# Stroke Prevention in Atrial Fibrillation through Anti-thrombotics: A White Paper on Optimization of Quality and Access to Care

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in Patients with Atrial Fibrillation
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# EXECUTIVE SUMMARY:

Atrial fibrillation (AF) is the most common cardiac rhythm disturbance and is a leading cause of stroke. Stroke in the setting of AF is more likely to be fatal or disabling. The occurrence of AF is directly linked to age and will triple in frequency over the next forty years. We can expect a substantial and increasing impact on mortality, disability and health care resources in the near future.

Atrial fibrillation (AF) is the most common cardiac rhythm disturbance and is a leading cause of stroke.

There is an urgent need to address this challenge. Effective medical strategies to prevent stroke in AF exist, but they require a coordinated approach which addresses treatment gaps and offers access to the most appropriate medications. A focused effort to influence stroke care at a time when new medications are available presents a unique opportunity to improve the lives of Canadians with AF.

The Canadian Council for Stroke Prevention in Patients with Atrial Fibrillation (CC-SPAF) is an independent multidisciplinary advisory council established to provide advice, insight and guidance to policy makers and other stakeholders (such as patient advocacy groups and health professionals) across Canada.

Council members included representatives from the fields of neurology, family medicine/general practice, cardiology, nursing, pharmacy and haematology. The government policy, drug plan and patient advocacy perspectives were also represented. The council was supported by an unconditional grant from Bayer Inc., however it retained full freedom to reach its own conclusions and communicate its views.

Objective of this Report

**The objective of this report is to advocate for appropriate access to current and evolving anti-thrombotic therapy in order to prevent stroke in patients with AF and improve outcomes and quality-of-life.**

The Council concluded that where appropriate, the following recommendations to improve the use of anti-thrombotic therapies to prevent strokes in patients with AF should be considered by policymakers, advocacy groups and health care providers:

Recommendation 1

**Ensure that appropriate systems and infrastructures are in place for effective anti-coagulation management.**

Recommendation 2

**All anti-thrombotic therapies approved for SPAF should be publicly reimbursed for appropriate patients.**

Recommendation 3

**Professional societies and advocacy groups should promote awareness of AF and its optimal treatment leading to better outcomes.**

# INTRODUCTION

Stroke is one of the most common causes of death and disability worldwide.[2] Its occurrence is strongly linked to age, beginning to rise at the age of 55 and doubling for each decade thereafter.[3] The most common type of stroke is ischemic stroke which occurs when a blood vessel to the brain is blocked, resulting in death of brain tissue.[4] Many individuals with ischemic stroke survive, but are left with ongoing disability for activities of daily living, self-care, mobility, communication and cognition. Stroke represents a significant burden on patients, their caregivers, health care providers and health care resources. According to the Heart and Stroke Foundation, strokes cost the Canadian economy $2.7 billion per year.[5]

Stroke is one of the most common causes of death and disability worldwide. As the age distribution of our population shifts, we can expect a substantial impact on mortality, disability and health care resources.

Atrial fibrillation (AF) is the most common cardiac rhythm disturbance and is a leading cause of stroke. In AF, blood clots form in the heart and travel through the arterial system until they cause a blockage, most frequently in the brain. A 2005 study suggested that AF is responsible for almost one in four strokes.[6] Individuals with AF have a three-to-fivefold higher risk of stroke than those without it.[7] Strokes due to AF are more severe than strokes resulting from other causes. In Canada, 20% of affected individuals die and 60% are left substantially disabled – roughly twice the rates for stroke in general.[8]

Demographic projections suggest an almost tripling of frequency of AF over the next four decades.[9] [10] Further, the risk of stroke for patients with AF rises from 5.9% for men and 3.0% for women in their late 50s to 22.3% for men and 23.9% of women in their early 80s.[11]

The time to make systematic changes is now.

Based on the increasing frequency of AF and its consequences as the age distribution of our population shifts, we can expect a substantial impact on mortality, disability and health care resources in the near future.

There is an urgent need to address this challenge. Effective medical strategies to prevent stroke in AF exist, but they require a coordinated approach which addresses treatment gaps and offers access to the most appropriate medications. We believe the time to make systematic changes in the care of individuals with AF is now.

A focused effort to influence stroke care at a time when new medications are available presents a unique opportunity to improve the lives of Canadians with AF.

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# BACKGROUND

> There are up to 50,000 Canadian hospital admissions annually due to stroke, which equates to one stroke every 10 minutes.

### What is Stroke?

Stroke is a sudden loss of brain function caused by interruption of normal blood flow to the brain. It is the second most common cause of death in the world and a leading cause of disability.[12] In Canada, there are up to 50,000 hospital admissions annually due to stroke,[13] which equates to one stroke every 10 minutes. Canadians spend a total of three million days in hospital each year because of stroke.[14] And each year, 16,000 people die from stroke, more women than men.[15] The Heart and Stroke Foundation indicates that fifteen per cent of strokes in Canada are due to atrial fibrillation (AF).[16]

### What is AF?

AF is a heart rhythm abnormality that is characterized by an irregular and often rapid heart rate.

### How does AF cause stroke?

AF predisposes to the formation of a blood clot in the heart, which can break away and can then become trapped in blood vessels in the brain, causing a stroke. Patients with AF at highest risk for stroke are older, have had a previous stroke or have a history of vascular disease, heart failure, hypertension and diabetes.[17]

### Why is AF such an important risk factor for stroke?

There are at least four reasons why AF is such an important risk factor for stroke:

1. AF accounts for a significant proportion of all strokes and one in twenty patients with AF will suffer a stroke each year if left untreated.[18]
2. Strokes in patients with AF are more severe than strokes in patients without AF. Twenty per cent of AF patients who suffer stroke die within one year and 60% are left with neurological disability.[19] Many patients characterize the effects of severe stroke as being equal to or worse than death because of loss of ability to swallow, talk, walk and manage their own activities of daily living.[20] Thus, stroke is a major burden for patients, their caregivers, health care providers and health care resources.
3. The burden of stroke due to AF is rising. Already now, between 200,000 and 600,000 Canadians are affected with AF,[21 22 23 24 25 26] and the burden of AF is rising because of the ageing population and the increasing survival of patients with risk factors for cardiovascular disease that are associated with AF.
4. Strokes in patients with AF are potentially preventable with the use of effective anti-thrombotic therapies. However, these treatments are under-utilized and managed inadequately.

### What treatment options are available to prevent stroke due to AF?

Stroke in AF can be prevented by the use of effective anti-thrombotic medications. For many years, acetylsalicylic acid (ASA) and warfarin have been approved in Canada for stroke prevention in AF.[27] Currently, warfarin is the first line treatment because it is much more effective than ASA, but it is used in only about 50% of eligible patients and, even when treated with warfarin, patients often are inadequately protected because of the difficulties of maintaining the correct levels of the medicine in the blood. Patients with poor warfarin control have higher rates of stroke complications than those who have good control.[28] Treatments aimed at controlling the heart rate or rhythm do not prevent stroke.[29]

### Why is warfarin so often underutilized and inadequately managed?

As stated above, warfarin is effective for the treatment of patients with AF, reducing the risk of stroke by about 2/3 and the risk of death by about 1/4.[30] Patients face challenges in accepting warfarin therapy and have concerns about how it affects their quality-of-life. Warfarin has many limitations that lessen its uptake and reduce its effectiveness. The most important of these is a variable and unpredictable anti-coagulant effect resulting from genetic variability and numerous food and drug interactions. Consequently, routine coagulation monitoring is required to maintain the international normalized ratio in the therapeutic range. This testing is inconvenient for patients and costly for the healthcare system. Warfarin also has a slow "onset" (i.e., time-to-take effect) and "offset" (i.e., time it takes to stop its therapeutic / anti-coagulant effect) but these limitations are less important than its variable anti-coagulant effects.

Fewer than 50% of patients indicated for warfarin are prescribed it.

Furthermore, of those patients prescribed warfarin, fewer than 50% are appropriately anti-coagulated.

Other challenges include the fear of warfarin-related bleeding and an inability to undertake frequent blood testing. Physicians also experience difficulties with keeping warfarin in therapeutic range due to the requirement for patients to adhere precisely to the prescribed regimen which may involve day-by-day dose variation; out-of-pocket expenses for patient and caregivers related to testing; limitations on activities such as travel due to the need for testing and the potential for interactions with medications or food, etc.[31]

In summary, fewer than 50% of patients indicated for warfarin are prescribed it.[32] Furthermore, of those patients prescribed warfarin, fewer than 50% are appropriately anti-coagulated.[33] This remains true for patients presenting with ischemic stroke. Even in this high-risk population, warfarin treatment remains sub-optimal.[34]

Potential approaches to optimize warfarin use in primary care could include increasing the availability of dedicated anti-coagulation clinics; the use of electronic medical records; incentives for appropriate anti-coagulation monitoring and follow-up; education programs for physicians focused on the Canadian Cardiovascular Society Guidelines for Management of Atrial Fibrillation[35]; lay education programs for all patients with AF, their families and caregivers and exploring the potential for point-of-care monitoring devices in physician offices and/or through home care services. One could also explore the use of patient self-management approaches, dosette medication dispensing and the like.

Electronic medical records (EMRs) can enable high-quality monitoring. They facilitate most steps of the process required for optimizing anti-coagulation therapy and follow-up. Unfortunately though, as of 2010, only 21.5% of primary care physicians and 10.1% of specialists are using EMRs.[36]

These challenges associated with managing warfarin effectively suggest the need for systematic processes designed to foster active monitoring of patients with clear communication and follow-up. One way to accomplish this would be through the establishment of a network of anti-coagulation clinics. These clinics typically utilize a multi-disciplinary approach involving physicians, pharmacists, nurses and educators to monitor and follow patients taking warfarin. However most Canadians with AF are managed in primary care and access to dedicated anti-coagulation clinics is limited.[37]

### New oral anti-coagulant medications: benefits…limitations; alternatives to warfarin

Within the past few years, a number of clinical trials comparing novel oral anti-coagulants (NOACs) with warfarin have demonstrated efficacy and safety advantages.[38] Two of these medications are currently approved for use in Canada: dabigatran and rivaroxaban.

NOACs offer predictable dose responses, thereby eliminating the need to perform routine coagulation monitoring. Furthermore, compared to warfarin, they have virtually no dietary interactions and limited drug-drug interactions. As such, they can be expected to be easier to use in routine clinical practice in the prevention of stroke.

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### Current situation

Considering the large number of stroke patients, the financial, societal and personal burden of stroke is significant.[39] Although dated, a study by Goeree et al. estimated that the average one-year cost of managing patients who have suffered an ischemic stroke was $53,576.[40] According to the Canadian Stroke Network's Burden of Ischemic Stroke (BURST) study, the direct and indirect health-care costs for new stroke patients add up to an average of $50,000 in the six-month period following a new stroke.[41]

As a result, more effective use of warfarin and NOACs potentially could result in significant savings to the healthcare system by preventing many ischemic strokes.[42] Typically, older medications for stroke prevention in AF are the ones that are reimbursed through public drug programs. Warfarin at a cost of $1.21 per day (including monitoring costs)[43] is fully reimbursed across Canada and can be an option for a number of patients, if it is used appropriately.

In the majority of provinces, all approved NOACs are not fully reimbursed by provincial drug benefit plans. A cost-effectiveness study conducted in Canada found that one of the NOACs, dabigatran, is "highly cost-effective" vs. warfarin. According to the study, "the findings provide confidence that…dabigatran…is a reasonable investment for the Canadian healthcare setting."[44] Given those findings, there could be an additional benefit in ensuring that a larger proportion of individuals needing anti-coagulation treatment have access to NOACs due to their simplicity of use and greater efficacy. Unfortunately, the lack of public formulary coverage for NOACs restricts their use to individuals with private coverage or those able to pay out-of-pocket.

The council believes that cost effectiveness analyses relied upon by drug plan decision-makers should include all direct and indirect costs (i.e., loss of wages, out-of-pocket expenses, caregiver costs) associated with the use of warfarin when comparing it to the NOACs. The addition of these considerations, along with available cost-effectiveness analyses, suggests that these agents are a cost effective treatment option in the Canadian setting.

# RECOMMENDATIONS

**Where appropriate, the following recommendations to improve the use of anti-thrombotic therapies to prevent strokes in patients with AF should be considered by policymakers, advocacy groups and health care providers.**

Optimal outcomes can be achieved by making the choice of appropriate anti-thrombotic based on a clinician's assessment of bleeding risk, stroke risk, general health, co-morbidities, age, patient adherence and capability and impact on quality-of-life, etc. Selection of anti-thrombotic agents should be based on patient characteristics, combined with the availability of systematic processes for monitoring.

Recommendation 1

## Ensure that appropriate systems and infrastructures are in place for effective anti-coagulation management.

When warfarin is used, a system must be in place to ensure that the appropriate blood tests are done at the correct times and that the patient is informed of dosage adjustments and required actions to address potential adverse events.
Critical components of this system include:

- Blood tests done at appropriate intervals (requiring access to laboratory services, transportation, etc.);
- A coordinated system to ensure that blood test results are communicated to physicians and patients in a timely fashion, (i.e., via e-health initiatives such as electronic medical records, etc.);
- A process to ensure transfer of complete and accurate information among health care providers and health care institutions and services, (i.e., from the acute care setting to the community);
- Improved access to anti-coagulation clinics, where possible expanding them in conjunction with existing clinics (e.g. stroke prevention, cardiac clinics, etc.).

It is important as well to ensure that patients taking NOACs have regular follow-up, including monitoring of renal function, to ensure that risks and benefits are re-assessed and adverse events are monitored.

Recommendation 2

## All anti-thrombotic therapies approved for SPAF should be publicly reimbursed for appropriate patients.

Most patients who require anti-coagulants for AF are older than 65. In most provinces, medications are publicly reimbursed for this group. However, in the majority of provinces, all approved NOACs are not fully reimbursed on provincial formularies. Many patients who are prescribed warfarin are sub-optimally managed due to patient, physician and healthcare system factors. This represents a large untreated population. NOACs address many of these shortcomings and have benefits of ensuring that this population is treated. A Canadian study has indicated that dabigatran, one of the two currently approved NOACs, is a cost-effective treatment alternative.

Recommendation 3

## Professional societies and advocacy groups should promote awareness of AF and its optimal treatment leading to better outcomes.

A large proportion of AF patients are undiagnosed.[45] Based on demographic projections, this number is increasing and will increase dramatically in coming years. Strokes due to AF are severe, resulting in death or significant disability. Costs relating to these strokes include direct costs, loss of productivity and significant costs and burden to caregivers. Professional societies and advocacy groups are in the best position to increase awareness of AF among physicians, other health care providers, patients and caregivers.

## CONCLUSION

It is clear that addressing the growing burden of stroke associated with AF must be a healthcare system priority in light of the likelihood of increased prevalence of the debilitating effects of this condition. Failure to act will result in an increasing societal, economic and health care burden.

Many patients with AF who are at risk for stroke are currently not well managed within our healthcare system. NOACs could offer an important cost-effective treatment for those who are either not on warfarin, or inadequately controlled while taking it.

Many patients with AF who are at risk for stroke are currently not well managed within our healthcare system. NOACs could offer an important cost-effective treatment for those who are either not on warfarin, or inadequately controlled while taking it.

In addressing this challenge, individual patient characteristics must be considered when deciding on the most appropriate treatment options. Appropriate infrastructure must be put in place (i.e., by improving communication and information exchange among health care providers and patients, by expanding the number of anti-coagulation clinics, by ensuring that, as appropriate, all patients have access to NOACs, and by increasing awareness about AF).

### *About the Canadian Council for Stroke Prevention in Patients with Atrial Fibrillation (CC-SPAF)*

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# Endnotes

1 All council members were involved in the preparation and review of this report. They are as follows:
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