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# Scientific Update™

## Advancing Stroke Prevention in Atrial Fibrillation: The Emerging Role of Factor Xa Inhibition

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**Satellite symposium presented at the European Society of Cardiology Congress 2011**

Paris, France August 27–30, 2011

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Up to 80% of patients with atrial fibrillation (AF) are at moderate to high risk for stroke.<sup>1</sup> Despite this figure, only a fraction of patients with AF and moderate to high stroke risk actually receive warfarin, and less than half of those patients have an international normalized ratio (INR) in the therapeutic range (ie, 2.0–3.0).<sup>1,7</sup> Thus, there is a desperate need for new oral anticoagulants that will allow more patients to be treated, and also allow more patients to receive predictable and effective anticoagulation. This issue of *Cardiology Scientific Update* presents the current data on the risk and clinical impact of stroke secondary to AF, and the emerging evidence supporting the benefit and safety of agents that inhibit factor Xa.

### The Burden of AF-Related Stroke

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, affecting approximately 1% of the general population.<sup>8</sup> The lifetime risk for the development of AF among adults aged ≥40 years is approximately 25%, and is similar in both men and women.<sup>9</sup> The prevalence of AF increases with increasing age, such that 10%–15% of individuals aged ≥80 years suffer from AF. Various projections for the future estimate at least a doubling of the prevalence of AF over the next 30–40 years.

AF is associated with substantial morbidity and mortality. Patients with AF often experience a variety of symptoms, including palpitations, dyspnea, fatigue and dizziness. In addition, AF is associated with up to a 2-fold increased risk of all-cause mortality.<sup>10–12</sup> Stroke is a serious and often disabling complication of AF. It is estimated that annually, approximately 5 million people worldwide are permanently disabled by stroke, and that 1.24 million Europeans die annually from stroke.<sup>13,14</sup> The Framingham Heart Study demonstrated a 4- to 5-fold increase in the risk

of stroke in patients with AF.<sup>15</sup> Overall, approximately one-sixth of all ischemic strokes are attributable to AF.<sup>16,17</sup>

AF-related strokes tend to be more severe than ischemic strokes of other etiologies, resulting in a higher rate of stroke-related disability.<sup>16,18</sup> As well, the risk of stroke appears to be independent of the clinical type or burden of AF. Thus, patients with paroxysmal, persistent, or permanent AF all need to be assessed for stroke risk, regardless of the burden or duration of AF itself.

### Vitamin K Antagonists

Vitamin K antagonists (VKAs) have been shown to be highly effective in reducing the risk of stroke in patients with AF. A recent meta-analysis of 6 trials of warfarin versus placebo, in over 2900 patients with AF, demonstrated a roughly 64% reduction in thromboembolic stroke with appropriate anticoagulation.<sup>19</sup> Thus, VKAs have been universally recommended for most AF patients believed to be at moderate to high risk for stroke. The CHADS<sub>2</sub> risk score fairly accurately distinguishes patients at low, moderate, and high risk for stroke using clinical variables as a bedside risk score (Table 1).<sup>20</sup> In recent years, VKAs have been recommended for AF patients with a CHADS<sub>2</sub> risk score of ≥2, with the optional use of either acetylsalicylic acid (ASA) or a VKA for those with a score of 1. The Canadian Cardiovascular Society's 2010 AF Guidelines<sup>21</sup> recommend anticoagulation for patients with a CHADS<sub>2</sub> risk score of ≥1, in the absence of increased bleeding risk.

While some physicians prefer to prescribe ASA for stroke prevention, antiplatelet therapy is only modestly effective in such patients, with a roughly 22% reduction in stroke risk.<sup>22</sup> In AF patients considered to be ineligible for warfarin, the ACTIVE A trial<sup>23</sup> demonstrated a small benefit of dual antiplatelet therapy with ASA plus clopidogrel when compared to ASA alone. However, dual antiplatelet therapy was associated with a significant increase in the risk of major hemorrhage. Importantly, VKA therapy is clearly superior to ASA alone for stroke prevention. Fur-

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Risk Factor	Score
Congestive heart failure	1
Hypertension	1
Age ≥75	1
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
<b>Maximum Score</b>	<b>6</b>

Patients (n = 1733)	Adjusted Stroke Rate (%/yr) 95% CI	CHADS <sub>2</sub> Score
120	1.9 (1.2 to 3.0)	0
463	2.8 (2.0 to 3.8)	1
523	4.0 (3.1 to 5.1)	2
337	5.9 (4.6 to 7.3)	3
220	8.5 (6.3 to 11.1)	4
65	12.5 (8.2 to 17.5)	5
5	18.2 (10.5 to 27.4)	6

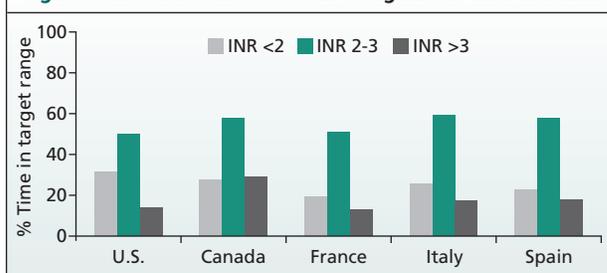
Adapted from Gage BF et al. *JAMA*. 2001;285:2864-2870.  
TIA = transient ischemic attack; CI = confidence interval

Furthermore, the ACTIVE W study<sup>24</sup> demonstrated that warfarin was more effective than the combination of ASA plus clopidogrel for stroke prevention in AF patients.

The benefits of VKAs are largely dependent upon achieving adequate anticoagulation, ideally an INR of 2.0–3.0, for the majority of treatment time. However, achieving and maintaining therapeutic anticoagulation in clinical practice can be challenging. Warfarin and other VKAs have significant limitations when used in clinical practice, including: often unpredictable response, with a narrow therapeutic window; slow onset and offset of action; need for regular INR monitoring and frequent dose adjustments; common adverse events, leading to a high rate of discontinuation;<sup>25</sup> numerous food and drug interactions; and the risk of bleeding complications, particularly the risk of intracranial hemorrhage, which rises substantially once the INR approaches 4 or beyond. Such fear of bleeding may lead physicians to underprescribe warfarin to patients at increased stroke risk. Partly because of these limitations, it is estimated that only half of eligible AF patients worldwide receive any VKA at all.<sup>26</sup> In those patients receiving VKA, only 40%-60% actually achieve therapeutic anticoagulation. The adequacy of anticoagulation with VKA is often defined by “time in therapeutic range” (TTR), which estimates the overall period of time that an individual patient or group of patients spend with an INR between 2.0–3.0. Numerous practice audits and observational registries suggest that the average TTR globally is roughly 50%-55%, whereas it is estimated that a TTR of 60%-65% is required to optimally reduce the risk of AF-related stroke (Figure 1).<sup>7</sup>

Thus, given the high and increasing prevalence of AF and associated stroke, coupled with the limitations of and barriers to optimal anticoagulation with VKA, there has been an urgent need for new anticoagulants that can provide predictable anticoagulation with minimal or no food/drug interactions, and ideally with an equal or better protection from stroke and with a

**Figure 1: International Use of Anticoagulation with Warfarin<sup>7</sup>**



Adapted from Ansell J et al. *J Thromb Thrombolysis*. 2007;23:83-91.  
INR = international normalized ratio

lower risk of major or intracranial hemorrhage. Intense activity in pursuit of new anticoagulant drugs over the past decade has led to the development of 2 distinct new classes of oral anticoagulants. Direct thrombin inhibition affects the final common pathway in the coagulation cascade.<sup>27</sup> The first approved oral direct thrombin inhibitor, dabigatran, became available for use in Canada in 2010.

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY),<sup>28</sup> lower-dose dabigatran (110 mg) was associated with similar rates of stroke and systemic embolism as warfarin in AF patients (1.5% versus 1.7%;  $P < 0.001$  for noninferiority) but lower rates of major hemorrhage (2.7% versus 3.4%;  $P = 0.003$ ). Higher-dose dabigatran (150 mg) conferred a significant reduction in stroke and systemic embolism (1.1%;  $P < 0.001$  for superiority), with a similar bleeding risk (3.11%) as warfarin.

The second class of agents involves the inhibition of activated factor X, a process that occurs earlier in the coagulation pathway.

## Factor Xa Inhibitors

### Rivaroxaban

Rivaroxaban is a direct, specific, and competitive oral inhibitor of factor Xa, with a half-life of 5-13 hours.<sup>29</sup> One-third of the drug is excreted through the kidney, and two-thirds are metabolized by the cytochrome P450 system. The drug is administered once daily, provides a predictable level of anticoagulation in a broad population of patients, and does not require routine coagulation monitoring. Rivaroxaban is the first oral factor Xa inhibitor to be tested for the prevention of AF-related stroke compared to warfarin. Rivaroxaban is currently indicated by Health Canada for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery;<sup>29</sup> it is not approved for the treatment of AF or related stroke prevention. Rivaroxaban was approved by the United States Food and Drug Administration in November 2011 to reduce the risk of stroke in AF patients.

The ROCKET AF trial<sup>30,31</sup> was a randomized, double-blind, double-dummy trial of rivaroxaban versus therapeutic warfarin in 14 264 patients with nonvalvular AF and multiple additional risk factors for stroke. In order to be eligible, patients had to have either a past history of stroke, transient ischemic attack (TIA), or systemic embolism, or at least 3 risk factors for stroke (age >75 years, hypertension, diabetes, or heart failure). Patients were randomized to either rivaroxaban or to dose-adjusted warfarin. Warfarin was administered as per guidelines to a target INR of 2.5

(range 2.0-3.0). Rivaroxaban was dosed once daily at 20 mg. The primary endpoint of the trial was the composite of stroke and non-central nervous system (CNS) systemic embolism. The main analysis was a prespecified per-protocol analysis to determine if rivaroxaban was noninferior to dose-adjusted warfarin for prevention of the primary endpoint of stroke and non-CNS systemic embolism. ROCKET AF also included a primary superiority analysis of safety involving all patients who received at least 1 dose of either study drug (n=14 143), as well as an intention-to-treat (ITT) superiority analysis (n=14 171).

The researchers determined a 21% relative risk reduction (RRR; hazard ratio [HR] 0.79, *P* for noninferiority <0.001) in the primary endpoint with rivaroxaban compared to warfarin, demonstrating noninferiority (Figure 2).<sup>31</sup> The event rate per 100 patient-years was 2.16 for warfarin and 1.71 for rivaroxaban. In the ITT superiority analysis, there was a 12% reduction in the primary endpoint in favour of rivaroxaban that failed to reach statistical significance (*P*=0.117). Thus, while rivaroxaban was not superior in the overall population studied, it did provide additional stroke reduction compared with warfarin in those patients who took the study drug.

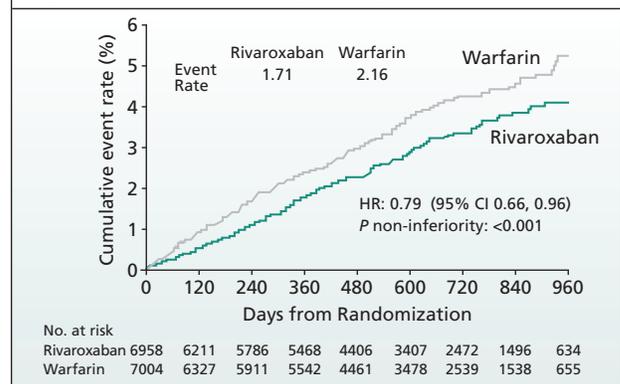
The TTR, as calculated using the Rosendaal method, has come under considerable scrutiny in recent years. While the TTR estimates an individual patient, centre, or region's likelihood of maintaining INR values between 2.0 and 3.0, it is not clear that a higher TTR results in a lower stroke risk. In general, however, optimal warfarin use should result in a TTR of at least 60%-65%, and this has become the standard goal of warfarin use in clinical trials.

In the RE-LY study,<sup>28</sup> the mean centre TTR was 65%. However, one must keep in mind that outcomes of clinical trials are often different than real-world results. Numerous studies have demonstrated that the TTR in clinical practice is usually well under 50%. In ROCKET AF, the mean TTR was 57.8%. Approximately 20% of centres had INRs ranging below 2.0, and about 12% were above 3.0. When centres were stratified by TTR quartiles, event rates on warfarin were lowest in centres with the highest TTR quartile, suggesting that better INR control does in fact result in fewer strokes. However, the relative benefit of rivaroxaban compared to warfarin was maintained across all 4 TTR quartiles, suggesting that the benefits of rivaroxaban are not restricted to only those patients or centres with suboptimal INR control.

With respect to safety, major and clinically relevant non-major bleeding was similar between both groups. While there was an excess of hemoglobin drops and transfusions among patients treated with rivaroxaban, the incidence of critical organ bleeding and fatal bleeding was reduced by rivaroxaban by 41%-50% compared to warfarin. The most feared complication of oral anticoagulation, namely intracranial hemorrhage, which is usually disabling or fatal, was reduced by 33% with rivaroxaban.

Rivaroxaban was well tolerated, with no greater incidence of adverse events compared with warfarin. Rates of adverse events leading to study drug discontinuation were also similar between the 2 groups. Importantly, while liver toxicity was a concern with the development of ximelagatran, the first oral direct thrombin inhibitor, there was no increase in liver enzyme abnormalities with rivaroxaban compared to warfarin in ROCKET AF.

**Figure 2: ROCKET AF: Primary Efficacy Outcome<sup>31</sup>**



Reproduced with permission from Patel MR et al. *N Engl J Med.* 2011;365:883-891. Copyright © 2011, Massachusetts Medical Society. HR = hazard ratio

### Apixaban

Apixaban is another oral factor Xa inhibitor. Its half-life is approximately 12 hours, and it is principally cleared through the fecal route; renal excretion represents 27% of total clearance.<sup>32</sup> Apixaban is not currently approved by Health Canada.

The Apixaban versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial<sup>33</sup> concluded that apixaban reduced the risk for stroke and systemic embolism compared with ASA (HR 0.45; *P*<0.001) without an associated increase in major or intracranial bleeding in AF patients who are not suitable candidates for warfarin therapy.

More recently, the results of the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) trial<sup>34</sup> were published. ARISTOTLE was a double-blind comparison of apixaban (5 mg twice daily) with warfarin in 18 201 AF patients with 1 additional risk factor for stroke, testing for noninferiority. The primary outcome was ischemic/hemorrhagic stroke or systemic embolism. Median duration of follow-up was 1.8 years. The primary outcome occurred in 1.3% of subjects in the apixaban group per year and 1.6% in the warfarin group (HR 0.79; *P*<0.001). Rates of major bleeding in the apixaban and warfarin groups were 2.1% and 3.1%, respectively (*P*<0.001).

### Edoxaban

Edoxaban is also not approved for use by Health Canada. It is being investigated in AF patients as part of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction (ENGAGE AF-TIMI) 48 study. Results are expected in 2012.

### The Challenge of Secondary Stroke Prevention in AF: Lessons from Contemporary Trials

The strongest risk factor for stroke in AF is a history of a prior stroke or systemic embolism. This is the reason that prior stroke is assigned a score of 2 points in the CHADS<sub>2</sub> risk algorithm, compared to only 1 point each for age, hypertension, diabetes, or prior heart failure. Prior stroke increases the risk of recurrent stroke by

2- to 3-fold, and also is associated with a higher risk of bleeding in algorithms such as HEMORRAGES<sup>35</sup> (Hepatic or renal failure, Ethanol abuse, Malignancy, Older [age >75], Reduced platelet count or function, 2 points for Rebleeding risk, Hypertension [uncontrolled], Anemia, Genetic factors, Excessive fall risk [including neurodegenerative and psychiatric disorders], and history of Stroke) or HAS-BLED<sup>36</sup> (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history/predisposition, Labile INR, Drugs/alcohol concomitantly). In fact, in secondary stroke prevention studies with warfarin, the absolute risk reduction in stroke is much larger (roughly 8.4%) than in primary prevention studies.

In RE-LY, patients with a history of prior stroke had a stroke recurrence at almost twice the rate of those without prior stroke, and this was true both for patients randomized to warfarin or to dabigatran. The relative risk reduction in stroke with either dose of dabigatran compared to warfarin was similar in patients with and without prior stroke. Similarly, the major bleeding rate was higher in patients with prior stroke.

In ROCKET AF, a substantial number of patients had experienced a prior stroke. Rivaroxaban's efficacy compared to warfarin was maintained in this population, whose overall stroke rate once again was higher than in patients without prior stroke.

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*Dr. Gupta has received honoraria or research grants from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer.*

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Bayer Inc. to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology, St. Michael's Hospital, and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party. This publication may include discussion of products or product indications that have not been granted approval by Health Canada. This content is intended for medical, scientific, and educational purposes only.