COMMENTARY

# New Anticoagulants for Atrial Fibrillation: The Beginning of a A New Era in Stroke Prevention

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Every day in Canada, patients are hospitalized with disabling and fatal strokes related to untreated – or sub-optimally treated – atrial fibrillation (AF). To avert a looming public health crisis of AF-related strokes, clinicians and policy-makers must take action to close the practice gaps and ensure Canadians with AF have access to optimal evidence-based therapies. To date, the provision of appropriate anticoagulant therapy to prevent ischemic stroke in individuals with AF has proven challenging due to the limitations of warfarin and system-related obstacles to its effective delivery. Now, as the first of a new generation of oral anticoagulants has launched, the field of AF is undergoing a renaissance and there is renewed optimism about the future of AF care. Approval of dabigatran etexilate for AF patients by Health Canada and the FDA in October 2010, together with the trial results of rivaroxaban and apixaban in AF announced in 2010, marks the beginning of a new era in AF management. This paper presents the views of an interdisciplinary group of healthcare professionals interested in stroke prevention to help put these developments into context. Part 1 reviews the "state of the gap" in the warfarin era. Part 2 presents the "state of the art" in new anticoagulant therapies and the potential impact for improving stroke prevention in Canada. Part 3 highlights limitations and uncertainties that need to be addressed in this new era of anticoagulation.

## The Burden of Atrial Fibrillation (AF)-Related Strokes

Stroke is the second leading cause of death globally for individuals over age 60 years and a major cause of long-term physical and cognitive disability. In Canada, approximately 50,000 strokes occur annually costing $3.6 billion.[1] Atrial fibrillation accounts for about one in six strokes (one in four in the elderly), and AF-related strokes are more severe on average than strokes in individuals without AF. As such, AF is a common and potentially preventable cause of stroke-related deaths, disability and dementia. In the Registry of the Canadian Stroke Network, AF was present in one-quarter of >12,000 consecutive patients presenting to hospital within an ischemic stroke event between 2003-2007.[2] The prevalence of AF in Canada is about 250,000, and with an aging population the burden of AF-related strokes is expected to increase further. The number of Canadians aged ≥65 years is predicted to rise from 4.8 to 10.4 million over the next 25 years,[3,4] and the number of individuals with AF is projected to increase 2.5 fold by 2050.[5] Thus, there is a pressing public health need to improve the appropriate use of existing therapy (warfarin) and to develop new therapies for primary and secondary stroke prevention.

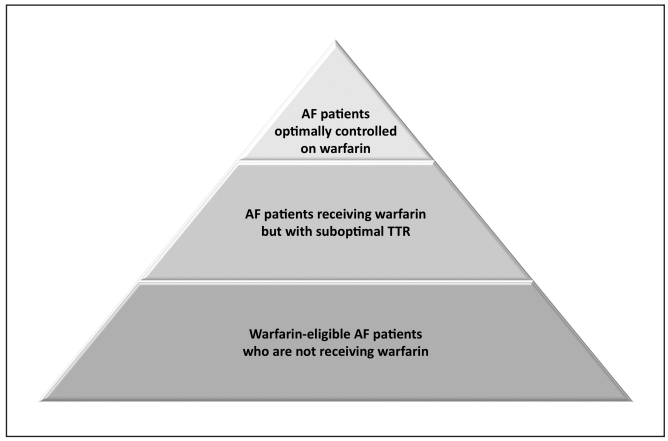


***Figure:*** *Schematic of the Practice Gap in Anticoagulation for Atrial Fibrillation. AF patients treated with warfarin who maintain a high time in therapeutic range (TTR) represent the "tip of the iceberg", whereas many more patients with AF are not being maximally treated for stroke prevention.*

## Part 1. Current Anticoagulant Therapy for AF: The State of the Gap

The underuse of warfarin for eligible high-risk patients with AF represents one of the greatest unsolved practice gaps in stroke prevention. Warfarin is a highly efficacious anticoagulant but despite its proven benefits in stroke risk reduction (64% RRR vs. placebo; 37% vs. antiplatelet therapy),[6] it remains greatly underutilized. The care gaps are staggering – simply put,

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only about half of eligible patients actually receive warfarin,[7] and those who are taking it are outside the therapeutic international normalized ratio (INR) range about half the time.[8,9] (Figure) In the Registry of the Canadian Stroke Network's study of 597 consecutive hospitalized ischemic stroke patients with pre-existing AF who were known to be at high risk for emboli and had no contraindications to anticoagulation, only 39% of this "ideal" cohort had been receiving warfarin pre-stroke and the majority was subtherapeutic; overall, only one in ten was therapeutically anticoagulated (INR ≥2.0) at the time of stroke.[10] Thus, many more strokes could likely be avoided (or lessened in severity[11]) if anticoagulant therapy were optimized.

The net benefit of warfarin in stroke prevention is dependent on maintaining the INR in a narrow therapeutic range, i.e. 2.0-3.0 for non-valvular AF.[12] Time in therapeutic range (TTR) is generally highest in well-controlled environments such as clinical trials and dedicated anticoagulant management programs, yet still only reaches approximately 65%.[8] The balance between benefit and risk favours warfarin over dual antiplatelet therapy (Acetylsalicyclic acid (ASA) plus clopidogrel) only when the TTR is at least 60%.[12] The vast majority of Canadians with AF are managed in primary care; unlike some countries, access to dedicated anticoagulant management programs in Canada is very limited.[8,13] In a Canadian study of warfarin treated AF patients presenting to hospital, INR was therapeutic in only 37%.[14] A recent Canadian study found warfarin was prescribed at emergency department (ED) discharge for only 45% of patients presenting with AF and CHADS2 score ≥2.[15] Warfarin discontinuation rates are also high: for patients prescribed warfarin, adherence in large studies is only 45% at two years and one-third at five years.[16,17]

The dictum *"primum non nocere"* may conflict with warfarin prescribing when doubt exists over how well the target anticoagulant level can be maintained. Intracranial hemorrhage is a feared outcome associated with anticoagulant therapy and is more common in patients with poor INR control.[12] Warfarin is the fourth most common medication implicated in ED visits for adverse drug events.[18] Fear of bleeding side effects is entrenched in practice; clinicians tend to overestimate warfarin's bleeding risks and underestimate its benefits,[19] an attitude that results in under-dosing or a decision not to initiate therapy for eligible patients who would benefit from anticoagulation. Unfortunately, most knowledge-translation attempts have failed to improve the quality of anticoagulation on a national basis. Clearly, new strategies are necessary.

## Part 2. Future Anticoagulant Therapy for AF: The State of the Art

To improve upon warfarin, new oral anticoagulants must be at least as effective and safe, and more convenient. Ideally they should not require frequent coagulation monitoring and should have minimal food, drug and lifestyle interactions. New agents meeting these criteria are the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban. The factor Xa inhibitors, apixaban and edoxaban, are in advanced stages of clinical development and also have the potential to meet these criteria.

Results from the 18,113 patient RE-LY trial have established a new standard in efficacy and safety for stroke prevention in AF.[20] (See Table 1 for summary of main results.) Compared with dose-adjusted warfarin, dabigatran 150 mg bid was superior for

**Table 1: Summary of efficacy and safety outcomes in RE-LY[17]**

| Event | Dabigatran, 110 mg (N=6015) | | Dabigatran, 150 mg (N=6076) | | Warfarin (N=6022) | | Dabigatran, 110 mg, vs Warfarin | | Dabigatran, 150 mg, vs Warfarin | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *# of patients* | *%/yr* | *# of patients* | *%/yr* | *# of patients* | *%/yr* | Relative Risk (95% CI) | P Value‡ | Relative Risk (95% CI) | P Value‡ |
| Stroke or systemic embolism*† | 182 | 1.53 | 134 | 1.11 | 199 | 1.69 | 0.91 (0.74-1.11) | 0.34 | 0.66 (0.53-0.82) | <0.001 |
| Net clinical benefit¶ | 844 | 7.09 | 832 | 6.91 | 901 | 7.64 | 0.92 (0.84-1.02) | 0.10 | 0.91 (0.82-1.00) | 0.04 |
| Myocardial infarction | 86 | 0.72 | 89 | 0.74 | 63 | 0.53 | 1.35 (0.98-1.87) | 0.07 | 1.38 (1.00-1.91) | 0.048 |
| Death from vascular causes | 289 | 2.43 | 274 | 2.28 | 317 | 2.69 | 0.90 (0.77-1.06) | 0.21 | 0.85 (0.72-0.99) | 0.04 |
| Major bleeding | 322 | 2.71 | 375 | 3.11 | 397 | 3.36 | 0.80 (0.69-0.93) | 0.003 | 0.93 (0.81-1.07) | 0.31 |
| Life threatening bleeding | 145 | 1.22 | 175 | 1.45 | 212 | 1.80 | 0.68 (0.55-0.83) | <0.001 | 0.81 (0.66-0.99) | 0.04 |
| Gastrointestinal bleeding | 133 | 1.12 | 182 | 1.51 | 120 | 1.02 | 1.10 (0.86-1.41) | 0.43 | 1.50 (1.19-1.89) | <0.001 |
| Intracranial hemorrhage** | 27 | 0.23 | 36 | 0.30 | 87 | 0.74 | 0.31 (0.20-0.47) | <0.001 | 0.40 (0.27-0.60) | <0.001 |

All analyses were based on the time to first event. * Data are shown for all patients who had at least one event. † P-value for non-inferiority < 0.001 for both doses of dabigatran compared with warfarin. ‡ P values are for superiority. ¶ Net clinical benefit was a composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding. ** Intracranial hemorrhage: defined as hemorrhagic stroke, subdural hemorrhage or subarachnoid hemorrhage.



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**Table 2: Summary of preliminary results from ROCKET-AF[22]***

| Event | Rivaroxaban (N=7081) | Warfarin (N=7090) | Rivaroxaban vs Warfarin | |
|---|---|---|---|---|
| | %/yr | %/yr | Hazard Ratio (95% CI) | P Value |
| Stroke and non-CNS embolism | 2.12 | 2.42 | 0.88 (0.74-1.03) | 0.117 |
| Major bleeding | 3.60 | 3.45 | 1.04 (0.90-1.20) | 0.576 |
| Intracranial hemorrhage | 0.49 | 0.74 | 0.67 (0.47-0.94) | 0.019 |
| Critical organ bleeding | 0.82 | 1.18 | 0.69 (0.53-0.91) | 0.007 |
| Bleeding causing death | 0.24 | 0.48 | 0.50 (0.31-0.79) | 0.003 |

* based on the intention-to-treat population.

prevention of stroke or systemic embolism with similar rates of major bleeding. The 110 mg bid dose of dabigatran was non-inferior to warfarin for prevention of stroke or systemic embolism and was associated with lower rates of major bleeding. The comparisons between dabigatran and warfarin were open-label in a PROBE design. Both doses of dabigatran had a lower risk of life-threatening bleeding and intracranial hemorrhage compared to warfarin. Patients treated with warfarin in this trial had a mean TTR of 64%, representing warfarin "at its best". The 0.58% absolute reduction in annual risk of stroke (ischemic or hemorrhagic) or systemic embolism demonstrated with the 150 mg dose translates to five to six fewer events per 1000 patients treated, with no increase in major bleeding.

There was a significant interaction between drug treatment and age for bleeding outcomes; dabigatran 110 mg bid was associated with a lower risk of major extracranial bleeding compared to warfarin in patients aged < 75 years; in patients ≥ age 75 years, dabigatran 110 mg bid compared with warfarin was associated with a similar rate of extracranial major bleeding whereas dabigatran 150 mg bid compared with warfarin was associated with an increased rate of extracranial major bleeding.[20(a)] Both doses of dabigatran compared with warfarin were associated with a reduction in intracranial hemorrhage irrespective of age. Dyspepsia was more common with dabigatran than warfarin. Gastrointestinal bleeding occurred more frequently with the 150 mg dose of dabigatran vs. warfarin and both doses of dabigatran were associated with a numerical excess of myocardial infarctions.[21] RE-LY excluded patients with severe renal impairment (creatinine clearance <30 ml/minute). Patients with a recent ischemic stroke (<2 weeks) or previous intracranial hemorrhage were also excluded, so results in these subgroups are unknown.

Preliminary results from ROCKET-AF, a double-blind phase III trial comparing once-daily rivaroxaban to dose-adjusted warfarin in a higher risk patient population than RE-LY, were presented in 2010 (not yet published at the time of this writing).[22] These results, summarized in Table 2, demonstrated that rivaroxaban was non-inferior to warfarin for the prevention of

**Table 3: Summary of efficacy and safety outcomes in AVERROES[23]**

| Event | Apixaban (N=2808) | | Aspirin (N=2791) | | Apixaban vs Aspirin | |
|---|---|---|---|---|---|---|
| | # of patients | %/yr | # of patients | %/yr | Hazard Ratio (95% CI) | P Value |
| Stroke or systemic embolism* | 51 | 1.6 | 113 | 3.7 | 0.45 (0.32-0.62) | <0.001 |
| Net benefit† | 163 | 5.3 | 220 | 7.2 | 0.74 (0.60-0.90) | 0.003 |
| Ischemic stroke | 35 | 1.1 | 93 | 3.0 | 0.37 (0.25-0.55) | <0.001 |
| Major bleeding | 44 | 1.4 | 39 | 1.2 | 1.13 (0.74-1.75) | 0.57 |
| Intracranial bleeding | 11 | 0.4 | 13 | 0.4 | 0.85 (0.38-1.90) | 0.69 |

All analyses were based on the time to first event. * Data are shown for all patients who had at least one event. † Net benefit was a composite of stroke, systemic embolism, myocardial infarction, death from vascular cause, or major bleeding.



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**Table 4: Estimated number of additional Canadian strokes prevented if dabigatran 150 mg bid were used instead of warfarin***

| $CHADS_2$ Score | Estimated # Canadian patients with AF (assuming N=250,000) | | Annual absolute risk reduction with 150 mg dabigatran vs. warfarin[20] | | Estimated # of additional events prevented annually if dabigatran 150 mg bid replaced warfarin in one half of AF patients | | Estimated # of additional events prevented annually if dabigatran 150 mg bid replaced warfarin in one third of AF patients | |
|---|---|---|---|---|---|---|---|---|
| | # | (%)[7] | Stroke or systemic embolism | Intracranial hemorrhage | Stroke or systemic embolism | Intracranial hemorrhage | Stroke or systemic embolism | Intracranial hemorrhage |
| 0 (low risk) | 50,000 | (20.0%) | - | - | - | - | | |
| 1 (low-moderate risk) | 84,500 | (33.8%) | 0.40% | 0.31% | 169 | 131 | 113 | 87 |
| 2 (moderate-high risk) | 69,250 | (27.7%) | 0.54% | 0.40% | 187 | 139 | 125 | 92 |
| ≥3 (highest risk) | 46,000 | (18.4%) | 0.80% | 0.58% | 184 | 134 | 123 | 89 |

* The estimated number of events prevented annually was calculated by using the ARR for dabigatran 150 mg bid vs. warfarin from the RE-LY trial results stratified by CHADS2 score[20] and applying it to the Canadian AF population. The numbers are likely to be an underestimate, because it is based on an assumption that all patients would otherwise be taking warfarin and well controlled (TTR 64%, as per RE-LY) in practice. We also assumed that only one third or one half of all AF patients would be eligible for anticoagulant therapy with dabigatran 150 mg bid (e.g., age <80 years, no contraindications) and adhere to therapy for one year without discontinuation.

stroke and non-central nervous system (CNS) embolism with similar rates of major bleeding (and lower rates of intracranial hemorrhage, critical organ hemorrhage and fatal hemorrhage). The median TTR in patients treated with warfarin was 58%. Rates of dyspepsia and myocardial infarction were not increased with rivaroxaban compared to warfarin.

Results from AVERROES, a phase III trial comparing apixaban with ASA, were recently published.[23] Apixaban was shown to be superior to ASA in preventing stroke or systemic embolism (RRR >50%) in AF patients who were considered unsuitable for warfarin therapy, and the two groups had similar rates of major bleeding. (See Table 3 for a summary of main results.)

Phase III results comparing apixaban and edoxaban to dose-adjusted warfarin are anticipated in 2011 and 2012, respectively.

### *Implementation in the Canadian Setting*

New guidelines state that individuals with non-valvular AF and CHADS2 score ≥1 would benefit from treatment with an anticoagulant.[24-26] Using data from RE-LY applied to the Canadian AF population, one can estimate that hundreds of strokes (ischemic and hemorrhagic) could potentially be prevented each year in Canada by treating patients with dabigatran 150 mg bid instead of warfarin (Table 4). The greatest impact of the new oral anticoagulants at a population level, however, will be their potential to reach the large population of currently untreated patients who could benefit from warfarin but do not receive it. (Figure) Targeting this group of untreated patients represents a major opportunity to reduce stroke rates. For example, if even a fraction of the total population of anticoagulant-eligible patients in Canada were switched from ASA to apixaban, we estimate that hundreds of additional strokes would be prevented annually.

We propose a prioritization hierarchy based on stroke risk for determining how dabigatran can be best utilized to improve patient outcomes. The same approach can be adapted to other new agents that demonstrate favorable efficacy/safety profiles compared to warfarin and aspirin in phase III trials. Patients at moderate to high stroke risk (CHADS2 score ≥2) would be a logical "highest priority" group. This population includes patients with a prior stroke or transient ischemic attack, as well as those with ≥2 stroke risk factors: age ≥75 years, hypertension, diabetes mellitus, and/or left ventricular dysfunction. Patients at lower stroke risk ($CHADS_2$ score =1) may be a "second priority" group. In determining the hierarchical cut-point for the use of dabigatran, a broad view of the healthcare system must be taken that encompasses population effectiveness, safety, and costs to the system as a whole. Patients not well controlled on warfarin should be considered a high priority.

Despite the advantages of new treatments, warfarin remains a time-tested therapy for AF (and many other indications), and system-level strategies to improve warfarin's effectiveness still need to be supported and enhanced.

It is anticipated that the new anticoagulants will enable many more patients to be effectively anticoagulated than has been possible with warfarin because they are easier to initiate, do not require coagulation monitoring, are more convenient for patients and physicians, and there may be less apprehension about bleeding risks. For dabigatran, while the 150 mg bid dose provides the greatest efficacy for stroke risk reduction, the Canadian product monograph recommends the 110 mg bid dose for individuals aged ≥ 80 years (although ≥ 75 years may be



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most appropriate based on new analyses).[20(a)] The 110 mg bid dose is recommended if creatinine clearance is 30-50 ml/minute, and it may become a preferred treatment option for patients judged to be at higher than average bleeding risk for whom clinicians may have otherwise excluded from warfarin therapy altogether. For example, high CHADS2 score patients who have had a previous intracranial hemorrhage are frequently excluded from warfarin therapy, but some may be reasonable candidates to consider for low-dose dabigatran, e.g. selected stable patients with a remote (non-acute) deep hypertensive intracerebral hemorrhage or magnetic resonance image (MRI)-detected microhemorrhages (although such patients were not studied in RE-LY). The rapid onset of action of the new anticoagulants is anticipated to streamline hospital and ED discharge protocols and facilitate rapid outpatient secondary prevention management for AF patients with acute transient ischemic attack. The safety of early initiation of the new anticoagulants in the acute/subacute phase after a transient ischemic attack or ischemic stroke, however, is unknown and is in need of study; caution is therefore advised. Also, given the widespread tendency toward overdiagnosis of transient ischemic attacks, accurate patient diagnosis and risk stratification are essential to avoid inappropriate anticoagulation of low risk patients.

## Part 3. Limitations and Caveats with the New Oral Anticoagulants

While the development of new oral anticoagulants for AF represents a welcome advance for the stroke prevention field, there are recognized limitations. One concern is the lack of a specific antidote (e.g. vitamin K, prothrombin complex concentrate) for the emergency reversal of anticoagulant effect of the new agents in the event of major bleeding or need for an emergency procedure or surgery; hospital protocols for managing such situations need to be urgently developed. There is currently no widely available way to measure the intensity of anticoagulation of the new drugs like there is with warfarin. The new drugs might make many patients ineligible for intravenous thrombolytic therapy, e.g. tPA in the event of an acute ischemic stroke (the role of endovascular rescue attempts with mechanical clot removal will inevitably need to be explored).

The lack of a need for routine coagulation monitoring that is a distinct advantage of the new drugs also represents a potential danger in real-world practice outside of a trial setting if patients stop being monitored and adherence stops being assessed. Given the short half-life of the new agents compared to warfarin, the consequence of missed doses could be more significant in terms of stroke risks. Therefore, concerted efforts to promote patient education and reinforce adherence to therapy will become more important than ever. Extra caution is advised in patients with renal impairment and periodic monitoring for declining renal function that may preclude continued therapy with a new anticoagulant should be considered. Phase IV surveillance studies will be important to ensure appropriate use and safety of the new agents in practice and to ensure the new agents do not become over-prescribed, i.e. for inappropriate indications. As with any new drug, we must tread cautiously, and clinicians and patients cannot risk becoming cavalier about anticoagulant therapy. The Canadian Cardiovascular Pharmacists Network has developed a pocket card of useful anticoagulant prescribing information to assist clinicians.[28] To avoid loss of potency, dabigatran capsules should not be removed from the original bottle or packaging in which it was dispensed and should be used within 60 days.[27] For all anticoagulated patients, regardless of the agent, ensuring optimal blood pressure control and avoiding concomitant antiplatelet therapy (unless otherwise indicated) will help to minimize bleeding risks.

### Summary

Preventing more AF-related strokes in Canada must become a top priority for clinicians, hospitals and government. Although warfarin is highly efficacious, we are facing an epidemic of strokes because too many eligible patients are not receiving warfarin and because stable therapeutic INR control can be difficult to achieve. The recent regulatory approval of dabigatran marks a milestone in the history of AF management since the introduction of warfarin about 60 years ago. Taken together with recent trial results for rivaroxaban and apixaban and the ongoing development of other oral anticoagulant drugs, there is real promise that many more patients with AF will be effectively anticoagulated and better protected against stroke. After decades of inertia with warfarin, we are now finally on the verge of a new treatment era. Careful patient selection and careful follow-up of patients prescribed new anticoagulants will be crucial in determining how successfully trial results will be translated into real world practice.

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Dr. Cox sits on advisory boards for Astra Zeneca, Bayer, Boehringer Ingelheim, BMS/Sanofi Aventis Pharmaceuticals Partnership and Sanofi Aventis. He has participated in research



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