk	P value	Relative Risk	P value
	%/yr	%/yr	%/yr	(95% CI)		(95% CI)	
Stroke/	1.5	1.61	1.18	1.07 (0.87 - 1.31)		0.79 (0.63 - 0.99)	
Systemic					**0.005 Non**		**<0.001 Non**
Embolism							
ICH	0.85	0.26	0.39	0.30 (0.21 - 0.43)		0.47 (0.34 - 0.63)	
					<0.001		**<0.001**
Major Bleeding	3.43	1.61	2.75	0.47 (0.41 - 0.55)		0.80 (0.71 - 0.91)	
					<0.001		**<0.001**
GI Bleed	1.23	0.82	1.51	0.67 (0.53 - 0.83)		1.23 (1.02 - 1.5)	
					<0.001		**0.03**
Myocardial	0.75	0.89	0.7	0.89 (0.95 - 1.49)		0.94 (0.74 - 1.19)	
Infarction					0.13		0.6
All-cause	4.35	3.8	3.99	0.87 (0.79 - 0.96)		0.92 (0.83 - 1.01)	
Mortality					**0.006**		0.08

care practice; each practitioner's choice of NOAC will depend on his/her understanding of the literature, experiences with each drug, and the individual characteristics of each patient. To date, there are no published head-to-head trials of NOACs and with trial costs, time, and market share on the line, it is unlikely that we will see trials of this nature any time soon. Primary care practitioners may need to take time to understand some of the subtle nuances of each NOAC in addition to knowing the general clinical trial descriptions reviewed above. Our consultant colleagues and national guidelines [37,38] can and should play a major supportive and educational role in this regard.

To summarize, risk stratification tools exist for stroke prophylaxis in non-valvular AF patients, and they have been well validated in regards to stroke and bleeding risks. Warfarin and the novel anticoagulants have been demonstrated to significantly reduce the risk of stroke (and in some cases all-cause mortality) in our patients. Although, the wide-spread use of novel oral anti-coagulants may be temporarily hampered by the uncertainties surrounding the management of serious bleeding, these new agents offer superior stroke protection, decreased risks of intracranial hemorrhage, and definite ease of use for our patients. Each new agent will, no doubt, carve out its niche as our collective clinical experience grows with time. All primary care practitioners should become well versed in the new reality that is stroke prevention in non-valvular AF.

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