October 2012

Atrial Fibrillation-Related Stroke across Latin America: A Preventable Problem

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This booklet was made possible by Bayer HealthCare Pharmaceuticals.
See reverse of title page and acknowledgements for further information.

Strike Out Stroke in Atrial Fibrillation
Action for Stroke Prevention

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The recommendations in this document are endorsed by the organizations shown below.

ISBN 978-0-9568536-8-4

Action for Stroke Prevention (ASP) has been initiated and funded by Bayer HealthCare as an independent alliance of experts with the aim to increase the awareness of atrial fibrillation and the associated risk of stroke. This booklet has been produced by ASP with the aid of financial support from Bayer HealthCare. Bayer HealthCare have also been given the opportunity to comment upon the booklet from a regulatory and compliance perspective. However, the content of this booklet has been determined, and full editorial control retained, by the authors independently of Bayer HealthCare in order to ensure the independence of the booklet and outputs of the group. The views expressed in this publication are not necessarily those of the sponsor

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Acknowledgments
Support for the writing and editing of this booklet was provided by Chameleon Communications International Ltd, with funding from Bayer HealthCare. We acknowledge with thanks the contribution of Oxford PharmaGenesis™ Ltd who provided editorial and writing support for a previous report on the European Union: How Can We Avoid a Stroke Crisis? (2009), with funding from Bayer HealthCare.

The content of this booklet has been determined by the authors independently of Bayer HealthCare in order to ensure the independence of the booklet and outputs of the group.

Endorsements

Academia Brasileira de Neurologia	www.sbdcv.com.br
Academia Nacional de Medicina	www.anm.org.uy/Inicio.php
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Uruguay Society for Cardiology (SUC)	www.suc.org.uy
Uruguayan Society for Intensive Care Medicine	www.sumi.org.uy
World Stroke Organization	www.world-stroke.org

Atrial fibrillation-related stroke: a global but preventable problem

- A stroke occurs when a blood vessel becomes blocked and the supply of blood to the brain becomes interrupted (ischemic stroke), or when blood from a ruptured vessel leaks into the brain (hemorrhagic stroke). Both can cause significant brain damage
- Approximately 15% of all strokes are associated with atrial fibrillation (AF),[1] an abnormal heart rhythm. The condition occurs with increasing frequency as people get older and is the most common heart rhythm disorder[2]
- AF causes a stroke when the abnormal heart rhythm leads to the formation of a blood clot in the heart that is then transported to the brain. Patients with AF are *five times* more likely to experience a stroke than those without AF,[3] and AF-related strokes are more severe than strokes unrelated to AF[4,5]
- Stroke causes approximately 6 million deaths globally each year.[6] In 2004, 437 000 people suffered a first-ever stroke in Latin America.[7] The costs associated with stroke are considerable. Aggregate national healthcare expenditures of initial hospitalization for stroke in Brazil and Argentina alone have been calculated at US$449.3 million and US$434.1 million, respectively[8,9]
- In this booklet, we look at key facts concerning the human and economic cost of this preventable type of stroke in Latin America, and how best to prevent it

AF-related stroke is a major problem in Latin America today. However, it is a problem that can be overcome

Atrial fibrillation-related stroke in Latin America: the avoidable burden

The clinical burden

- Although data regarding the prevalence of AF in Latin America are scarce, it is thought that there are a large number of people in the region living with the condition. In Brazil, an estimated 1.5 million patients are living with AF; in Venezuela, approximately 230 000 patients live with AF, with this figure predicted to rise to 1 million by 2050[10,11]
- Stroke survivors often have permanent physical and cognitive disabilities; family members can also experience depression and a loss of independence[12–14]
- AF is the most common sustained abnormal heart rhythm (arrhythmia) and occurs with increasing frequency as people get older[2]
- In Latin America, the World Health Organization (WHO) estimated that the prevalence (i.e. total number of cases) of patients surviving a stroke in Latin America was 1.9 million in 2004.[15] For that same year, the WHO estimated that 437 000 people suffered a first-ever stroke.[7] The number of strokes per year is predicted to rise dramatically as the population ages, and it has been predicted that deaths resulting from ischemic heart disease and stroke in Latin America will almost triple by the year 2024[16,17]
- Because of the larger size of the clot, AF-related stroke is more severe than non-AF-related stroke. It is associated with a higher risk of in-hospital death, greater disability, longer hospital stays, a reduced likelihood of patients returning to their own home, and increased risk of recurrent stroke[4,5]
- As a result, AF-related stroke imposes a much greater burden on patients and their families than non-AF-related stroke

The financial burden

- The financial burden placed on Latin American countries by stroke is huge. As noted above, national healthcare expenditures for initial hospitalization for stroke in Brazil and Argentina alone have been calculated at US$449.3 million and US$434.1 million, respectively[8,9]
- Stroke costs are also higher in patients with AF compared with costs in patients without AF. Although mean cost data for cardioembolic stroke in patients in Latin American countries are scarce, cost data from Europe may offer an indication of the cost spread across the countries of the Latin American region
  - The mean costs of acute hospital care were shown to be higher for cardioembolic stroke (€4890 per patient; US$6948) than for non-cardioembolic stroke (€3550; US$5044) in a study of more than 500 patients in Germany[18]
  - Cardioembolic strokes are associated with a higher risk of recurrence than other types of stroke[19]
- In addition, the financial burden of stroke in patients with AF is likely to be even greater for patients in Latin American countries where there is a high level of out-of-pocket expenditure on healthcare[20]

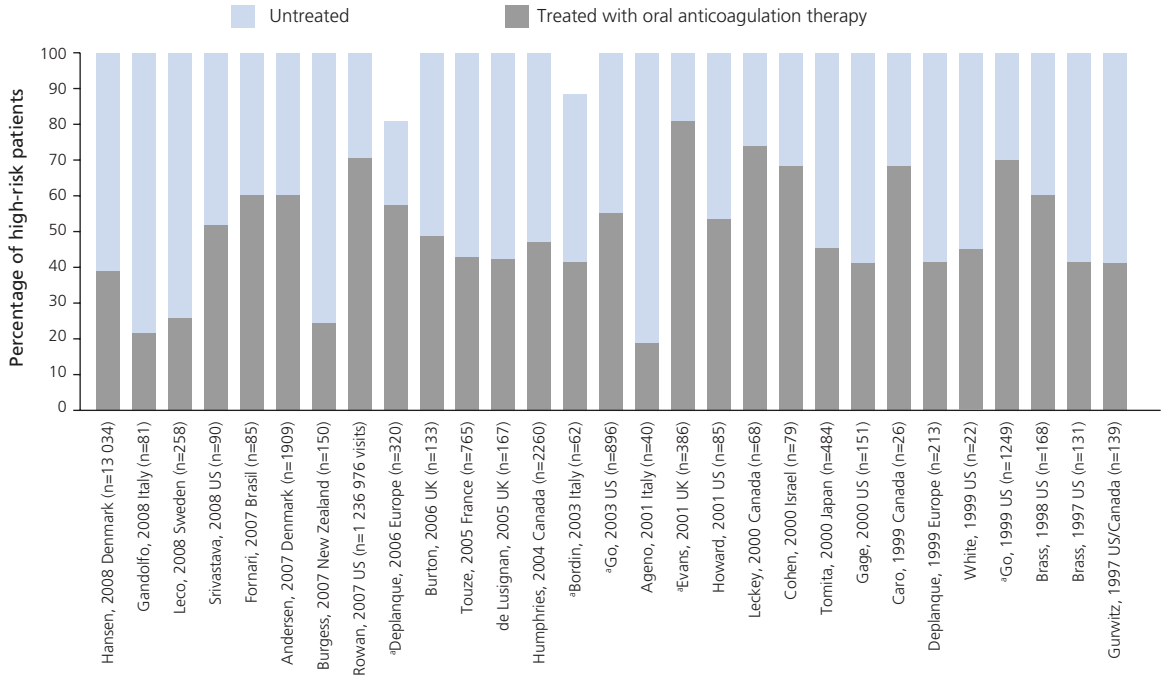
Improving stroke prevention: diagnosing atrial fibrillation earlier

- Although AF itself can be simple to diagnose, in many cases it goes undetected
- One major problem with AF is that it is often asymptomatic.[21] As a result, many patients are not diagnosed and do not receive the anticoagulation that they need
- In recent years, strategies have been developed to improve detection of AF: a first step towards providing therapy for the prevention of AF-related stroke
- Checking patients aged ≥65 years for an irregular pulse at their next visit and referring them for an electrocardiogram was an effective way of screening patients for AF in one UK-based primary care study[22]
- The Pan American Health Organization (PAHO) has proactively adapted the WHO's STEPwise Method to Stroke Surveillance (STEPS Stroke) in Latin American countries as a useful tool to improve data collection, prevention, and treatment of stroke[23]

Preventing stroke in patients with atrial fibrillation: feasible and cost-effective, but underutilized

- For many years, oral anticoagulation with vitamin K antagonists (VKAs), such as warfarin, has been the 'gold standard' therapy for long-term stroke prevention in patients with moderate to high risk of stroke. In clinical studies, VKAs reduce stroke risk by an average of 64% compared with no therapy and by 38% versus aspirin[24]
- However, clinical trials are 'controlled' environments with strict trial conditions and careful anticoagulation monitoring.[25,26] In real-life, VKAs are underused; several studies report anticoagulant use in <50% of patients with AF who are at high risk of stroke (Figure 1)[27]
- Patients on VKAs may also spend much of their time (perhaps 45% on average) outside the 'target' therapeutic range for optimal therapy (referred to as the 'international normalized ratio' [INR] of 2.0–3.0).[28] Based on these numbers, perhaps 25–30% of patients with AF receive optimal VKA therapy at any one time

Figure 1. Patients with atrial fibrillation and prior stroke/transient ischemic attack: oral anticoagulation levels as a proportion of patients eligible for oral anticoagulation therapy.



Adapted from *Am J Med*, vol. 123, Ogilvie IM *et al*. Underuse of oral anticoagulants in atrial fibrillation: a systematic review, 638–645.e4, copyright 2012, with permission from Elsevier.[27]

[a]Contraindications taken into account.

- Low time in therapeutic range (TTR) means that, for much of the time, a patient's INR is either too low, increasing the risk of ischemic stroke, or too high, resulting in an increased risk of bleeding, especially intracranial hemorrhage (ICH). Because of this, low TTR (poor INR control) is associated with increased event rates and higher costs

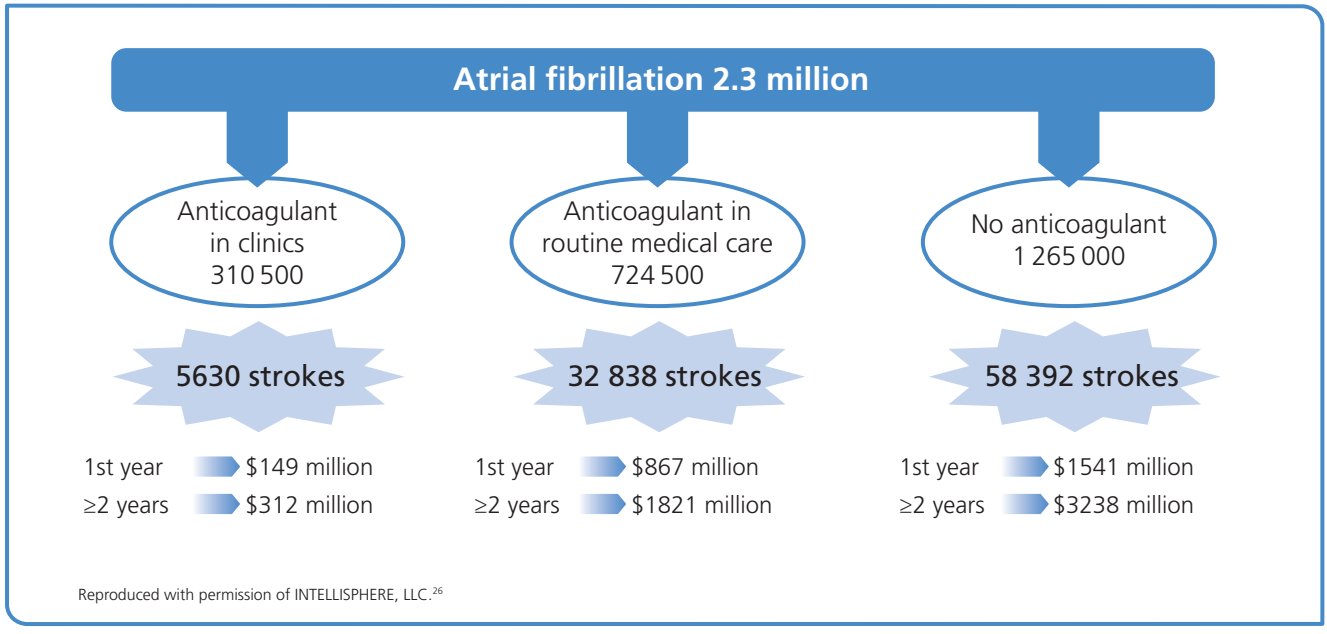
Why is optimal prevention not achieved in practice?

- Successful VKA therapy requires frequent monitoring and dose adjustment to keep the patient within the INR range of 2.0–3.0.[29] VKAs also have an unpredictable and variable dose-response and interact with many different foods, alcohol, and drug classes[30]
- Many physicians overestimate the risk of bleeding associated with VKAs and underestimate their benefits, particularly in elderly individuals.[31] Patients themselves may also be unwilling to use them because of fears of side-effects[32]
- Physicians are often concerned about a patient's ability to comply with VKA therapy because of the requirement for regular monitoring and dose adjustment, especially if the patient is elderly, lives alone, or has cognitive impairment[33,34]
- Regular INR monitoring may be especially difficult in some Latin American countries where some patients have limited access to healthcare resources, including INR monitoring facilities

Suboptimal use of VKAs increases costs

- VKA therapy can be cost-effective for the prevention of AF-related stroke, even in elderly patients;[35] however, this depends on how well it is managed
- Data comparing the cost of AF-related stroke prevention using VKA therapy with the cost of treating stroke are not available for Latin American countries. However, data from the US highlight the cost reduction associated with optimal anticoagulation
- The cost of stroke per patient with AF in those who were anticoagulated in routine medical care (approximately 70% of patients) was more than double that for patients attending specialized anticoagulation clinics (approximately 30% of patients) ($3710 vs $1485) in one US model (Figure 2).[36] Much of this extra cost stemmed from managing complications associated with VKA therapy, such as bleeding. It is likely that further strokes resulting from underuse also increased costs

Figure 2. Results of a 2004 economic model showing potential cost savings with optimal anticoagulation for stroke prevention in patients with atrial fibrillation in the US.



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Cost of VKA monitoring[a]

- Data on the cost of attending anticoagulation clinics in Latin American countries are not available. However, there are European studies that provide costs related to anticoagulation clinics
  - The direct cost of routine INR monitoring has been estimated to be approximately €519 in the UK[37] and €513 in Denmark,[38] but can vary substantially depending on country and healthcare system.[39] For example, considerably higher annual costs of approximately €1787 for the first year and approximately €980 for the second year have been estimated for Swedish primary care[40]
- Cost estimates often do not take into account the indirect costs incurred by the patient and their family (e.g. lost productivity and transport to clinic). A questionnaire-based study of patients in the SPORTIF trial found that the average cost to patients of attending an anticoagulation clinic varied from €6.90 (France) to €20.50 (Portugal) per visit.[41] Over the course of many years, this can translate into substantial costs

Recent advances in prevention of atrial fibrillation-related stroke: non-vitamin K antagonist oral anticoagulants

- VKAs have their limitations, which contribute to their underuse
- In recent years, the efficacy and safety of the non-VKA oral anticoagulants (OACs) rivaroxaban, dabigatran, and apixaban have been tested in large-scale global trials: ROCKET AF, RELY, and ARISTOTLE[42–44]
- These non-VKA OACs have distinct advantages over VKAs in that they:
  - Have predictable pharmacokinetics/ pharmacodynamics. This means that, unlike the VKAs, a given dose of a non-VKA OAC always achieves the same degree of anticoagulation
  - Have few food or drug interactions, in contrast to VKAs
  - Are taken as fixed once-daily (rivaroxaban) or twice-daily (dabigatran) doses
  - Require no routine coagulation monitoring
- The ROCKET AF and RE-LY trials with rivaroxaban and dabigatran, respectively, have shown that these agents are at least as effective as VKAs for the prevention of AF-related stroke. They are also associated with significant reductions in ICH compared with VKA therapy – a particularly feared complication among physicians[42,44]
- Although the introduction of agents such as the non-VKA OACs are associated with increased drug costs relative to VKAs, the overall impact on the healthcare budget may be offset to some extent by the introduction of 'generics' for some key cardiovascular drugs. Furthermore, the improved safety profile of the non-VKA OACs can also be expected to further offset costs versus the VKAs

What can be done: action steps

- Huge numbers of strokes that are attributable to AF occur each year in Latin American countries. The associated clinical, social, and human burdens are tremendous
- The critical challenge is for key parties – healthcare professionals, policy-makers, industry, medical societies and patient advocacy groups alike – to work together to reduce the burden of AF-related stroke across Latin America

Actions for policy-makers

- Raise public awareness and understanding of AF and the risk of AF-related stroke
- Implement and support effective practice standards and targets for healthcare professionals; for example, standards for AF screening and availability of a choice of therapeutic options that meets patient needs
- Implement national strategies for the early diagnosis of AF; these might include identifying patients who are at high risk of AF (owing to age, heart disease, alcohol consumption, high blood pressure or other chronic conditions), or promoting routine screening
- Ensure equal and timely access to the best available care (such as anticoagulation clinics and newer therapies) for all patients with AF across Latin America, regardless of where they live or their background
- Ensure that stroke prevention is addressed in national healthcare plans and that AF is recognized as a serious and significant risk factor for stroke

[a]Costs have been converted to Euros based on exchange rates at the time the study was carried out.

Actions for medical societies and healthcare professionals

- Maintain a good working knowledge of the most recent clinical guidelines and educate practising physicians to help ensure that patients with AF receive the best possible care available to them[45,46]
- Inform colleagues in the healthcare profession of the importance of diagnostic checks for AF and of the benefit–risk of anticoagulation in patients with AF
- Ensure colleagues are aware of advances in development of new therapeutic options and of their potential benefits
- Ensure colleagues in the healthcare profession are trained on the appropriate use of approved non-VKA OACs
- Educate patients on why they are receiving treatment and the importance of taking their anticoagulation therapy as prescribed
- Ensure that healthcare payers understand the clinical and economic advantages of having access to new, alternative therapeutic options and how this will help to reduce the number of at-risk patients receiving sub-optimal treatment, through increased efficiency of treatment, thereby increasing prevention of AF-related stroke

Actions for patient advocacy groups

- Improve public awareness and understanding of AF and the risk of AF-related stroke. Campaigns such as the global 'Know Your Pulse' campaign and the 'Sign Against Stroke in Atrial Fibrillation' campaign both increase patient understanding and provide a collective means for patients to call on local policy-makers to improve care[47]
- Help patients to understand the benefits and risks of different therapies and to make informed choices regarding their own therapy. In addition, help patients to understand why they always need to take their therapy according to the prescribed schedule
- Ensure healthcare payers not only consider robust clinical data but also listen to the patient voice to ensure their decisions reflect patient need

AF-related stroke is a major burden that will continue to grow, and urgent action to tackle the problem is needed. However, the solution is in our hands – earlier diagnosis and better treatment will allow us to dramatically limit the impact of this devastating but preventable condition

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Conflicts of Interest

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The European Brain Council is a not for profit organisation which receives core funding from it's members including scientific societies, patient groups and the pharmaceutical and device industries. It also receives specific project funding from EU institutions and industry

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None disclosed