How Can We Avoid a Stroke Crisis in Latin America?

Working Group Report:
Stroke Prevention in Patients with Atrial Fibrillation

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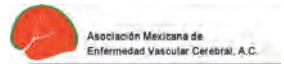


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Endorsements

The organizations listed below endorse the recommendations contained in this report.

Academia Brasileira de Neurologia (Brazil Academy of Neurology) – www.abneuro.org

Academia Nacional de Medicina Uruguay (National Academy of Medicine Uruguay) – www.anm.org.uy

ADKA (The German Society of Hospital Pharmacists) – www.adka.de

Anticoagulation Europe – www.anticoagulationeurope.org

Arrhythmia Alliance – www.heartrhythmcharity.org.uk

Arrhythmia Alliance International – www.aa-international.org

Arrhythmia Alliance Argentina – www.arritmias.org.ar

Arrhythmia Alliance Chile – website to be launched

Arrhythmia Alliance Uruguay – www.aa-international.org/uy

Asociación Médica Argentina (Argentina Medical Association) – www.ama-med.org.ar

Asociación Mexicana de Enfermedad Vascular Cerebral, A.C. (Mexican Stroke Association) – www.amevasc.org

Atrial Fibrillation Association – www.atrialfibrillation.org.uk

Atrial Fibrillation Association International – www.afa-international.org

Atrial Fibrillation Association Argentina – website to be launched

Atrial Fibrillation Association Brazil – website to be launched

Atrial Fibrillation Association Canada – website to be launched

Atrial Fibrillation Association Mexico – website to be launched

Atrial Fibrillation Association Peru – website to be launched

Atrial Fibrillation Association US – website to be launched

Atrial Fibrillation Association Venezuela – website to be launched

Comisión Honoraria para la Salud Cardiovascular (Honorary Commission for Cardiovascular Health) – www.cardiosalud.org

European Heart Rhythm Association – www.escardio.org/EHRA

European Primary Care Cardiovascular Society – www.epccs.eu

European Stroke Conference – www.eurostroke.eu

European Stroke Organisation – www.eso-stroke.org

Federación Argentina de Cardiología (Argentina Federation of Cardiology) – www.fac.org.ar

German Competence Network on Atrial Fibrillation (AFNET) – www.kompetenznetz-vorhofflimmern.de

InterAmerican Heart Foundation (Fundación InterAméricana del Corazón; Funação InterAmericana do Coração) – www.interamericanheart.org

Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology) – www.cardiol.br

Sociedade de Cardiologia do Estado de São Paulo (São Paulo Cardiology Society) – www.socesp.org.br

Sociedad Chilena de Neurología, Psiquiatría y Neurocirugía (Chilean Society for Neurology, Psychiatry and Neurosurgery) – www.sonepsyn.cl

Sociedad Iberoamericana de Enfermedad Cerebrovascular (Iberoamerican Society of Cerebrovascular Disease) – www.siecv.net

Sociedad Neurológica Argentina (Argentina Neurological Society) – www.sna.org.ar

Sociedad Peruana de Neurologia (Peruvian Neurological Society) – www.spneurologia.org.pe

Sociedad Uruguaya de Cardiología (Uruguayan Society of Cardiology) – www.suc.org.uy

Sociedad Uruguaya de Medicina Intensiva (Uruguayan Society of Intensive Care Medicine) – www.sumi.org.uy

StopAfib.org – www.stopafib.org

World Stroke Organization – www.world-stroke.org

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Foreword

Stroke affects millions of people in the Latin American region. In 2004 alone, 437000 people in Latin America suffered a first-ever stroke, and over a quarter of a million people died from a stroke. For many sufferers, death is often the first and last manifestation of stroke. For those who survive a stroke, the impact on their lives can be catastrophic – stroke survivors can be left severely disabled, with the condition having a drastic impact on their health and wellbeing. Stroke also places a substantial emotional and physical burden upon caregivers, who are often close family members, of stroke survivors. Unsurprisingly, the economic burden of stroke is huge. For example, total aggregate national healthcare expenditure of initial hospitalization for stroke in Brazil and Argentina alone has been calculated at almost US$900 million. It is likely that the socioeconomic cost of stroke in the Latin American region will rise dramatically in the coming years as the population ages and many more people suffer the consequences of stroke. This is an epidemic already beginning to happen, and prompt action is required to avoid a crisis.

There are simple actions, which if taken now, could prevent a substantial number of deaths, disabilities, and costs resulting from stroke. If we do nothing, then the Latin American region faces a stroke crisis. Recommendations made in this report are of particular significance for patients with atrial fibrillation (AF) – the most common sustained abnormality of the heart rhythm. AF increases the risk of stroke fivefold, and is responsible for 15–20% of all strokes. The consequences of AF-related stroke are devastating – patients with AF are significantly more likely to have a severe stroke than those who do not have AF. Furthermore, AF increases the risk of remaining disabled after a stroke by almost 50%, and patients with AF who have a stroke have a 50% risk of death within 1 year. Therefore, patients with AF are an important target population for reducing the overall burden of stroke.

Despite being a common condition, AF is often under-diagnosed, and, consequently, undertreated, resulting in inadequate stroke prevention. In the Latin American region there is a clear lack of information regarding the burden of AF that needs to be urgently addressed. The recommendations made in this report draw attention to the poor understanding of AF, and aim to help policy makers and healthcare professionals gain a greater understanding of AF, including its causes and management. This report is a positive step forward in raising awareness of the need for greater investment in the prevention of AF-related stroke in all countries of the Latin American region. It contains a clear Call to Action – we urge that you give it your full attention.

So how can we avoid a stroke crisis in the Latin American region? Stroke prevention in AF requires improved delivery of existing therapies, new strategies to understand and manage AF, and better therapies to prevent stroke. In addition, improved patient education on the risk of AF-related stroke and the symptoms of AF, as well as equal access to therapy and information for all patients across the region, is paramount. The countries of the Latin American region need a clear strategy now to help coordinate the various domains of policy development, raising awareness, research, and educational activities to focus them on the improvement of AF management and effective stroke prevention.

As cardiologists with a global interest in the prevention and management of AF-related stroke, it is a privilege for us to participate actively in an initiative that will help to push forward this important issue in the Latin American region. We firmly believe that only through the coordinated actions of all participants – both at a country and regional level – will we see the highest number of strokes avoided, and the greatest improvements in patient quality of life achieved. In the future, we would like to see the best prevention strategies and treatments for AF-related stroke made available to all patients in all countries of the Latin American region irrespective of their socioeconomic background. The steps outlined in this report will hopefully put us on the right path to achieving this goal. In closing, we hope for the support of all policy makers, healthcare professionals, and medical societies across the region in driving forward this vital initiative.

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Executive summary

Every year, 15 million people worldwide experience a stroke.[1] In 2004, stroke accounted for 5.7 million deaths annually worldwide (9.7% of all deaths).[2] Among Latin American countries, Brazil and Mexico have the largest populations and the highest number of deaths from stroke, with 129 200 and 33 000, respectively.[3] The number of strokes per year is predicted to rise dramatically as the population ages[2] and it has been predicted that deaths due to ischemic heart disease and stroke in Latin America will almost triple by 2024.[4] This is an epidemic already beginning to happen, and prompt action is required to avoid a crisis.

In 2004, stroke accounted for 5.7 million deaths annually worldwide (9.7% of all deaths)

Surviving a stroke can often be worse than dying from one. Patients can be left immobile, incontinent, and unable to speak.[5] The consequences of stroke can devastate not only the patient's quality of life,[6] but also the lives of their family who are most often their caregivers.[7] In Latin America, 437 000 people suffered a first-ever stroke in 2004.[8] The economic burden of stroke is huge. Aggregate national healthcare expenditures of initial hospitalization for stroke in Brazil and Argentina on their own have been calculated at US$449.3 million and US$434.1 million, respectively.[9,10]

Atrial fibrillation (AF) is the most common sustained abnormality of heart rhythm. Compared with the general population, people with AF have a fivefold increased risk of stroke.[11,12] An important risk factor for stroke, AF is responsible for 20% of ischemic strokes (strokes caused by a blood clot blocking a blood vessel in the brain).[13] It is also possible that many strokes of unknown origin (so-called 'cryptogenic' strokes) are caused by undiagnosed AF. The risk of stroke in patients with AF increases with age and with the addition of other risk factors (e.g. high blood pressure, previous stroke, and diabetes).[14]

Among the factors that place a patient with AF at highest risk of stroke are: congestive heart failure, high blood pressure, age over 75 years, diabetes, and previous stroke or transient ischemic attack. More recently, additional risk factors have been included – such as, vascular disease, age 65–74 years, and female gender.[15]

Furthermore, AF-related strokes are more severe, cause greater disability, and have a worse outcome than strokes in people without AF.[13,16–18] In an analysis from a Mexican study, the case death rate at 30 days after an acute stroke event was 22.0% in patients with a history of AF compared with 13.7% without AF.[19] Furthermore, the rate of severe disability in those patients who survived was significantly higher in the AF patient cohort (69% vs 52% in the non-AF patient cohort).

Stroke risk is increased fivefold in patients with AF

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, it has been estimated that there are around 1.5 million patients living with AF;[20] in Venezuela, it is thought there are 230 000 AF sufferers, with this figure predicted to rise to 1 million by 2050.[21]

It is clear that patients with AF represent a vast population at high risk of stroke, and in particular severe stroke. AF patients are therefore an important target population for reducing the overall burden of stroke.

Strokes in people with AF are more severe, cause greater disability, and have worse outcomes than strokes in people without AF

Stroke related to AF can be prevented, but current therapies often have poor outcomes

To prevent AF-related stroke, the ideal would be to prevent or reverse AF itself; however, current techniques can only prevent AF in some patients. Hence, there is a clear need to improve not only detection but also therapy of AF in Latin American countries.

Earlier detection and improved treatment of AF can help to prevent stroke

Anticlotting therapy reduces stroke risk in patients with AF. When appropriately used and properly monitored, it lowers stroke risk by about two-thirds.[22] Despite the existence of guidelines for its use and management, however, such therapy is both underused and misused in clinical practice, largely owing to the significant drawbacks[16,23,24] associated with both vitamin K antagonists[25,26] and aspirin.[27–30]

Stroke prevention in patients with AF therefore requires improved delivery of existing therapies, new strategies to understand and manage AF, and better therapies to prevent stroke.

The incidence and prevalence of AF and AF-related stroke in many countries of Latin America is not known and further research is required

Furthermore, the symptoms of AF may be vague or non-specific, so it is often not detected in time to administer treatment that could prevent a stroke.[31,32] Thus, many potentially preventable strokes occur every year, leading to thousands of early deaths and a devastating burden on individuals, families, and society in terms of disability, and medical and social care costs. The financial burden of stroke in patients with AF is likely to be even greater for those patients in Latin American countries where there is a high level of out-of-pocket expenditure on healthcare.[33]

Currently, the incidence and prevalence of AF and AF-related stroke is unknown in many countries of Latin America. Further studies are urgently needed to provide data on the present and future impact of AF and AF-related stroke in the region. Continued research is also recommended to improve the prevention of stroke in patients with AF. In addition, improved patient education on the risk of AF-related stroke and the early detection of AF is required.

In conclusion, there is a pressing need for Latin American countries to promote the recommendation for earlier diagnosis and better management of AF, thereby reducing the risk of stroke in patients with AF. These recommendations should include:

- Educational and awareness initiatives undertaken in each country to improve early detection of AF
- Better use of interventions for the management of AF and strategies to prevent stroke in patients with AF
- Equal and adequate administration of therapy for patients with AF
- Development of, and greater implementation of and adherence to, guideline recommendations for AF management
- Ongoing research into all aspects of the epidemiology, causes, prevention, and management of AF

Call to action

The authors of this report, and all those individuals and societies who endorse these recommendations, call for national governments of Latin America to ensure better detection and management of atrial fibrillation (AF) and more effective measures to prevent AF-related stroke across all Latin American countries. Through this, we will be able to reduce the major social and economic burden of a largely preventable condition: AF-related stroke.

Latin America needs a clear policy on stroke prevention in patients with atrial fibrillation

Latin America is vast and diverse, encompassing both small and large countries. From a socioeconomic perspective, wide variations also exist in the region. In 2006, 38.5% of the population of Latin America and the Caribbean lived in poverty, and the region has been shown to have the greatest inequality in income distribution in the world, with the exception of Sub-Saharan Africa.[34] Overall, the gap between the richest and poorest in Latin America is widening, with the greatest poverty found in Paraguay and Bolivia.

Although each nation faces unique health challenges, they share a common need to turn the tide on the growing burden of cardiovascular diseases. With cancers and chronic respiratory diseases, cardiovascular diseases are one of the major group of non-communicable diseases and account for 60% of deaths globally.[35] In response to the burden of chronic disease in the region, and recognizing that a strategy to tackle this issue was needed, the Pan American Health Organization (PAHO) developed a regional strategy and plan of action.[36] The report highlighted four main areas of action: (i) recognize that chronic diseases need to be prioritized in the political and public health agendas, (ii) identify surveillance as a key component, (iii) recognize that health systems must be reoriented to respond to the needs of people with chronic conditions, and (iv) note the essential role of health promotion and disease prevention.

The need to tackle this issue was also highlighted by the Ministers and Secretaries of Health of the Americas in the 2007 report *Health Agenda for the Americas 2008–2017*.[37]

The PAHO, in collaboration with the World Health Organization (WHO), has also produced the *Stepwise Approach to Risk-Factor (RF) Surveillance* (STEPS) instrument to aid the collection of chronic non-communicable disease risk factor data for the region.[38] This instrument is an adaption of the original STEPS methodology, and offers a simple, standardized means for collecting, analyzing, and disseminating data in member countries. By using this approach, all countries in the region can use STEPS information, not only for monitoring country-specific trends, but also for making cross-country comparisons.

Cardiovascular disease makes up the largest proportion of all deaths from non-communicable disease, and is the leading cause of death globally.[2,39] Moreover, this disease is on the

increase, and is expected to account for 23.6 million deaths by 2030.[40] It has no geographic, gender, or socioeconomic boundary, and accounts for approximately one-third of all deaths in the world; of these, 80% of deaths occur in low- and middle-income countries.[41]

It has been predicted that deaths from ischemic heart disease and stroke in the Latin American region will almost triple by 2024

In 2004, 896 000 patients in Latin America died as a result of cardiovascular disease.[39] The rate of cardiovascular mortality in Latin America varies across the region. In 2004, death rates from cardiovascular disease, as a proportion of total deaths from all causes, were approximately 30% in Mexico, Chile, and Venezuela; 30–35% in Brazil and Argentina; and >35% in Uruguay.[3] The rate of cardiovascular mortality for the entire Latin American region is predicted to rise from 28.4% in 2004 to 32.2% in 2030, with 1 476 000 deaths projected in 2030.[39,42] Latin American countries are undergoing some rapid environmental changes, with the rate of urbanization in Latin America and the Caribbean, where 77% of the population live in cities, being the highest in the developing world.[34] It is important to monitor the impact of these changes on cardiovascular risk factors.

AF is a major cause of severe, disabling stroke

The future rise in cardiovascular mortality in Latin America has been estimated to exceed that in developed countries. In Latin America, the death rates from cardiovascular disease, as a proportion of total deaths from all causes is predicted to increase by 13.4% from 2004 to 2030, compared with a 1.0% increase over the same time period in developed countries.[39,42]

Cardiovascular disease has an enormous impact on a country's economy. For example, it is estimated that Brazil will lose US$49 billion in national income between 2005 and 2015 because of the combined effects of heart disease, stroke, and diabetes.[43]

Many potentially preventable strokes occur because of delayed diagnosis of AF and underuse of anticlotting therapies

The most prevalent cardiovascular diseases are coronary heart disease and stroke.[44] In 2004, Brazil and Mexico had the largest populations and the highest number of deaths from stroke in the region, with 129 200 and 33 000, respectively.[3] It has been predicted that deaths from ischemic heart disease and stroke in the Latin American region will almost triple by 2024.[4]

AF, the most common type of sustained abnormal heart rhythm, is a major cause of stroke – in particular, of severe, disabling strokes, the majority of which are preventable. Thus, earlier detection and treatment of AF, and more effective prevention of AF-related stroke, would help to substantially reduce the burden of stroke. This concurs with the aims of the PAHO, which 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.[45]

When properly used, therapy that helps to prevent blood clots has been shown to reduce the risk of stroke in patients with AF by more than 60%.[46–48] However, some of the drugs that help to prevent unwanted clotting, such as vitamin K antagonists (VKAs), are underused in clinical practice, or used suboptimally. This may be for several reasons, including the complexity of managing such therapy well and a widely held belief that the bleeding risks of therapy may outweigh the benefits.[16,23,24]

Furthermore, AF is often not diagnosed until the patient suffers a first stroke. This increases the size of the problem, meaning that many potentially preventable strokes occur every year because of delayed diagnosis of AF as well as underuse of anticlotting therapy. The result is a devastating impact on the health and wellbeing of the individual and an increased economic and social burden to society.

As the age of the population and survival from conditions predisposing to

Principal recommendations

- Raise awareness of the impact of AF and AF-related stroke
- Develop coordinated strategies for early diagnosis of AF
- Improve the education of patients and caregivers regarding AF
- Encourage new approaches to the management of AF and the prevention of AF-related stroke
- Improve awareness of AF management and the benefits of stroke prevention among physicians
- Promote equality of access to services and information for patients across countries in the Latin American region
- Implement, and advocate adherence to, guidelines for AF management
- Exchange best practice between countries in Latin America
- Boost research into the causes, prevention, and management of AF, and address paucity of information around epidemiology

AF increase, so do the prevalence and incidence of AF.[49] Therefore, a clear policy on stroke prevention in patients with AF will give greater prominence to the management of AF over the coming decades.

Initiatives for the prevention of stroke and cardiovascular disorders in Latin America should include action at country level, which will involve national government initiatives for:

- Adequate diagnosis of AF prior to the first stroke
- Appropriate and effective management of AF
- Effective stroke prevention in patients who have already developed AF
- Continuing research into the causes of AF

Such actions would be in line with one of the aims of the PAHO: that is, to prevent and reduce the burden of chronic diseases and related risk factors in the Americas.[36]

Principal recommendations

1. Create and raise awareness among national governments and the general public of the impact of AF and AF-related stroke

Once an individual has AF, their risk of a stroke is increased fivefold or more compared with the risk in individuals without the condition.[11,12] There is a lack of information regarding the incidence, prevalence, and economic impact of AF in many Latin American countries. It has been estimated that in Brazil in 2005 there were 275 000 cases of AF in people aged 70–80 years and 200 000 cases in people aged >80 years.[50] Overall, it has been estimated that 1.5 million people in Brazil and 230 000 in Venezuela suffer from AF.[20,21] Results from a study in Brazil have shown the prevalence of AF to increase with age, from around 0.8% in those aged 65–69 years to 7% in those aged ≥80 years.[51] Aggregate national healthcare expenditures of initial hospitalization for stroke in Brazil and Argentina have been calculated at US$449.3 million and US$434.1 million, respectively.[9,10] This suggests that, across the region, the economic impact of AF and AF-related stroke is likely to be considerable.

Despite the high burden of stroke, appropriate management can substantially reduce the risk of stroke in patients with AF. There is a critical need across Latin America for increased awareness among national governments and the general population of the economic and social impact of AF-related stroke, for better understanding of AF and its diagnosis/detection, and for

We call on Latin American governments to drive policy initiatives to improve early detection and management of AF, and to prevent stroke in patients with AF

improved strategies for AF management. We call on national governments to drive policy initiatives to promote understanding, earlier detection, and improved management of AF and better stroke prevention.

We advocate a campaign of routine pulse-taking across Latin America, to promote better early detection of AF

2. Develop coordinated strategies for early and adequate diagnosis of AF

AF is often detected only after a stroke, because many patients are unaware of their heart condition. However, a simple procedure such as routine pulse-taking (which is not always carried out as a matter of routine) followed by electro-cardiographic monitoring, if necessary, can play a crucial role in helping to improve detection of AF in patients at risk. This may also be performed during follow-up visits when no arrhythmias were detected during the first visit. Increased awareness of its early signs, and those of other conditions that are commonly observed in patients with AF, can improve AF diagnosis in patients without symptoms. Opportunistic assessment for AF in the primary care setting may also be prudent, particularly among patients with other risk factors for stroke. Among the factors that place a patient with AF at highest risk of stroke are: congestive heart failure, high blood pressure, age over 75 years, diabetes, and previous stroke or transient ischemic attack (TIA). Campaigns that raise awareness of the relevance of an irregular pulse as a sign of AF, and of the importance of detecting abnormal heart rhythm, would allow timely initiation of AF therapy and may help to reduce the need for specific stroke prevention treatment.

We call on Latin American governments to drive educational initiatives to improve patient understanding of AF

3. Improve awareness in patients and caregivers about AF and its detection

Poor understanding of AF and of the drugs prescribed to prevent AF-related stroke is often a barrier to maintaining anticlotting therapy within the effective target range. There is an urgent need to provide the public with better information about the risk of AF-related stroke and the methodology for its prevention. Furthermore, pharmaceutical and technological developments – such as new anticlotting drugs and patient-operated monitoring techniques for existing drugs – may make it easier in future to provide appropriate treatment to protect patients with AF against stroke. Better patient education is needed to make such innovations widely known. We call on national governments to fund, drive, and encourage participation in such educational initiatives to raise awareness of AF, because this could play a significant role in improving adherence to therapy.

Furthermore, collaboration between existing and newly established patient organizations in the Latin American region, together with the creation of a common platform for patients with AF (to exchange and disseminate information on AF, its diagnosis and management, and on stroke prevention), would enable the pooling and comparison of data between different Latin American countries. Driven by national governments, such an initiative would make it possible to identify best practice for the successful management of AF, leading to benchmarks for management that would stimulate improvements across the region.

We call on Latin American governments to establish a common platform to identify best practice for the management of AF

4. Encourage the development and use of new approaches to the management of AF and the prevention of AF-related stroke

Ideally, minimizing risk factors such as high blood pressure, structural heart disease, and diabetes will reduce the likelihood of AF developing in the first place. However, some factors that contribute to the emergence of AF, such as genetics and the natural aging process, are not modifiable, so it will not be possible to eliminate AF entirely.[52]

Thus, other important areas of focus are early diagnosis of AF – prior to the first stroke – and management of the signs and symptoms of AF. Effective

use of anticlotting therapy is essential in most patients who have already developed AF, in order to prevent complications (such as stroke) resulting from a circulating blood clot.

The ideal anticlotting drug would be effective; have a favorable safety profile in a wide range of patients, including the elderly; have a low risk of interactions with food and other drugs; and have a simple dosing regimen, with no need for routine monitoring or dose adjustment. Such an agent could eventually increase adherence to therapy and, potentially, improve outcomes in patients with AF.

5. Improve the awareness of physicians involved in AF management

Physicians may be so concerned about the bleeding risks associated with anti-clotting therapy that they underestimate its benefits in reducing stroke risk.[53–55] Improving awareness of the substantially increased risk of stroke in patients with AF compared with those without AF is therefore important. Physician education is needed to help in the recognition of undiagnosed ('silent') AF before complications occur. Physicians should also understand fully the management options for patients with AF and recognize that, when implemented properly according to guidelines, the benefits of therapy generally outweigh the risks.

6. Promote equity of access to therapy, monitoring services, and information for all patients across Latin America

All patients have a basic right to equal access to quality medical treatment for all their health needs, regardless of where they live, their status, or their income. Efforts should be consolidated to ensure that all patients have equal and timely access to diagnostic procedures that identify AF, to adequate therapy to manage the arrhythmia and its underlying clinical conditions, to anticlotting therapy for the prevention of stroke, and to better information on AF and its consequences. Resources are needed, throughout Latin American countries, to ensure clear and relevant communication with patients so that they are partners in determining their care.

We call for a coordinated Latin American effort to initiate appropriate physician education and awareness strategies, supported by adequate resources

7. Implement and strongly advocate adherence to guidelines for the management of patients with AF

Several sets of guidelines exist for the management of AF. Their recommendations largely overlap, but the degree to which they are properly implemented varies. This can be demonstrated when the use of anti-clotting therapy is analyzed in large cohorts of AF patients. In Brazil, the proportion of patients with AF at risk of stroke and who received oral anticoagulation has been shown to range from 24% to 61.7%.[56,57] Furthermore, in a study in Mexico, only 35.9% of patients with a history of AF and a recurrent TIA/ischemic stroke, and 24% of patients with a history of AF and a first-ever TIA/ischemic stroke were receiving oral anticoagulation therapy (VKAs).[58] Moreover, the proportion of patients receiving guideline-adherent anticlotting therapy varies. In a Brazilian study, the proportion of patients with AF receiving warfarin within the optimal international normalized ratio (INR) range of 2.0–3.0 was as low as 15.6%,[59] and in another study only 55% of patients with AF were receiving warfarin at the correctly indicated dose according to Brazilian Society of Cardiology and American College of Cardiology, the American Heart Association and the European Society of Cardiology guidelines (ACC/AHA/ESC).[56] It has been shown that non-adherence to guidelines is associated with poor outcomes.[60] There is therefore a need across much of Latin America to improve the implementation of, and adherence to, guidelines for the prevention of stroke in patients with AF. Initiatives aimed at improving the implementation of existing guidelines for stroke into clinical practice have been carried out by the American Heart/Stroke Associations.[61]

We call on Latin American governments to promote equal access to all diagnostic, treatment, and monitoring services for AF, supported by clear information

We call on Latin American governments to support initiatives to raise awareness of existing relevant guidelines for the management of AF

Mechanisms to implement a similar program for guidelines in AF for Latin American countries should be explored.

All governments in Latin America can encourage guideline adherence by calling for better implementation of the existing guidelines such as the 2006 ACC/AHA/ESC guidelines,[31] the 2010 ESC guidelines,[62] and the 2011 ACC Foundation (ACCF)/AHA/Heart Rhythm Society (HRS) guidelines.[63] Alongside these guidelines, country-specific ones are available, such as the Brazilian, Mexican, and Argentinian guidelines.[20,64,65] We call on national governments in Latin America to raise awareness of the existing guidelines – improved implementation and adherence to these will help to increase the number of eligible patients in the region who receive adequate anticlotting therapy and ensure that such therapy is optimally delivered. This in turn would help to reduce the number of new cases of AF-related stroke. Improved guideline implementation and adherence, and the timely updating of guidelines as appropriate, would also enhance patient safety.

We advocate a Latin American initiative to develop a unified regional set of guidelines for the management of AF, and to share and promote best practice among all countries in the region

8. Facilitate exchange of best practice between Latin American countries

A Latin American initiative to harmonize existing national guidelines into one set of unified Latin American guidelines would help to further the goal of stroke prevention. As a second stage, coordination would be needed between the professional bodies overseeing the guidelines. An approach such as this would help directly in the sharing of best practice and the development of a focused policy on stroke prevention in patients with AF extending to all countries in the region. It would also ensure that the principle of healthcare equality across Latin American countries is implemented and individual patients receive similar care. It would also be beneficial if better alignment between countries in the region occurred to identify key areas where the guidance is being overlooked or where agreement is required on divergent advice.

We call on Latin American governments to support a coordinated research initiative to increase understanding of AF and improve the prevention of AF-related stroke

9. Boost research into the epidemiology, prevention, and management of AF

The ideal would be to prevent AF-related strokes by preventing AF itself. To achieve this requires an increased understanding of the causes of AF, and the development of strategies for its prevention and treatment through research.

Latin American countries could provide funding to boost research into these areas via a coordinated research strategy. Research topics that Latin American countries could stimulate and help to coordinate include:

- Systematic analysis of the epidemiology of AF (that is, the factors that determine the frequency and distribution of AF, including 'silent' AF) and its relationship to stroke
- Assessment of the burden and severity of disease for all patients with stroke, based on patient experience in the region and quality-adjusted life-years (QALYs)
- Research to identify patients at risk of AF and AF-related stroke, and new therapeutic approaches to the management of AF
- Latin American studies monitoring the effect of interventions to manage AF and prevent AF-related stroke

The PAHO already acknowledges the importance of stimulating cardiovascular disease research activities at the regional level, for example through the development and use of the Pan American STEPS and STEPS Stroke instruments.[38,45] To augment and complement these efforts, a coordinated research initiative encompassing all the Latin American countries is urgently needed, aimed at improving the management of AF, at understanding more fully its causes and epidemiology, and at preventing AF-related stroke.

Stroke: a significant cause of poor health and death

Key points

- Worldwide, 15 million people suffer a stroke each year. Of these, more than 5 million die and another 5 million are left permanently disabled
- In 2004, there were approximately 1.9 million people in Latin America who had survived an episode of stroke at some time in their life
- In 2004, 437 000 people in Latin America suffered a first-ever stroke, and the number of strokes per year is predicted to rise dramatically as the population ages
- Stroke has a huge impact on the health and wellbeing of an individual and is an economic and social burden to society
- Aggregate national healthcare expenditures of initial hospitalization for stroke in Brazil and Argentina were calculated to be US$449.3 million and US$434.1 million, respectively

What is stroke?

A stroke occurs when interruption of blood supply or leakage of blood from a blood vessel causes damage to the brain. There are two main types of stroke: hemorrhagic and ischemic. A hemorrhagic stroke is caused by bleeding from a blood vessel in the brain. Ischemic strokes are more common, accounting for approximately 85% of all strokes,[5] and are caused by a blood clot in the brain. This blood clot may have developed in the brain, or it may have formed somewhere else in the body and traveled to the brain (in this case, the blood clot is said to have 'embolized'). For example, an ischemic stroke caused by a blood clot that formed in the heart is known as a cardioembolic stroke.

A TIA occurs when the blood supply to the brain is briefly interrupted. The symptoms of a TIA are very similar to those of a full stroke but last less than 24 hours. Individuals who have had a TIA are at increased risk of stroke compared with the general population – particularly within the first 24 hours, when the risk is around 4–5%.[66,67] Studies have shown that in the 90 days after a TIA, the risk of stroke exceeds 10%.[66]

85% of all strokes are ischemic – caused by a blood clot in the brain

Prevalence and incidence of stroke in Latin America

Every year, 15 million people worldwide experience a stroke. Approximately 5 million of these suffer permanent disabilities and over 5 million more die.[68] In 2004, stroke accounted for 9.7% of all deaths worldwide.[2]

In 2004, the WHO estimated that the prevalence (i.e. total number of cases) of patients surviving a stroke in Latin America was 1.9 million.[8]

In 2004, 1.9 million people in Latin America survived a stroke, and about 437 000 had a first-ever stroke

In the same year, the incidence (i.e. number of new cases) of first-ever stroke was 437 000 in Latin America.[8]

There are no data from the WHO for the incidence and prevalence of stroke by country in 2004; however, individual studies have assessed the prevalence and incidence of stroke in Latin

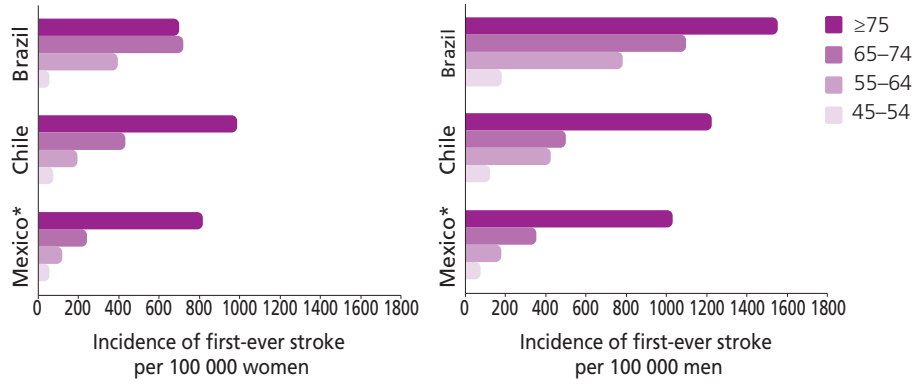
American populations. Stroke prevalence studies have been carried out in both rural and urban settings (Table 1). Crude prevalence rates ranged from 1.7 per 1000 in rural Bolivia to 7.7 per 1000 in Mexico. In people older than 60 years, the range increased from 18.2 per 1000 in Mexico to 46.7 per 1000 in Columbia.[69]

The incidence of stroke in individual countries of Latin America has also been estimated (Figure 1).[70–72] The number of men and women experiencing stroke increases substantially with age. For example, in Chile the incidence of stroke in men aged ≥75 years is 10 times that in men aged 45–54 years; in women aged ≥75 years, it is nearly 13 times that in women aged 45–54 years.[71] Furthermore, these data show that stroke incidence is higher in men than in women irrespective of age.[70–72]

Table 1. Door-to-door prevalence studies of stroke in Latin America. Adapted from Cantú-Brito *et al*. 2011 with permission.[69]

Study	Population screened	Number of strokes	Stroke prevalence per 1000	Stroke prevalence in the elderly (>60 years) per 1000
Peru, 1995 (Cuzco)	3246 older than 15 years from an urban population of 210 000	21	6.2	NR
Colombia, 1997 (Sabaneta)	13 588 people (all ages) from an urban population of 17 670	76	5.6	46.7
Bolivia, 2000 (Cordillera)	9995 people (all ages) from a rural population of 55 675	16	1.7	19.3
Honduras, 2003 (Tegucigalpa)	1553 people (all ages) from an urban population of 1 180 676	9	5.7	NR
Ecuador, 2004 (Atahualpa)	1568 people older than 15 years from a rural population of 1671	10	6.4	36.1
Honduras, 2007 (Salama)	5608 people (all ages) from a rural population of 6289	20	3.6	32.7
Mexico, 2010 (Durango)	2437 older than 35 years from an urban and rural population of 168 859	20	7.7	18.2

Figure 1. Estimates of stroke incidence (a) per 100 000 women and (b) per 100 000 men at selected ages in studies from Brazil, Chile, and Mexico. The number of individuals experiencing stroke increases substantially with age. Data taken from Cantú-Brito *et al*. 2010,[70] Lavados *et al.* 2005,[71] and Minelli *et al*. 2007.[72]



*For Mexico, annual first-ever stroke hospitalization rate data are presented.

The world population is aging rapidly and as a result it has been predicted that stroke incidence will increase in the future.[2] In Brazil, the proportion of people aged 60 years and over is expected to rise from 7.8% in 2000 to 23.6% in 2050.[73] An increase in the proportion of older people (≥60 years) globally is being accompanied by a decline in the proportion of the young (<15 years).[74] It is expected that by 2050, the number of older people in the world will exceed the number of young for the first time in history.[74] The expected rise in the aging population of Latin America will further increase the incidence and socioeconomic burden of stroke and limit the medical resources available to provide for the needs of stroke suffers and their families.

Although strokes in young adults are relatively uncommon, approximately 25% of strokes occur in people aged below 65 years,[75] and a national survey of stroke in the US estimated that 3.7% of strokes occurred in patients aged 15–45 years.[76] Availability of data on the prevalence of stroke from a greater number of countries would help to inform the best policy for stroke prevention across all Latin American countries.

Some ethnic differences in stroke epidemiology may exist, reflecting differences in the predisposition to some of the risk factors associated with stroke. A comparison of analogous studies suggests that the prevalence of intracerebral hemorrhage is consistently higher in Latin American compared with white populations, but is similar to that among Asians.[77] The results of the BASIC (The Brain Attack Surveillance in Corpus Christi) study clearly demonstrated an increased stroke incidence amongst Mexican Americans compared with non-Hispanic Whites in a representative South East Texas community where approximately half of the population is Mexican American. The crude cumulative incidence of total completed cerebrovascular events was 168 per 10 000 in Mexican Americans and 136 per 10 000 in non-Hispanic Whites. Specifically, Mexican Americans had a higher cumulative incidence of first-ever and recurrent ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage (bleeding between the surface of the brain and the skull) compared with non-Hispanic Whites.[78] This increased risk of stroke in Mexican Americans has also recently been shown to extend to patients with atrial fibrillation (AF). In a follow-up to the BASIC study, patients with ischemic stroke or TIA, and who were found to have either a chart history of AF or a history of AF noted on the admission electrocardiogram (ECG) were assessed. In total, 236 patients (88 Mexican Americans and 148 non-Hispanic Whites) with ischemic stroke/TIA and AF were included in the study. The risk of stroke recurrence was significantly higher in Mexican Americans compared with non-Hispanic Whites. The severity of the recurrent stroke was also significantly higher in Mexican Americans than non-Hispanic Whites, although there was no difference in survival after stroke in the two populations.[79]

Death and poor health in patients with stroke

Stroke accounts for nearly 10% of all deaths worldwide.[2,5] Although stroke is generally considered a healthcare issue for elderly people, its impact on younger individuals should not be underestimated. In 2004, the death rate from stroke in people under 60 years was calculated as 11.3 per 100 000 for Latin America.[39] This figure rises substantially in individuals aged 60 years or over: the death rate from stroke in Latin America in patients aged 60–79 years was 301.3 per 100 000.[39]

Stroke death rates vary between countries of the Latin American region. For example, in 2004, stroke death rates ranged from 31.6 per 100 000 in

Venezuela to 115.3 per 100 000 in Uruguay.[3] Population-based studies have also shown 30-day case death rates for stroke to vary in countries in Latin America; rates were reported as 19.1% in Brazil,[80] 23.3% in Chile,[71] and 39% in Mexico.[70] Case death rates also varied according to stroke type – exceeding 50% for subarachnoid hemorrhage in Mexico (Figure 2).

Each year, 5 million stroke sufferers worldwide are left permanently disabled

Additionally, stroke is a major cause of long-term disability worldwide; each year, 5 million stroke sufferers are left permanently disabled.[5] The young are not exempt from the devastating effects of stroke. A long-term study assessing outcomes after stroke in young adults aged 15–45 years found that after 6 years only 49% were still alive, not disabled, had not suffered from recurrent vascular events, and had not undergone major vascular surgery; a majority of survivors reported emotional, social, or physical effects that lessened their quality of life.[81]

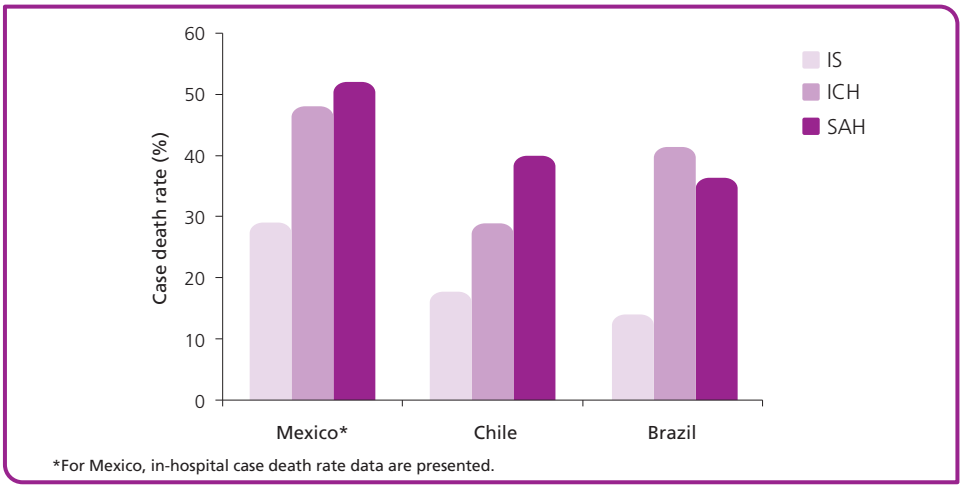
Stroke can affect virtually all human functions, making it difficult for many patients to get out of bed, walk short distances, and perform basic activities of daily living. As well as impairing speech and physical functioning,[5] stroke can also adversely affect mental health.[82]

Because its onset is sudden, affected individuals and their families are often poorly prepared to deal with the consequences of stroke.[82] The development of chronic disability can severely affect quality of life of both the patient and their relatives, who are often the caregivers.[6,7] It is also important to consider the role of caregivers and the subsequent impact stroke can have on them and their families' lives. In addition, the impact of stroke on society, in terms of morbidity (ill health) and health burden, is substantial.

Financial cost of stroke in Latin America

Although data are not available on the financial cost of stroke for the whole of Latin America, information is available from individual countries. In two separate studies, aggregate national healthcare expenditures of initial hospitalization for stroke in Brazil and Argentina were calculated to be US$449.3 million and US$434.1 million, respectively.[9,10] Aggregate national healthcare expenditures were found to be higher for ischemic stroke than for intracerebral hemorrhage (Brazil, US$326.9 million vs US$122.4 million; Argentina, US$239.9 million vs US$194.2 million). However, the mean

Figure 2. 30-day case death rate by stroke type of first-ever stroke in Latin America (IS, ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage). Data taken from Cabral *et al.* 2009,[80] Cantú-Brito *et al.* 2010,[70] and Lavados *et al.* 2005.[71]



*For Mexico, in-hospital case death rate data are presented.

total costs of initial hospitalization were higher for intracerebral hemorrhage than for ischemic stroke (Brazil, US$4101 vs US$1902; Argentina, US$12 285 vs US$3888).[9,10] The mean length of hospital stay for ischemic stroke was similar in the two studies (Brazil, 13.3 days vs Argentina, 13.0 days).[9,10] In contrast, mean length of hospital stay for intracranial hemorrhage was 12.0 days in Brazil and 35.4 days in Argentina.[9,10] In a study from Chile, 530 patients who had suffered a stroke (ischemic stroke, 84% of the population) and who were admitted to a general hospital or stroke unit, were evaluated.[83] The mean costs of hospitalization per patient at the stroke unit and hospital were US$5550 (mean length of stay, 6.6 days) and US$4815 (mean length of stay, 9.9 days), respectively.[83] The estimated cost of acute stroke care in Mexico in 1994 was US$7700 per patient in private hospitals and US$6600 in health sector institutions.[84]

It is therefore evident that stroke is a costly health problem in Latin American countries, although further research is required to provide a more comprehensive picture of the burden of the cost of stroke across a wider selection of countries. Stroke places a burden on patients; their caregivers, families, and friends; and society. This burden falls disproportionately on the elderly, as they are most at risk. Early diagnosis and effective management of AF would help to reduce the burden of stroke in Latin America. Furthermore, the prevention of stroke with pharmacologic or non-pharmacologic therapies in patients at high risk has the potential to reduce this economic burden significantly.[85] The cost-effectiveness of anticlotting treatments in patients with AF is discussed further in the section 'Cost of vitamin K antagonist therapy in stroke prevention in atrial fibrillation' (page 45).

Stroke places a burden on patients; their families, caregivers, and friends; and society

Case study: the impact of stroke

José Luis was a 62-year-old man who lived in Mexico City and had 8 children and 16 grandchildren. Previously, he worked for himself selling electrical domestic appliances. For the past 20 years, José Luis has been living with diabetes mellitus and hypertension, and 5 years ago he was diagnosed with non-valvular AF. Although he was advised to take oral anticoagulation therapy (warfarin), he found it difficult to adhere with the medication. This was mainly due to the monitoring that was required to adequately control his anticoagulation levels. In June 2010, José Luis suffered a sudden large ischemic stroke that left him with weakness down the left-hand side of his body, an inability to speak, and severe communication problems. As a result of the stroke, José Luis is now confined to a wheelchair. He is completely dependent on his family to take care of his needs, fulfilled principally by his wife who is almost always at his side. As José Luis has no social security, he has to pay for his own medication, diapers, any laboratory tests required, doctors, and any treatment for any other medical complications that arise. One of his sons now runs the electrical domestic appliances business solely to pay for his father's needs. The majority of the family's income is being used for José Luis's medical care. Unfortunately, José Luis recently suffered several generalized convulsive seizures that required hospitalization. This has complicated his medical management because he currently receives antiepileptic drugs that interact with the warfarin that José Luis takes to prevent stroke recurrence.

Atrial fibrillation: a major risk factor for stroke

Key points

- AF is the most common sustained heart rhythm abnormality
- AF increases the risk of stroke fivefold and is responsible for approximately 15–20% of all strokes
- The number of people affected by AF in Latin America is currently unknown
- The five major modifiable risk factors for stroke are high blood pressure, smoking, lack of physical exercise, diabetes, and AF
- Common underlying causes of AF include high blood pressure, heart valve defects, rheumatic heart disease, ischemic heart disease, and diabetes
- The likelihood of developing AF increases with advancing age
- Data from the US show that people over the age of 40 years have a 1 in 4 risk of developing AF over their remaining lifetime. Similar data for Latin American populations are unavailable
- The present and future impact of AF on Latin American populations is currently unknown; further studies are urgently needed in order to provide these data

AF has been shown to be responsible for approximately 15–20% of stroke occurrences

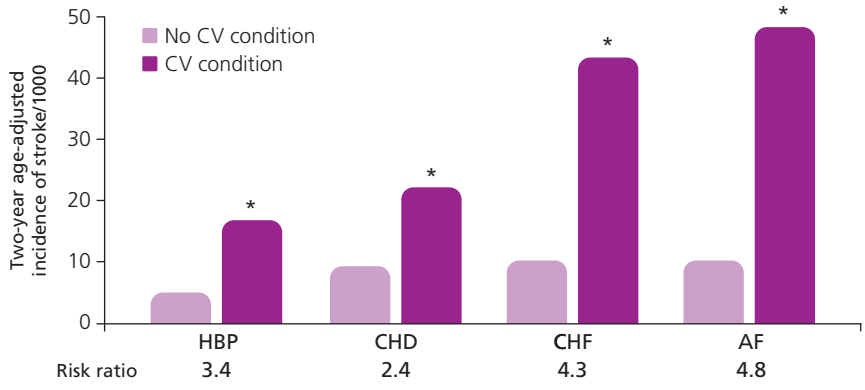
AF is the most common sustained heart rhythm abnormality,[86] and is a major risk factor for ischemic stroke and death in the general population.[13,86] Other established risk factors for stroke include high blood pressure, diabetes, heart disease, and lifestyle factors such as smoking, alcohol consumption, poor diet, and insufficient physical activity.[87] The five major modifiable risk factors – the 'big five' – that merit targeting in the prevention of stroke have been identified as:[88]

- High blood pressure
- Smoking
- Lack of physical exercise
- Diabetes
- AF

The risk of stroke is higher in an individual with AF than in someone with high blood pressure

Owing to its high prevalence, high blood pressure is the leading modifiable risk factor for stroke,[68] accounting for approximately 40% of all strokes.[5,68,89] AF, by comparison, is estimated to be responsible for approximately 15–20% of all strokes,[90] and patients with AF have a 3–4% risk per year of developing stroke.[91] High blood pressure is therefore responsible for a greater proportion of the global burden of stroke than AF, but the risk of having a stroke is higher in an individual with AF, whatever the type (lone, paroxysmal, persistent, or permanent) than in an individual with high blood pressure: AF confers a fivefold increase in the risk of stroke, compared with an approximately threefold increase in risk with high blood pressure (Figure 3).[11,12] Moreover, many patients with AF also have high blood pressure, so a multidisciplinary approach to management is required (see section on 'Management of other conditions that increase stroke risk: a multidisciplinary approach', page 46). In a study of 215 patients with ischemic stroke admitted to a hospital in São Paulo, Brazil, a diagnosis of AF was made in

Figure 3. Two-year age-adjusted incidence of stroke in the presence and absence of cardiovascular (CV) conditions. Atrial fibrillation confers a fivefold increase in the risk of stroke; in patients with high blood pressure, stroke risk is increased threefold. *p<0.001. Adapted from Wolf *et al*. 1991 with permission.[12]



AF, atrial fibrillation; CHD, coronary heart disease; CHF, congestive heart failure; HBP, high blood pressure.

16.3% of patients. The prevalence of AF was significantly higher in those patients over the age of 80 years (26%).[92]

Development of atrial fibrillation: causes and contributing factors

AF occurs when the upper chambers of the heart (known as the atria) tremble irregularly rather than beating regularly and effectively. The junction of the upper and lower chambers of the heart receives more electrical impulses than it can conduct, resulting in irregular squeezing of the lower chambers (known as the ventricles) and an erratic pulse rate. Because the atria do not empty completely when in fibrillation, blood does not flow properly. This means that blood clots can develop, break up, travel to vessels in the brain, and cause an ischemic stroke.[93]

Among the most common underlying causes of AF are high blood pressure, mitral stenosis (narrowing of a valve in the heart), rheumatic heart disease, and, to a lesser extent, ischemic heart disease (reduced blood supply to the heart muscle) and diabetes.[17,94] The term 'non-valvular AF' is used to describe cases where rhythm disturbance is not associated with a problem with the mitral valve in the heart;[31] the majority of studies discussed in the following sections involve patients with non-valvular, rather than valvular, AF. In a study of 840 patients with chronic AF in Argentina, underlying heart disease was detected in 84.7% of patients. Furthermore, 30.2% of patients had a previous history of heart failure, 59.0% had arterial hypertension, and 12.3% had diabetes.[95]

High blood pressure and diabetes are among the common causes of AF

The likelihood of developing AF increases with advancing age. In the previously described study involving 840 patients with AF from Argentina, the average patient age was 71 years.[95] However, some patients seem to have genetic abnormalities that predispose to AF, and these abnormalities are most often seen in young patients who develop AF.[52,96] In addition, there are limited data suggesting that the incidence of AF is higher than normal in athletes.[97,98] Furthermore, an increased frequency of vigorous exercise (i.e. above-average levels of 5–7 days per week) has been associated with an increased risk of developing AF in joggers and men aged below 50 years.[97] Therefore, AF is not just a condition of the elderly.

Signs and symptoms of atrial fibrillation

There is an average delay of 2.6 years between the onset of symptoms and the diagnosis of AF

A simple and easily identifiable sign of AF is an irregular pulse, and the symptoms may include palpitations, chest pain or discomfort, shortness of breath, dizziness, and fainting.[99] However, many people with AF have no symptoms, or vague, non-specific symptoms.[31] Physicians may encounter AF when patients consult them about other conditions, related or unrelated to the heart. Often, AF is not apparent until a person presents to their doctor with a complication such as ischemic stroke, a blood clot in the leg, or heart failure. In AF-related emergency admissions to hospital, AF most often presents as difficulty with breathing, chest pain, and palpitations.[100] Patients who do experience symptoms of AF are not always diagnosed immediately. In a recent international survey, there was an average delay of 2.6 years between the onset of symptoms and the diagnosis of AF.[101] This indicates that many patients with AF are not being managed effectively and are at risk of serious long-term consequences, such as stroke.

Guidelines often give useful advice for the assessment of conditions as well as their management. Guidelines covering the pharmacologic management of AF are available in Brazil, Argentina, and Mexico.[20,64,65] The Brazilian Society of Cardiology has recently published updated guidelines on the management of AF. In a patient with proven AF, an initial examination would include an assessment of the pattern of occurrence of the arrhythmia, the tolerability of the episodes, a determination of the cause, and evaluation of any associated factors. An ECG would be required to confirm the diagnosis of AF.[20] In guidelines produced by the Argentine Society of Cardiology, a clinical evaluation for AF should include in all cases: (1) a clinical history, (2) a physical examination, and (3) complementary tests (ECG, chest X-ray, Holter monitoring, echocardiography, and laboratory analysis).[65] The Mexican Ministry of Health recommends that an ECG, chest X-ray and laboratory tests are performed in adults with a clinical suspicion of AF. An echocardiogram should then be carried out when a final diagnosis of AF is made.[64] Management of AF is discussed in more detail in the chapter 'Stroke prevention in patients with atrial fibrillation', page 39.

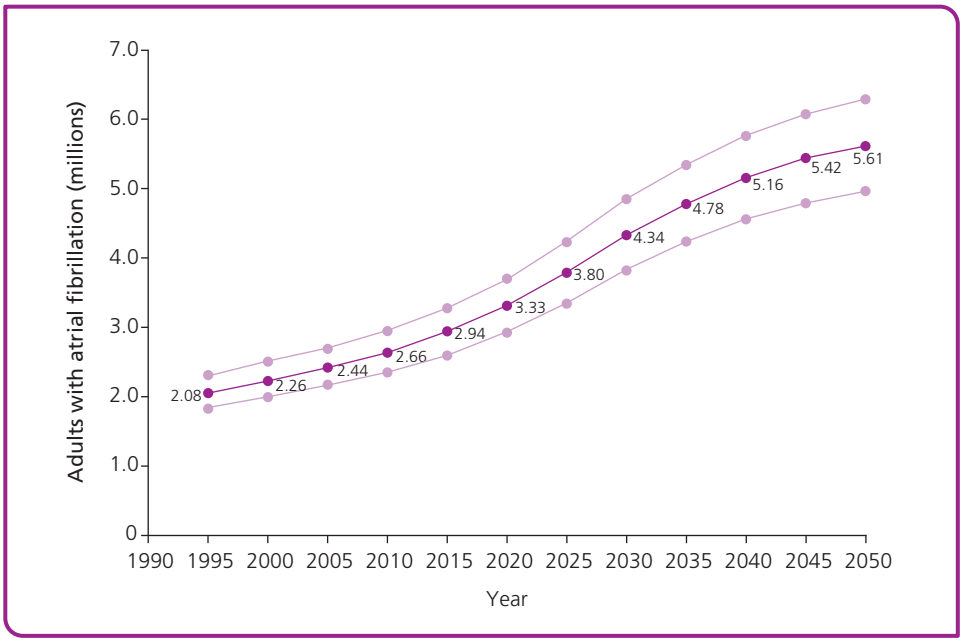
It should be noted that AF may occur in isolation, or in association with other disturbances of normal heart rhythm, most commonly atrial flutter. Atrial flutter can precede or co-exist with AF, but there are differences in the mechanisms of the two rhythm disturbances.[31] Atrial flutter will not be discussed further in this report.

Prevalence and incidence of atrial fibrillation

The prevalence and incidence of AF in many Latin American countries is currently unknown

Although data regarding the prevalence of AF in Latin America are scarce, it has been estimated that a large number of people in the region suffer from the condition. In Brazil, it has been estimated that there are around 1.5 million patients living with AF.[20] In a population-based study that assessed electrocardiographic findings in 1524 participants aged ≥65 years in São Paulo, Brazil, the age-adjusted prevalence of AF was 2.4%.[51] Using data extrapolated from the US, it was estimated that 230 000 people in Venezuela suffer from AF, with this figure predicted to rise to 1 million cases by 2050.[21] The actual incidence of AF in Latin American countries is currently unknown; however, it has been estimated that there were 275 000 cases of AF in people aged 70–80 years in Brazil in 2005, and 200 000 in people aged >80 years.[50] Further research is urgently needed in order to assess the prevalence and incidence of AF in many Latin American countries.

Figure 4. The number of people with atrial fibrillation is expected to continue to rise: projected number of adults with the condition in the US between 1995 and 2050. Upper, middle, and lower curves represent upper, middle, and lower boundaries of estimate. Adapted from Go *et al.* 2001 with permission from the American Medical Association.[102]



Increase over time

The prevalence of AF worldwide appears to be increasing over time. In one cross-sectional study of almost 18000 adults with AF diagnosed between July 1996 and December 1997 in California, US, it was estimated that approximately 2.1 million people in the US had AF.[102] By 2001, this number was thought to have risen to 2.3 million, and it is projected to increase approximately 2.5-fold – to more than 5.6 million – by 2050 (Figure 4).[102] The prevalence and incidence of AF are thought to be rising because population age is increasing and survival from conditions predisposing to AF (such as heart attack) is improving.[49]

Increase with age

The prevalence of AF has also been shown to increase with advancing age. In the previously described population-based study from São Paulo, Brazil, the prevalence of AF increased from around 0.8% at the age of 65–69 years to 7% in those aged ≥80 years.[51] At present, information regarding the incidence of AF for Latin American countries is scarce; however, data from European studies are indicative of the increased incidence of AF with advancing age. In a population-based cohort study in Rotterdam, the incidence of AF was investigated during a mean follow-up period of almost 7 years in 6432 individuals. This revealed an incidence of 1.1 per 1000 person-years in those aged 55–59 years, rising to 20.7 per 1000 person-years in those aged 80–84 years.[103] The incidence was higher in men than in women.

The prevalence and incidence of AF are rising as population age increases

Lifetime risk of atrial fibrillation

The Framingham Heart Study, a large, long-term US-based study initiated in the early 1950s, investigated the lifetime risk of AF in individuals who were free of the condition at first examination. The study sample involved 3999 men and 4726 women who were followed from 1968 to 1999.[104] For men and women aged 40 years and older, the remaining lifetime risk of AF developing was found to be 1 in 4. Unfortunately, similar data are not yet available for Latin American populations.

People aged 40 years and older have a 1 in 4 remaining lifetime risk of developing AF

The remaining lifetime risk of AF developing underscores the important public health burden posed by this condition – particularly when compared with the lifetime risk of other major conditions and morbidities. For example, in the US Framingham Study the remaining lifetime risk of dementia in middle-aged individuals was approximately 1 in 6;[105] for breast cancer, the remaining lifetime risk was 1 in 8 for women aged 40 years.[104]

This chapter has set the scene for understanding some of the causes of AF, its signs and symptoms, and who is most at risk of developing the condition. It also highlights the magnitude of the growing problem of AF and the risk it poses to public health. Research is needed in the individual Latin American countries to gain a better understanding of the patterns of incidence and prevalence of AF throughout the region. The following chapters will discuss AF as a risk factor for stroke.

Detecting atrial fibrillation and stratifying stroke risk

Key points

- AF is often not detected until a serious complication such as stroke or heart failure develops
- Routine pulse-taking plays an important role in the detection of AF in at-risk patients
- A history of stroke in patients with AF increases the likelihood of another stroke threefold
- Female gender, advanced age, high blood pressure, heart disease, diabetes, and vascular disease also increase the risk of stroke in patients with AF
- Patients in Latin American countries may currently be receiving inconsistent advice and therapy because of a lack of consensus on AF risk stratification

Atrial fibrillation is often present without symptoms

Although AF may be recognized by a sensation of palpitations or other presenting symptoms (see section on 'Signs and symptoms of atrial fibrillation', page 24), it is commonly without symptoms and may have been so for an unknown period.[31] Ambulatory ECG recordings (i.e. ECG recordings taken using a device that is worn during normal daily activities) and device-based monitoring have shown that an individual may experience periods of both symptomatic and asymptomatic AF.[31] Often, though, AF is not detected until an individual presents with a serious complication such as stroke or heart failure.[100]

Detection and diagnosis of atrial fibrillation

Increased detection and diagnosis of silent AF are therefore imperative for timely initiation of effective treatment, thus preventing many of the complications related to AF, including AF-related stroke. Indeed, the Brazilian, Mexican, and Argentinian guidelines all recommend that an ECG should be performed in all patients in whom AF is suspected.[20,64,65] Given that some patients with other risk factors for stroke, such as high blood pressure, diabetes, and ischemic heart disease, frequently undergo check-ups in the primary care setting, opportunistic assessment for AF during consultations may be beneficial where possible.

Increased detection and treatment of AF are needed to prevent stroke

Systematic versus opportunistic screening

A multicenter study – the Screening for AF in the Elderly (SAFE) study – was initiated in primary care in the UK. Its aim was to determine the rate of detection of new cases of AF in the population aged 65 years and over, based on a variety of screening strategies.[106] The SAFE study involved 50 primary care practices and almost 15 000 patients, identified randomly from computerized lists of patients in the target study group. Of these, 5000 were assigned to the control group (who received routine clinical care) and 10 000 to systematic or opportunistic screening for 12 months:

- All patients in the systematic screening arm were invited by letter to attend a screening clinic

- Patients in the opportunistic screening arm had their notes flagged to remind practice staff to record the patient's pulse during routine consultation. Those with an irregular pulse were given an information sheet and invited to attend a further appointment, where pulse rate and a 12-lead ECG were recorded

Screening can identify more new cases of AF than routine clinical care

Overall, both systematic and opportunistic screening identified substantially more cases of AF than routine care (mean incidence: 1.52% and 1.71% compared with 0.99%, respectively). The cost per case detected by systematic screening was £1787 (US$2936) compared with £363 (US$597) per patient identified opportunistically. Pre-screening by taking the pulse reduces the number of ECGs to be performed, thus making opportunistic screening more cost-effective than systematic screening.[106]

In Latin America's developing and rural countries, systematic screening is unlikely to take place, therefore opportunistic screening would be more suitable and cost-effective.

The SAFE study highlights the important role of a simple procedure, such as routine pulse-taking, in helping to improve detection of AF in at-risk patients. The policy implications arising from the results of this study are that an opportunistic approach using pulse-taking followed by ECG is probably the most cost-effective option for any screening program implemented through primary care.[106] Several recommendations are made for future research that could help define further the optimum patient pathway (Table 2)

Additional risk factors for stroke in patients with atrial fibrillation

Factors reported to further increase the risk of stroke in patients with AF include:[31,49,107]

- Female gender
- Advanced age
- Prior stroke or TIA
- High blood pressure
- Heart disease, for example, heart failure and valvular heart disease
- Diabetes
- Vascular disease

Although stroke and AF are both more prevalent in men than in women,[108–110] the literature shows that death rate from stroke is increased fourfold in women with AF compared with twofold in men with AF.[111] However, not all studies have demonstrated such a significant difference between the genders.[18,111]

Previous stroke or TIA increases the risk of another stroke threefold in patients with AF

A history of stroke or TIA is the strongest independent predictor of stroke in patients with AF, increasing the risk of another stroke approximately threefold.[31] Increasing age also has a marked effect on the risk of stroke. Among patients with AF, the incidence of stroke has been shown to be sevenfold higher in patients in their 80s compared with those in their 40s.[112] High blood pressure increases the risk of stroke approximately threefold in patients with AF.[12] However, it should be borne in mind that neither of these studies report data specific to particular countries within the Latin American region.

Table 2. Some of the recommendations for further research, based on the findings of the Screening for AF in the Elderly (SAFE) study.[106]

- How the implementation of a screening program for atrial fibrillation (AF) influences the uptake and maintenance of anticoagulation therapy in patients aged 65 years and over
- The role of computerized software in assisting with the diagnosis of cardiac arrhythmias
- How best to improve the performance of healthcare professionals in interpreting electrocardiograms
- Development of a robust economic model to incorporate data on new drugs to prevent the development of blood clots in patients with AF

Risk stratification schemes for patients with AF, incorporating the available evidence on these additional risk factors, have been developed and are discussed in more detail in the next section.

Approaches to risk stratification

To guide the choice of the most appropriate preventive therapy, some means of classifying the level of stroke risk is needed. Several different models have attempted to grade the risk of stroke among patients with non-valvular AF, according to the presence of coexisting conditions (e.g. previous stroke, TIA, or blood clot; impaired left ventricular function; high blood pressure; diabetes) and other factors, such as age and gender.[15] Risk stratification systems currently used are summarized in Table 3.

Among patients not receiving anticoagulation therapy, the $CHADS_2$ scheme has been found to be a more accurate stroke predictor than AFI[114] and SPAF[115] – two preexisting schemes.[14] In patients receiving therapy, three schemes have predicted stroke significantly better than chance: Framingham, $CHADS_2$, and SPAF.[116] However, several patients classified as being at moderate risk according to $CHADS_2$ were at high risk according to other schemes (Figure 5) and at low risk according to Framingham

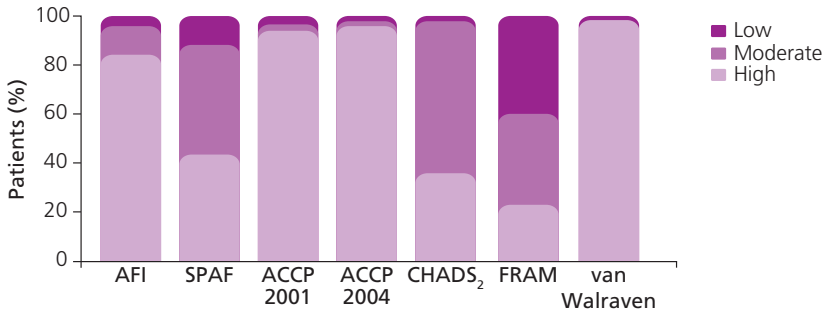
Several models have graded the likelihood of stroke according to widely accepted risk factors

Table 3. Risk stratification schemes used to predict thromboembolism in atrial fibrillation. Adapted from Lip *et al.* 2010b with permission.[113]

Reference	Stroke risk strata		
	High	**Intermediate**	**Low**
$CHADS_2$-Classical*[14]	Score 3–6	Score 1–2	Score 0
$CHADS_2$-Revised[15]	Score 2–6	Score 1	Score 0
ACC/AHA/ESC[31]	Previous stroke, TIA or thromboembolism; or ≥2 moderate risk factors (age ≥75 years, hypertension, heart failure, LVEF ≤35%; or diabetes)	Age ≥75 years; hypertension; heart failure; LVEF ≤35%; or diabetes	AF (no other risk factors)
CHA_2DS_2-VASc[15]	One 'major' risk factor (previous stroke, TIA or thromboembolism, or age ≥75 years), or ≥2 'clinically relevant non-major' risk factors (heart failure/LVEF ≤40, hypertension, diabetes, vascular disease [myocardial infarction, peripheral artery disease or aortic plaque], female gender, age 65–74 years)	One 'clinically relevant non-major' risk factor: heart failure/LVEF ≤40, hypertension, diabetes, vascular disease (myocardial infarction, peripheral artery disease or aortic plaque), female gender, age 65–74 years	No risk factors
ACCF/AHA/HRS[63]	Previous stroke, TIA or thromboembolism; or ≥2 moderate risk factors (age ≥75 years, hypertension, heart failure, LVEF ≤35%, or diabetes)	Age ≥75 years, hypertension, heart failure, LVEF ≤35%, or diabetes	AF (no risk factors)

*Secondary prevention study. $CHADS_2$ score is a sum of numerical scores assigned to five risk factors: Congestive heart failure (1 point); Hypertension (1 point); Age ≥75 years (1 point); Diabetes (1 point); and Stroke or transient ischemic attack (2 points). For definition of CHA_2DS_2-VASc see below.
ACCF, American College of Cardiology Foundation; AF, atrial fibrillation; AHA, American Heart Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

Figure 5. Percentage of patients with atrial fibrillation (enrolled in the SPORTIF III and V trials) classified as being at low, moderate, and high risk of stroke, based on the individual risk stratification schemes. The results show that different models predict stroke risk differently. Adapted from Baruch *et al.* 2007 with permission.[116]



ACCP, American College of Chest Physicians; AFI, Atrial Fibrillation Investigators; SPAF, Stroke Prevention in Atrial Fibrillation; SPORTIF, Stroke Prevention using a ORal Thrombin Inhibitor in atrial Fibrillation; FRAM, Framingham.

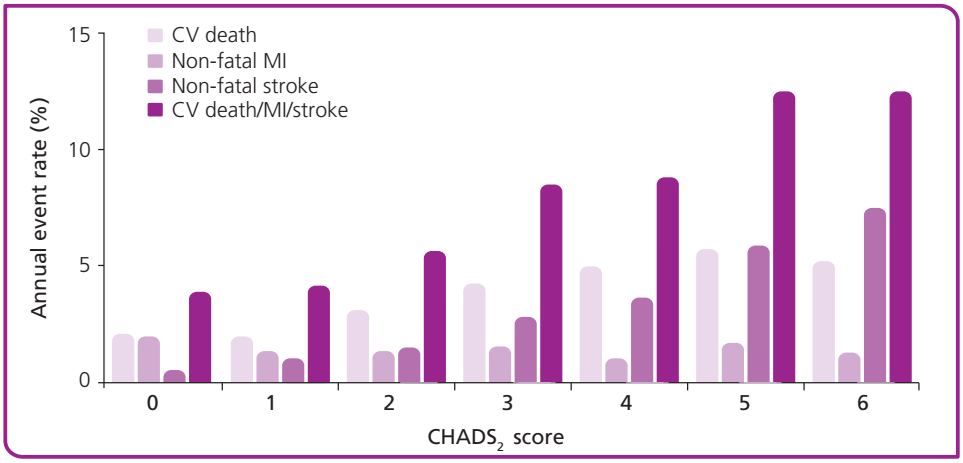
and SPAF.[116,117] Few models have addressed the cumulative nature of risk factors, whereby a combination of factors would confer a greater risk than any factor alone.[111]

In real-world clinical practice for patients who have, or are at a high risk of, atherothrombosis, and who may not have been prescribed anticoagulant therapy, $CHADS_2$ can predict not only the risk of non-fatal stroke, but also various other cardiovascular outcomes such as cardiovascular death and combined events (Figure 6).[118]

In light of the variable understanding and use of risk stratification schemes, the $CHADS_2$ scheme has been expanded and clarified.[15] The $CHADS_2$ score has been refined by including additional risk factors such as vascular disease, sex, and age 65–74 years. This risk factor-based scheme can be expressed as the acronym, CHA_2DS_2-VASc, and has been validated in an analysis from the Euro Heart Survey[15] and in several other studies.[113,119,120] CHA_2DS_2-VASc denotes:

- Congestive heart failure/left ventricular dysfunction: 1 point
- Hypertension: 1 point
- Age ≥75 years: 2 points
- Diabetes: 1 point
- Stroke, TIA or thromboembolism: 2 points
- Vascular disease: 1 point

Figure 6. Annual cardiovascular (CV) event risk in patients with atrial fibrillation with various $CHADS_2$ scores. Annual event rate of CV death, non-fatal stroke, and combined cardiovascular outcomes of CV death/non-fatal myocardial infarction (MI)/non-fatal stroke are increased for patients with higher $CHADS_2$ scoring, whereas the rate of non-fatal MI was not influenced by $CHADS_2$ scoring. Reprinted from Goto *et al.* 2008 with permission from Elsevier.[118]



- Age 65–74 years: 1 point
- Sex category female: 1 point

When tested with a point-based scoring system (0 = low risk, 1 = intermediate risk, and ≥2 = high risk), CHA_2DS_2-VASc provided some improvement in the predictive value for thromboembolism over the $CHADS_2$ score, with low event rates in the 'low-risk' group and the classification of only a small proportion of subjects into the 'intermediate-risk' group.[15]

In patients with a low-risk $CHADS_2$ score (0 or 1), or when a more comprehensive risk assessment is needed, CHA_2DS_2-VASc may be helpful and complement the use of the $CHADS_2$ score (Figure 7).[62]

Using data on risk factors for major bleeding from the Euro Heart Survey as well as those found in the literature from systematic reviews, a new simple bleeding risk score – HAS-BLED – has been derived for patients with AF:[121]

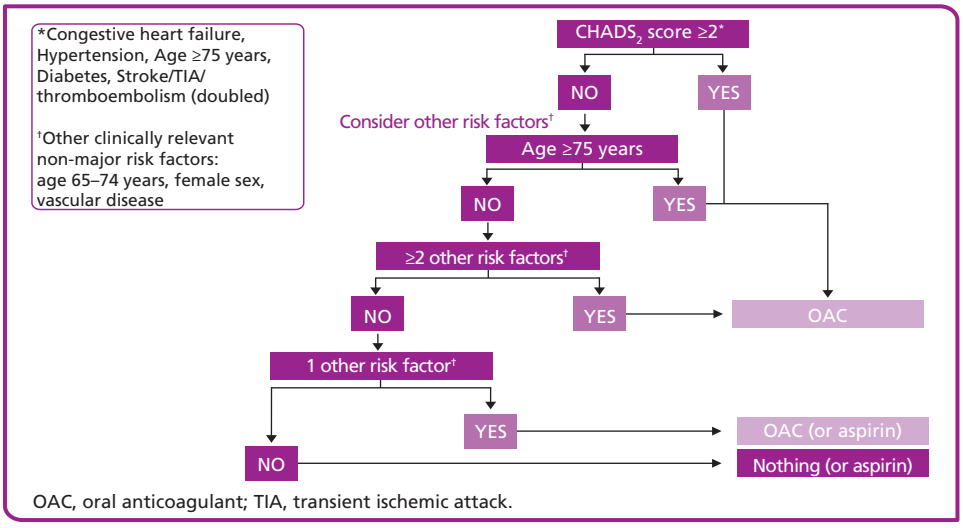
- Hypertension (uncontrolled, >160 mmHg systolic): 1 point
- Abnormal renal/liver function: 1 point each – maximum 2 points
- Stroke (previous history, particularly lacunar): 1 point
- Bleeding history or predisposition (e.g. anemia): 1 point
- Labile INR (unstable/high INRs or in therapeutic range <60% of time): 1 point
- Elderly (>65 years): 1 point
- Drugs/alcohol (concomitant use of drugs such as antiplatelet agents and non-steroidal anti-inflammatory drugs or alcohol): 1 point for drugs plus 1 point for alcohol excess – maximum 2 points

Although the HAS-BLED score still needs to be validated in at least one other large contemporary cohort of AF patients before it can be widely implemented into daily practice,[121] the recent ESC guidelines stated that it would seem reasonable to use the HAS-BLED score to assess bleeding risk in AF patients on the basis that a score of ≥3 indicates 'high risk'.[62] In addition, some caution and regular review of the patient would be needed after the initiation of anticlotting therapy.[62]

It therefore appears that different risk stratification schemes predict the risk of stroke in patients with AF differently, which means that selection of patients for therapy may depend on the scheme chosen to assess risk. As a result, patients in Latin America may receive inconsistent advice and therapy, depending on local choices.

Predictions from risk stratification models may be inconsistent, which could result in inequality of advice and therapy

Figure 7. Clinical flow chart for the use of oral anticoagulation for stroke prevention in atrial fibrillation. Adapted from Camm *et al*. 2010 with permission from Oxford University Press.[62]



OAC, oral anticoagulant; TIA, transient ischemic attack.

Features of stroke in patients with atrial fibrillation

Key points

- Strokes in people with AF are more severe and have worse outcomes than strokes in people without AF
- AF almost doubles the death rate from stroke
- AF increases the risk of remaining disabled or handicapped following stroke by almost 50%

Increased severity of stroke

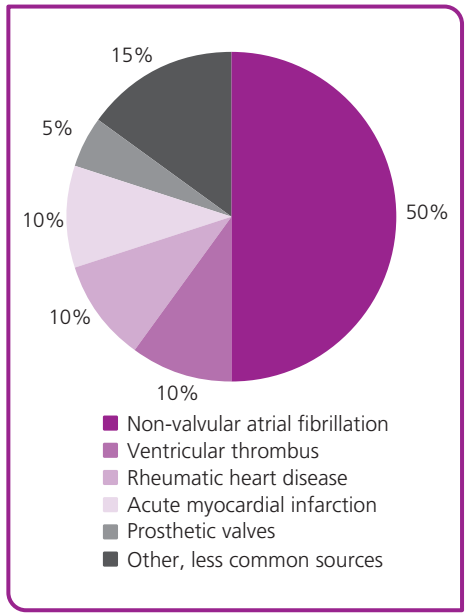
Strokes in people with AF are more severe than strokes in people without AF

In addition to a high risk of stroke, patients with AF suffer from more severe strokes and have a poorer prognosis after the event than patients without AF.[18] The increased severity of strokes in patients with AF is thought to be because such strokes are predominantly cardioembolic.[18] A cardioembolic stroke is caused by a blood clot in the heart, part of which breaks away and becomes trapped in large arteries in the brain.[18] Blockage of the larger arteries in the brain, compared with blockage of smaller arteries characteristic of other types of stroke, results in greater damage and therefore more severe stroke. Half of all cardioembolic strokes are caused by AF (Figure 8).[122]

In a Chilean study of 239 patients with ischemic stroke, AF was the most common cause of cardioembolic stroke (46%).[123] The case death rate at 30 days was highest in cardioembolic strokes (28%) and lowest in small-vessel infarction (0%). Dependency or death at 6 months was also highest in cardioembolic strokes (62%) and lowest in small-vessel infarction (21%).[123]

In the Mexican PREMIER study, which was a multicenter stroke registry study of 1040 patients with first-ever ischemic stroke, 188 patients had cardioembolic stroke.[124] Patients with cardioembolic strokes were associated with higher severity scores (NIHSS [National Institutes of Health Stroke Scale] score >18 points in 31.5% of patients) and a worse short-term outcome as measured by the modified Rankin scale (mRs) at day 30: mRs 2–3 in 27.7% of patients, mRs 4–5 in 29.3% of patients, and death in 23.4% of patients. The modified Rankin scale is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke.

Figure 8. The main cause of cardioembolic stroke is non-valvular atrial fibrillation.[122] Image reprinted with permission from e.Medicine.com, 2011. Available at: http://emedicine.medscape.com/article/1160370-overview.



The original scale was introduced by J Rankin in 1957 and modified to its currently accepted form by Professor Warlow in the late 1980s. At the 1-year follow-up, ~40% of patients with cardioembolic stroke had died.

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.[125] In addition to being more severe, cardioembolic strokes are associated with a higher risk of recurrence than other types of stroke.[126]

The increased severity of strokes in patients with AF compared with other strokes suggests that these patients will experience a greater impairment in quality of life than patients without AF. A systematic review has shown that post-stroke quality of life is significantly poorer in patients with AF compared with healthy controls, the general population, and other patients with coronary heart disease.[127] Patients with AF are therefore a key target population for reducing the overall burden of stroke on society.

Increased death rate

The death rate from stroke is significantly higher in patients with AF than in those without AF. In the Argentinian National Stroke Registry (ReNACer), a countrywide hospital-based stroke registry across Argentina, 1991 patients with acute ischemic stroke were admitted to the 74 participating institutions between November 2004 and October 2006.[128] Patient demographics from the study showed that a history of AF in stroke patients was significantly associated with in-hospital mortality.[128] In an analysis of subjects aged 55 to 94 years who developed AF during 40 years of follow-up of the original US Framingham study, AF was associated with a doubling in mortality in men and women.[129] In a large-scale Italian study of patients who had suffered a first stroke, AF was found to increase the 5-year death rate from stroke almost twofold (Table 4) and to be an independent predictor of death rate even after adjusting for other outcome predictors, such as age, sex, and vascular risk factors.[13]

Patients with AF are a key target population for reducing the overall burden of stroke

A trend towards an increase in the overall early death rate in patients with AF over the past 20 years has been reported,[130] which may reflect the increasing age of the population. With both its prevalence[102] and the associated death rate increasing, there is an urgent need to improve the management of AF, in particular to prevent the most common fatal consequences, such as stroke.

Data from the REduction of Atherothrombosis for Continued Health (REACH) Registry showed that the presence of AF in patients with atherothrombosis was associated with a higher rate of all-cause mortality (4.3%) than in those patients without AF (2.3%). This higher mortality in patients with AF was observed across all subgroups with established atherothrombosis or at risk for atherothrombosis.[118]

Death rate from stroke is higher in patients with AF than in those without AF

Table 4. Annual death rates from first stroke (rounded to nearest whole number) in patients with and without atrial fibrillation (AF). Adapted from Marini *et al*. 2005 with permission.[13]

Year	Annual death rate (%)	
	With AF	Without AF
1	50	27
2	14	8
3	14	6
4	10	6
5	11	6
6	4	3
7	5	4
8	4	3

Increased disability and poor health

AF-related stroke is more severe and is associated with more ill health than stroke unrelated to AF.[13,16–18]

AF increases the risk of remaining disabled or handicapped following stroke by almost 50%

Data from the previously described PREMIER study were used to assess the severity of stroke in patients with and without a history of AF. In total, 1246 patients with ischemic stroke were included in the registry; 159 patients had history of AF and in 64 others AF was diagnosed during the acute stroke event. The case death rate at 30 days was 22.0% in patients with AF compared with 13.7% in those without AF. In patients who survived, the rate of severe disability (as measured by a score of 3–5 on the Rankin scale) was significantly higher in the AF patient cohort compared with the non-AF patient cohort (69% vs 52%, respectively, Figure 9) (Dr. Cantú-Brito, personal communication).

Data from the US has shown utilization rates for hospital in-patient, emergency and outpatient/physician visits to be higher for patients with AF compared with patients without the condition.[131] Overall, per-patient medical costs have been shown to be fivefold higher in AF vs non-AF patient populations.[131] In total, AF-attributable costs in the US have been estimated at US$6.65 billion.[132] This was split between direct patient costs of US$2.93 billion (44%), indirect patient costs of US$1.95 billion (29%), outpatient costs of US$1.53 billion (23%), and drug treatment costs of US$235 million (4%).

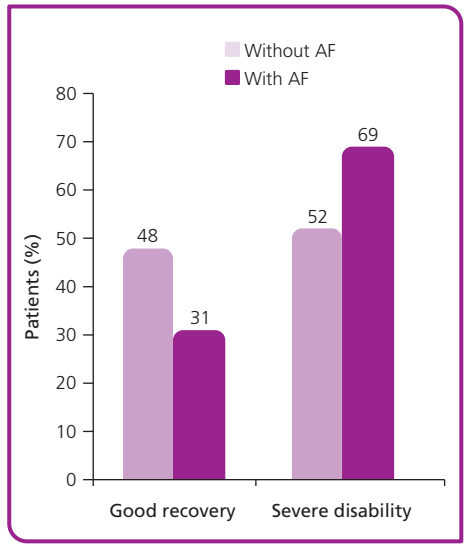
Data from the Copenhagen Stroke Study were used to investigate the impact of stroke on morbidity. Loss of ability to perform normal daily activities after stroke, and decline in neurologic function – including level of consciousness; partial paralysis of the arm, hand, and/or leg; and difficulty in swallowing – were significantly greater in patients with AF than in those without AF, both immediately after the stroke and after rehabilitation.[18] In addition, AF was associated with a 20% increase in the length of hospital stay and a 40% decrease in the likelihood of discharge to home.

At present, there are no data for the entire Latin American region to indicate the increased risk of disability that the presence of AF confers on stroke patients; however, data from a European-wide study are indicative of the increased risk and levels of disability associated with AF-related stroke.

In a European study involving seven countries and 4462 patients hospitalized for first-in-a-lifetime stroke, the presence of AF increased the risk of remaining disabled or handicapped after a stroke by almost 50%.[16]

While data regarding the impact of AF-related stroke exist in a limited number of countries in Latin America, further studies are required in the rest of the region to provide a complete perspective of the effect of AF-related stroke in Latin America.

Figure 9. Patient outcomes after an acute stroke event in patients with and without a history of atrial fibrillation (AF). (Dr. Cantú-Brito, personal communication.)



High cost of stroke in atrial fibrillation to individuals and society

Key points

- AF-related stroke impairs stroke survivors' quality of life more than non-AF-related stroke
- Permanent disability and other consequences of AF-related stroke place a heavy burden on caregivers, family members, and health and social services
- Studies in European populations have shown that healthcare costs associated with stroke are higher for patients with AF than for patients without AF. Similar studies are required in Latin American populations

Significant impact on quality of life

The impact of a stroke on an individual's health can be expressed as a utility score. These scores are used to express the impact of a state of health on health-related quality of life on a scale of 0 to 10, where 10 represents perfect health and 0 represents death. Murphy *et al.* found that mild stroke yielded a higher utility score (9/10) than severe stroke (4/10).[133] This indicates that AF-related strokes, which are more severe than strokes in patients without AF, result in lower utility scores (i.e. poorer health-related quality of life) than other types of stroke. In a study of the impact of stroke on quality of life in patients with AF, the average utility score was 9/10 for a mild stroke, 1/10 for a moderate stroke and 0/10 for a severe stroke; 83% of patients rated their quality of life after a severe stroke as equal to, or worse than, death.[134]

In addition to general utility scores, other scores assess the impact of a state of health on a specific aspect of quality of life (such as neurologic function). Some quality of life scores for patients with and without AF who experience stroke are shown in Table 5. Like the utility scores discussed above, the scores given in the table indicate

AF-related stroke has a more negative impact on quality of life than stroke unrelated to AF

Table 5. Outcome of stroke in patients with and without atrial fibrillation (AF). Adapted from Jørgensen *et al.* 1996 with permission.[18]

	Patients with AF	Patients without AF
Initial stroke severity (SSS* score; lower score = greater neurologic impairment)	30	38
Neurologic outcome (SSS score at discharge)	46	50
Initial disability (BI† score; lower score = decreased ability to perform normal daily activities)	35	52
Functional outcome (BI score at discharge)	67	78
Length of hospital stay (days)	50	40
In-hospital death, n (%)	72 (33)	171 (17)
Discharged to nursing home, n (%)	41 (19)	135 (14)
Discharged to own home, n (%)	104 (48)	662 (69)

Data are presented as mean, rounded to nearest decimal place.
*Scandinavian Stroke Scale.[125]
†Barthel Index.[126]

that AF-related stroke has a more negative impact on quality of life than non-AF-related stroke.

AF also increases the risk of medical complications following stroke. Patients with AF suffer more frequently from pneumonia, pulmonary edema (accumulation of fluid in the lungs), and bleeding in the brain after stroke than those without AF.[135]

AF increases the risk of medical complications following stroke

Heavy burden on carers, families and society

More than one-third of patients who experience a stroke return to their home with some level of permanent disability.[5] They then rely on informal caregivers, typically family members, to help with their normal daily activities and to arrange the required additional assistance from healthcare services. In addition to giving practical help, caregivers have to manage the often considerable cognitive, behavioral, and emotional changes in the patient. These changes include mood swings, personality changes, irritability, anxiety, memory loss, and depression.[5,136] Caregivers can therefore experience a loss of identity, independence, and social life, and extreme tiredness and depression. They also report fears regarding the safety of the patient and distress at not having time to attend to all of the patient's needs.[5,136] In a Brazilian cross-sectional study, the burden and perceived health status among 200 caregivers of stroke survivors was assessed. All of the caregivers in the study were close relatives of the stroke patients, with over three-quarters of the caregivers being female. Overall, more than a quarter of caregivers found their role emotionally exhausting. Female caregivers reported significantly higher test scores for anxiety and had significantly worse caregiver burden scores than their male counterparts. Caregiver burden significantly worsened as stroke severity increased. Patient's disability and caregiver factors (female sex and levels of depression) were significant independent predictors of caregiver burden.[7]

More than one-third of patients who experience a stroke return home with some permanent disability

Stroke can have a devastating impact not only on the individual and their caregivers but also on the wider family, particularly children.

Illustrative example: a caregiver's perspective

"It is now three years since my father's stroke. He found it very difficult to cope at first. Straight after the stroke, his power of speech and understanding were badly affected and he was very frustrated. He also had visual disturbances, loss of balance and emotional problems, and required full-time care. I wanted the best for him and it made me sad to see him like that. I felt totally exhausted, yet could not get any rest because I was constantly up and down looking after him. Nowadays, he's better in himself, but sometimes staggers when he walks and his coordination and speech are poor especially when he is tired. He says I tend to wrap him up in cotton wool but I constantly worry about him and that it could happen again"

Illustrative example: a child's perspective

"When my mother had her stroke, I couldn't wait to go and see her in the hospital. As I got to her room, I could tell straight away that something was wrong. She couldn't move her left arm and leg and was speaking funny. I was a bit afraid of her, but then she hugged me and my father said she would be alright. I still couldn't understand what she said. They kept her in the hospital eight days until it was safe for her to come home to us."

The rehabilitation and long-term care of stroke survivors also place a significant demand on health and social services, often involving nursing, social care, and speech, occupational, and physical therapy.[5,137] Together with loss of time in employment and contribution to the community of the patient, and most probably also the caregiver, this amounts to a significant overall burden on society.

High economic cost

The total cost of stroke for the whole Latin American region is unknown. However, data from individual countries attest to the high cost of stroke in the region. In Brazil and Argentina, aggregate national healthcare expenditures of initial hospitalization for stroke for acute treatment of incident stroke (ischemic stroke and intracerebral hemorrhage) were calculated to be US$449.3 million and US$434.1 million, respectively.[9,10]

Data from Western countries also serve to indicate the high cost of stroke. According to a review of data from eight Western countries, stroke accounts for approximately 3% of national healthcare expenditure and 0.3% of gross domestic product.[138] The total economic cost of stroke is probably even greater than this, as these calculations largely omit costs incurred by the patient and caregivers, because they may be difficult to capture. In 2006, the total cost of stroke in the whole of Europe, including healthcare costs, productivity costs, and informal costs, was calculated to be over €38 billion (US$54 billion).[139]

Government healthcare expenditure in Latin American countries can have an impact on the financial burden of stroke imposed on patients and their families. Inequalities in access to health services and resources have constantly been present in the Latin American region. The percentage of health expenditure as a proportion of the gross domestic product is unequally distributed amongst the income quintiles of the population. For example, in Paraguay, healthcare costs accounted for 14.0% of the expenditure for the poorest quintile versus 8.8% for the richest quintile.[33] The more socioeconomically disadvantaged individuals are those with disproportionately higher health risks.[140]

National health expenditure as a proportion of the gross domestic product also influences the healthcare for populations in Latin America. The share of public health expenditure as a percentage of gross domestic product, which serves as an indicator of the health provision provided by governments, is lower for Latin America (3.3%) compared with a high-income country such as the US (7.2%).[33] Overall, national health expenditure for all countries in Latin America and the Caribbean was 6.8% of the region's gross domestic product.[33] This percentage varied for each country in the region; e.g. 5.5% in Mexico, 7.0% in Brazil, and 8.6% in Argentina.[33]

In Latin America and the Caribbean, 48% of national healthcare expenditure is for public health, and 52% for private health (including direct out-of-pocket expenditure for health goods and services and to cover health services consumed through private health insurance plans).[33] Individuals on higher incomes are more likely to be covered by private health insurance, thereby reducing levels of out-of-pocket expenditure on health care.[33] In poor countries, where public health sector expenditure is low, it is the poorest individuals who are most affected.[140]

Because stroke in patients with AF is more severe than stroke in those without AF,[18] it is likely to incur greater costs. Data comparing the cost of AF-related stroke and stroke not related to AF are not available for Latin American countries. However, data are available

Healthcare costs associated with stroke are higher for patients with AF than for patients without AF

from European countries. In the Berlin Acute Stroke Study, the average direct costs of stroke per patient were significantly higher in patients with AF (€11 799 [US$16 770]) than in patients without AF (€8817 [US$12 532]).[141] The effect of AF on stroke-related inpatient costs was also analyzed over a 3-year period in Sweden.[142] Among stroke survivors, the inpatient costs over this period were on average €818 (US$1163) higher in patients with AF compared with patients without AF (€10 192 [US$14 487] vs €9374 [US$13 325]) after controlling for additional risk factors and death rates. Studies are required in Latin American countries to confirm the high economic cost of stroke in patients with AF across the region.

Strong rationale for stroke prevention in patients with atrial fibrillation

In conclusion, patients with AF have a higher risk of stroke and suffer from more severe strokes than patients without AF. Thus, AF-related stroke imposes an even greater burden on individuals, caregivers, families, society, and healthcare resources than stroke in patients without AF, providing a strong rationale for effective management of AF and prevention of stroke in this high-risk population.

Stroke prevention in patients with atrial fibrillation

Key points

- Direct treatment of AF can help to prevent strokes. Drugs and non-pharmacologic methods are used to control heart rate and rhythm
- It is recommended that patients receiving treatment for AF also receive therapy to reduce the risk of blood clots
- Maintaining the INR within the target range for patients on VKA therapy is a universal problem that is compounded in Latin American countries for a number of reasons. These include the lack of access to, and the cost of attending, INR monitoring facilities, problems associated with INR blood testing in remote/rural areas, and lack of physician knowledge in this area
- Currently available anticlotting therapies, such as VKAs and aspirin, are effective in the prevention of AF-related stroke but have drawbacks
- High blood pressure and diabetes, which commonly affect patients with AF, also require management to reduce the risk of stroke

The ultimate aim of AF management is to reduce the risk that a patient will suffer serious long-term consequences of the condition, particularly stroke. This objective may be achieved by direct management of AF through control of heart rate and control of heart rhythm, and by use of drugs to reduce the risk of blood clots and hence stroke. These strategies are discussed in this chapter.

The aim of AF management is to reduce the risk of long-term consequences, such as stroke

Strategies for stabilizing heart rhythm

Effective management of AF will in itself prevent stroke. AF is most commonly managed using 'rhythm control' or 'rate control' strategies.[17] In rhythm control, drugs are used to maintain the heart's rhythm (these are known as antiarrhythmic drugs); in rate control, the drugs are used to maintain a steady heart rate.[17] Examples of drugs used for rhythm or rate control include amiodarone, digoxin, and β-blockers. Non-pharmacologic methods used to treat AF include electrical cardioversion (a process by which an abnormally fast heart rate or abnormal heart rhythm is terminated by the delivery of a therapeutic dose of electric current to the heart), catheter ablation (an invasive procedure used to remove a faulty electrical pathway from the heart), and surgical maze procedures (open-heart surgical ablation using an energy source to scar the tissue with the faulty electrical pathway).

AF is commonly managed using 'rhythm control' or 'rate control' strategies

Anticlotting therapies for preventing stroke

AF predisposes to the formation of a blood clot, or thrombus, in the heart. Part of the blood clot can break away, forming what is known as an embolus, which can then become trapped in blood vessels in the brain, causing a stroke. Thus, strategies for the prevention of stroke in patients with AF involve the use of anticlotting drug therapy. It is recommended that patients receiving treatment for AF to stabilize heart rhythm also receive some form of

Patients receiving treatment for AF should also receive anticlotting therapy

anticlotting therapy (see 'Guidelines for stroke prevention in patients with atrial fibrillation', page 47).[31]

There are three main classes of 'blood-thinning' drugs currently used in the prevention of stroke in patients with AF:

- Anticoagulants, which interrupt the series of chemical reactions that result in the formation of a blood clot (the coagulation pathway; Figure 10)
- Antiplatelet drugs, which limit the aggregation (clumping together) of platelets (components of the blood that form a significant part of the blood clot, particularly in the arteries)
- Thrombolytics (in the acute setting), which break up blood clots once they are formed

VKAs and aspirin are currently the most widely used drugs for stroke prevention in patients with AF

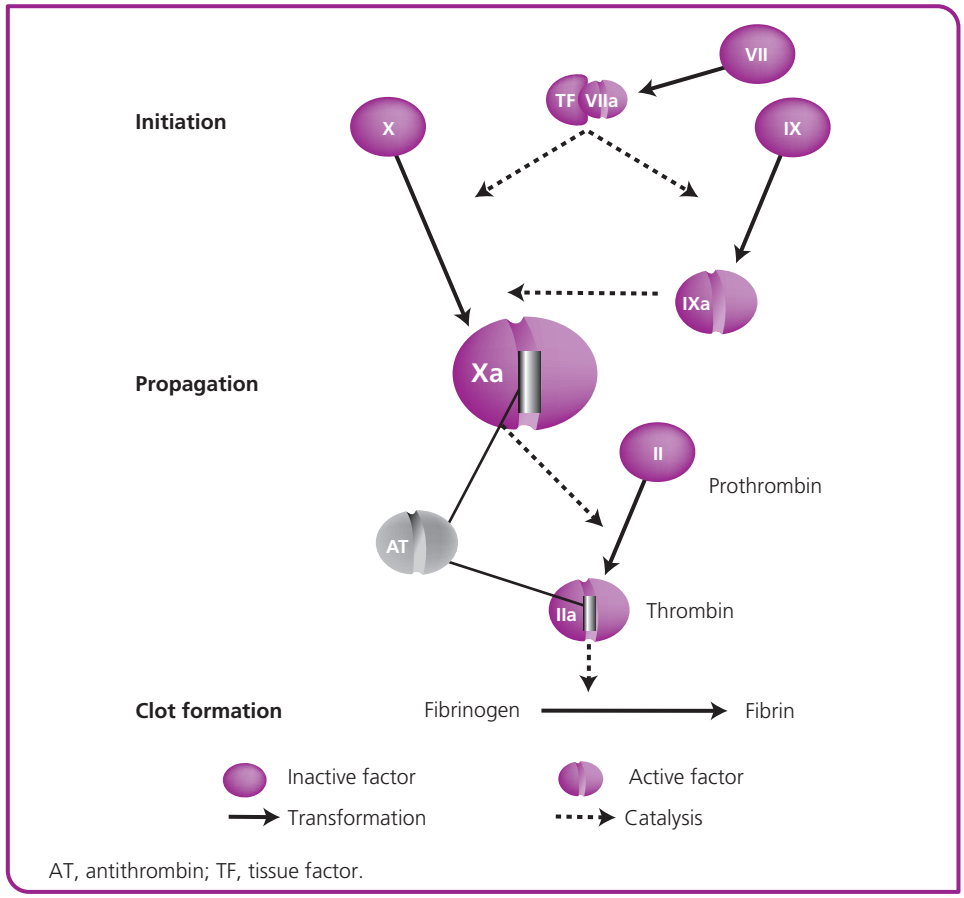
VKAs, which are oral anticoagulants, and acetylsalicylic acid (or aspirin), an antiplatelet agent, are currently the most widely used drugs in the prevention of stroke in patients with AF.

Vitamin K antagonists

VKAs, which include the coumarins warfarin, phenprocoumon, and acenocoumarol, are widely used anticoagulant agents that have been available for many years. Acenocoumarol and phenprocoumon are widely prescribed in Latin America as well as in continental Europe, whereas warfarin is more commonly used in the US, UK, and Scandinavian countries.[143]

VKAs exert their anticoagulant effects by inhibiting the production of four vitamin K-dependent factors that play key roles in the coagulation pathway.[13,25] By inhibiting the enzyme vitamin K epoxide reductase, VKAs prevent the regeneration of the

Figure 10. Simplified diagram of the coagulation pathway – a series of enzyme reactions involved in the formation of a blood clot. Different enzymes are involved at different steps in the pathway. The end product of the pathway is fibrin, an insoluble protein that combines with platelets to form a blood clot.



AT, antithrombin; TF, tissue factor.

reduced form of vitamin K, an essential cofactor in the synthesis of a number of factors in the coagulation cascade, including Factor II (prothrombin), Factor VII, Factor IX, and Factor XI. Depletion of the reduced form of vitamin K ultimately impairs the ability to form thrombin, which subsequently inhibits the conversion of fibrinogen to fibrin.

Although effective in preventing stroke in patients with AF, oral VKAs have several limitations that make the routine, and acute, medical care of patients receiving long-term VKA therapy relatively complicated. The effects of VKAs can be significantly modified by genetic factors[144] and by interactions between other foods and drugs, including amiodarone, an antiarrhythmic drug used in the treatment of AF.[26,145] Furthermore, there is a narrow window between the dose of VKA that achieves therapeutic efficacy and the dose that confers an increased bleeding risk (i.e. the therapeutic range of the drug is small).

The management of patients receiving VKAs can therefore be challenging, and frequent monitoring is required. For monitoring, the patient's prothrombin time (a measure of clotting time) is divided by a reference prothrombin time; the resulting value is then converted to an INR. Using INRs standardizes results by removing differences between laboratories. A target INR range of 2.0–3.0 is typically recommended for patients receiving VKA therapy.[31,87] If the INR is too high, a patient is at increased risk of bleeding; too low, and the risk of a blood clot is high. If a patient's INR is found to be outside the target range, the dose of the VKA should be adjusted accordingly.

Maintenance of the INR within a target range requires not only frequent monitoring but constant dose adjustment, and represents a significant barrier to effective anticoagulation in everyday practice. This is especially difficult in some Latin American countries where some patients have limited access to healthcare resources, including to INR monitoring facilities. In addition, the cost of attending INR monitoring clinics may be prohibitive for some patients. The regularity of INR monitoring may also be less stringent than is optimal in more remote/rural areas because of the difficulties in transport or cold chain processes required in INR testing. The issue of INR control has also been strongly linked to physician knowledge in this area. In a study that assessed the use of anticlotting therapy among AF patients in a Brazilian hospital, the proportion of patients receiving oral anticoagulant therapy (warfarin) within the optimal INR range of 2.0–3.0 was as low as 15.6%.[59]

Patients on VKAs need frequent monitoring and dose adjustment to keep INRs within the target range

Efficacy of vitamin K antagonists in clinicial trials

Systematic reviews of clinical trials in patients with AF have shown that, compared with no therapy, warfarin (with close monitoring and dose adjustment if necessary) provides a 62–68% reduction in the risk of stroke (Figure 11) and a 26–33% reduction in death rate[46–48,114] without significantly increasing the risk of major bleeding. The implication is that for every 1000 patients treated with warfarin, 31 ischemic strokes will be prevented each year.[48] There are few studies of the effect of VKA therapy in Hispanic populations – this could be addressed by carrying out subset analyses in existing studies involving Hispanic populations where VKA therapy has been administered.

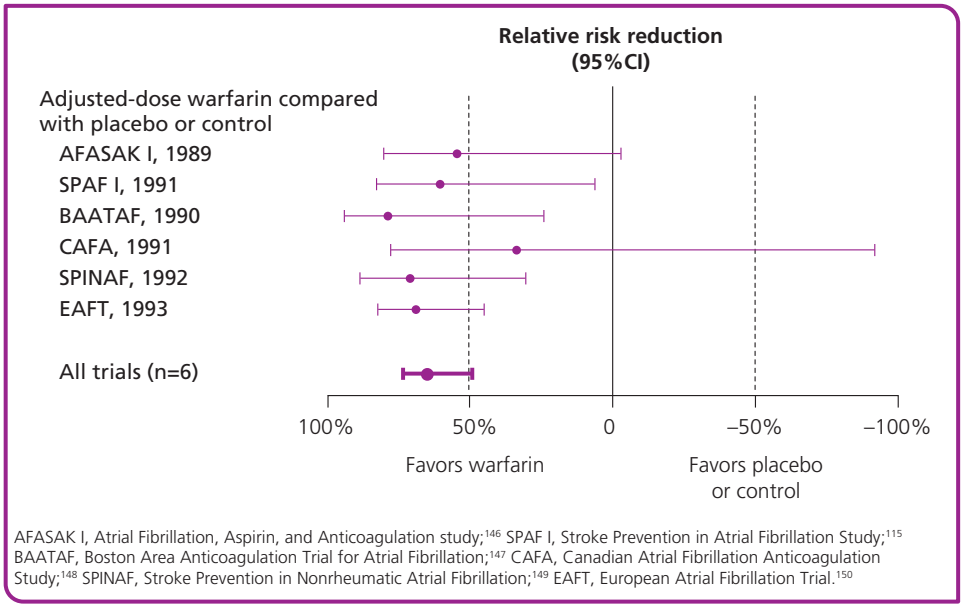
Importantly for patients with AF, it has been shown that when the dose is monitored and – where necessary – adjusted, VKAs are effective in preventing both mild and severe strokes.[151,152]

VKAs are currently recommended as first-line therapy in patients with AF at moderate or high risk of stroke

Clinical use of vitamin K antagonists

VKAs are currently recommended as first-line therapy in patients with AF and a moderate or high risk of developing stroke.[31,87] This is despite

Figure 11. Results from a meta-analysis of six randomized studies, showing that warfarin provides a greater reduction in the risk of stroke in patients with atrial fibrillation than does placebo. Adapted from Hart *et al.* 2007 with permission from the American College of Physicians.[47]



AFASAK I, Atrial Fibrillation, Aspirin, and Anticoagulation study;[146] SPAF I, Stroke Prevention in Atrial Fibrillation Study;[115] BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation;[147] CAFA, Canadian Atrial Fibrillation Anticoagulation Study;[148] SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation;[149] EAFT, European Atrial Fibrillation Trial.[150]

Patient populations in clinical trials may not reflect normal clinical practice

the major drawbacks associated with VKA therapy, including unpredictable interactions with food and other drugs, which often necessitate significant lifestyle changes; the inconvenience and burden of INR monitoring; the need for dose adjustment, which often does not happen; and the perceived risk of bleeding, particularly in the elderly. As a result of these drawbacks, which may cause patients to discontinue taking VKAs, guidelines are not always followed, despite the fact that guideline-adherent management is associated with improved outcomes.[125] Thus, many patients with AF and a moderate to high risk of stroke do not receive anticoagulant therapy and therefore remain unprotected.[60,153] Current guidelines and adherence to these guidelines are discussed in more detail in the chapter 'Guidelines for stroke prevention in patients with atrial fibrillation' (page 47).

Vitamin K antagonists: clinical practice versus controlled clinical trials

Owing to the considerable practical difficulties in maintaining the INR within the target range, there is often concern that the efficacy and the low risk of bleeding observed with VKAs in the controlled clinical trial setting are not reflective of, and cannot be achieved in, clinical practice.[154] Not only are highly motivated patients monitored closely in clinical trials, but relatively few elderly patients are recruited, and patients at high risk of bleeding are frequently excluded.[48,154]

Retrospective cohort studies with an observational design have provided some evidence on this matter. In a large-scale cohort of more than 11 500 patients with non-valvular AF treated in a clinical practice setting, warfarin provided a 51% reduction in the risk of thromboembolism (formation of a blood clot and then circulation of part of the blood clot in the bloodstream) and a 31% reduction in the risk of death compared with either no therapy or aspirin, after adjusting for potentially confounding factors.[155] Overall, there were 148 cases of ischemic stroke or other thromboembolic event among patients receiving warfarin therapy (1.17 per 100 person-years) and 249 events in patients not receiving

warfarin (2.03 per 100 person-years). The incidence of cerebral bleeding was almost doubled with warfarin, but still remained low. The authors concluded that the study adds further support for the routine use of anticoagulation in eligible patients with AF who are at moderate to high risk of stroke.

An investigation in the clinical practice setting in Argentina demonstrated a reduction of approximately 44% in the risk of stroke in patients with AF receiving VKA therapy compared with those not receiving VKA therapy. Mortality rate and the combined events of death and/or stroke were also significantly lower in the VKA therapy compared with non-VKA therapy patient group (mortality 17.6% vs 29.4%; combined events 21.2% vs 34.0%, respectively).[156] However, the reduction in the risk of stroke observed in this study was lower than that in clinical trials that assessed VKA therapy.[47,156] An analysis of the process and quality of oral anticoagulation use in clinical practice has highlighted major management differences between anticoagulation clinic care and routine medical care, with less time within the therapeutic INR range being achieved in routine medical care.[157,158] Two studies carried out in Brazil have indicated that there are a high percentage of patients who do not comply with VKA treatment. In the first study, patients taking warfarin and phenprocoumon were within their therapeutic INR range for only 45.6% and 60.7% of clinic visits, respectively.[159] In the second study, only 38% and 62% of patients again taking warfarin and phenprocoumon, respectively, were within their target INR. Moreover, 50.6% of the patients prescribed oral anticoagulation for AF were outside their therapeutic INR range.[160] Thus, patient outcomes after VKA therapy do appear to be less favorable in clinical practice than in clinical trials. Overall, however, the benefits still outweigh the risks in the majority of patients with AF.

Acetylsalicylic acid (aspirin)

Aspirin reduces platelet aggregation and blood vessel constriction, which in turn reduces the risk of a blood clot forming and helps to prevent a stroke.[161] It is most effective in the prevention of blood clots that are rich in platelets, such as those that form in arteries.

Studies support the use of anticoagulation in patients with AF at moderate to high risk of stroke

In patients with AF, aspirin reduces the risk of all strokes by approximately 22% compared with placebo; for severe, disabling strokes, the reduction in risk with aspirin compared with placebo is smaller (13%).[47] In addition, aspirin was associated with a non-significant 19% reduction in stroke compared with no treatment.[47] Clinical trials directly comparing aspirin with VKA therapy in the prevention of stroke in AF have shown VKAs to be significantly superior, providing a risk reduction of approximately 50% compared with aspirin.[162,163] Despite the perception that it may be safer than warfarin, a major drawback of aspirin is that it increases the risk of bleeding, particularly in the gastrointestinal tract.[27–30]

Patient outcomes after VKA therapy may be less favorable in routine medical practice than in clinical trials

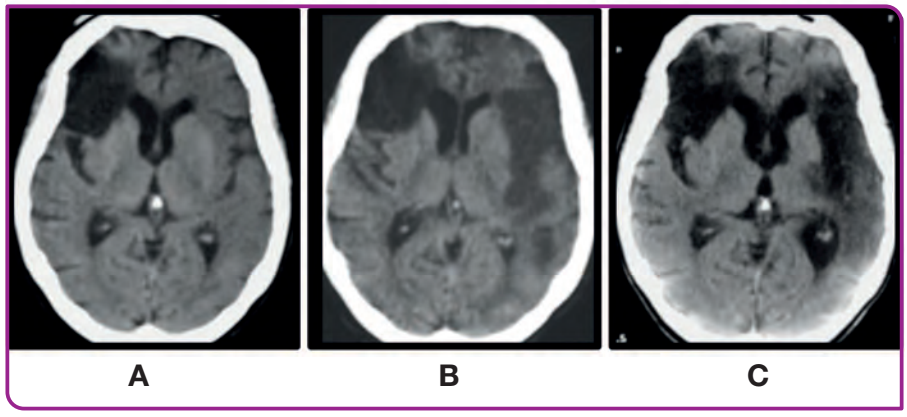
The current ESC guidelines recommend that patients with one clinically relevant non-major risk factor, including hypertension, age 64–75 years, and female sex, should receive an oral anticoagulant in preference to aspirin.[62] In addition, no treatment with any anticlotting therapy should be considered over aspirin in patients without any stroke risk factors.[62] It should be noted that there is some doubt as to the real benefit of aspirin in patients at low risk of stroke.[164,165] Similar advice is given in local Latin American guidelines such as the Argentinian, Brazilian, and Mexican guidelines.[20,64,65] Summaries of these guidelines are given in Appendix 1.

Recent studies underline the use of alternative strategies to aspirin in some patients with AF. In a contemporary study of patients with AF, the oral anticoagulant apixaban was shown to

Case study: an elderly woman receiving warfarin

Mrs. M, a 76-year-old Mexican woman with a history of smoking and arterial hypertension, was diagnosed in 1998 with AF after an episode of acute dyspnea (shortness of breath) and palpitations. She was given aspirin until December 2004 when she had weakness down the left-hand side of her body. A Computed Tomography (CT) scan showed a right frontal infarction (Figure 12A) and she was started on oral anticoagulation with warfarin. During warfarin monitoring in October 2006, her INR rose to 5.2 and, because of the risk of bleeding, warfarin was stopped. On the fourth day after stopping warfarin, Mrs. M developed acute aphasia (impairment of speech and writing) and weakness down the right-hand side of her body. A CT scan revealed a recurrent cerebral infarction, now in the left frontal region (Figure 12B). Her INR was 1.3. The patient recovered from this second infarction with only mild disability, and warfarin was restarted. Again during warfarin monitoring in September 2007, her INR rose to 3.9 and warfarin was once again stopped. On the third day after stopping warfarin, she had a further episode of acute aphasia and weakness down the right-hand side of her body. A CT scan showed a new cerebral infarction, now in the left parietal region (Figure 12C). Her INR was 1.2. Unfortunately, the issues with maintaining Mrs. M's INR within the correct range caused immediate life-threatening problems. After the third recurrent cerebral infarction, Mrs. M was severely disabled, unable to walk, and she died 2 months later from pneumonia. Therefore, it would be ideal if an oral anticoagulant existed that did not require frequent monitoring, could be given at a fixed daily dose, and was also unaffected by changes in diet or other medications.

Figure 12. Various CT images of a patient (Mrs. M) taken at different time points showing the presence of a cerebral infarction in different locations. Permission for use granted by Dr. Cantú-Brito.



be superior to aspirin for the prevention of stroke in patients with AF for whom VKA therapy was unsuitable and had been discontinued, or for patients who had not previously been prescribed VKA therapy but in whom it would be expected to be unsuitable.[166,167] VKA therapy was considered unsuitable if the patient was unlikely to comply with dosing or monitoring requirements; there was a need for other treatments that may interact with the VKA; the patient was unlikely to adhere to restrictions on alcohol, diet, or non-prescription medications; the risk of VKA therapy was considered to outweigh the risk of stroke or systemic embolism; or the patient was unwilling to take VKA. Reasons for discontinuation of VKA therapy included poor anticoagulant

control, adverse events, the need for other treatments that may interact with VKAs, or the patient was unable or unwilling to adhere to dose or INR monitoring instructions.

Cost of vitamin K antagonist therapy in stroke prevention in atrial fibrillation

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 Europe suggest that the cost of stroke prevention appears to be favorable compared with the average direct per capita cost for treatment after stroke. In a UK study, the cost of preventing one AF-related stroke per year using VKA therapy was estimated to be £5260 (US$8642), with regular INR monitoring and hospital admissions for bleeding complications being the major cost drivers.[168] The cost of prevention thus appears to be favorable compared with an average direct per capita cost of €11 799 for treating stroke in the European Union (US$19 386).[141] Although VKA therapy imposes an added economic burden on healthcare resources, the cost remains considerably lower than the cost of managing the consequences of blood clots, such as stroke. In another study of patients with AF in the UK, the cost of treatment of a stroke over a 10-year period was estimated to be almost fourfold greater than the estimated 10-year direct costs of anticoagulation,[169] indicating that prevention is substantially more cost-effective than treatment.

Numerous other studies have provided further evidence that anticoagulation with VKAs is cost-effective in patients with AF at a moderate or high risk of stroke, compared with no therapy or aspirin.[111,170] Management of complications after suboptimal anticoagulation is the major driver of cost.[170]

Little is known regarding the cost-effectiveness of VKA therapy versus no stroke prophylaxis in Latin America, despite its relevance for some countries. Nevertheless, for other countries, the relevance of assessing cost-effectiveness of VKA is less clear, given the unbalanced distribution of health care in Latin America.[34] Despite this, similar country-specific studies are needed in Latin America, particularly because of the growing burden of stroke in the region.

Clinical trials have shown VKAs to be cost-effective compared with aspirin in the prevention of stroke in AF

The cost-effectiveness of VKA therapy is dependent on achieving a significant reduction in the risk of thromboembolism. Practical difficulties in maintaining INR values within the therapeutic range may result in VKA therapy being less cost-effective in clinical practice than in controlled clinical trials. Monitoring INR in clinical practice may also incur additional costs, to the patient, caregiver, and society, not captured in the cost-effectiveness studies. 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. One study of the cost associated with accompanying patients to clinic visits has shown that caregivers experience a cost of €17 (US$24) per visit in Portugal and €10 (US$14) per visit in the UK.[171] In addition, in the UK – where the frequency of clinic visits is typically 8–12 per year – this figure would equate to an annual cost to the caregiver of up to €120 (US$171). As mentioned previously, access to INR monitoring facilities is unequal in some countries of Latin America and this needs to be addressed before the relevance of assessing the cost-effectiveness of attending anticoagulation clinics can be discussed for the whole of the Latin American region.

Studies assessing the cost-effectiveness of VKA therapy are needed for Latin American countries

Thus, it is important that stroke prevention in clinical practice is improved so that it is as cost-effective as in clinical trials. Ways in which this can be achieved include optimizing the management of patients receiving VKAs and developing novel therapies

or other strategies that are easier to manage and offer favorable efficacy and safety profiles.

Management of other conditions that increase stroke risk: a multidisciplinary approach

High blood pressure and diabetes in patients with AF further increase the risk of stroke and require multidisciplinary patient management

AF commonly coexists with other conditions, such as high blood pressure and diabetes, which themselves can predispose to blood clots and stroke. The risk in patients with several of these conditions is accumulative – that is, the more conditions that predispose to stroke, the greater the risk. Even in patients who are receiving antiarrhythmic and anticlotting therapy, these conditions may need proactive management to reduce stroke risk.

Blood pressure control is particularly important in the management of AF, and uncontrolled blood pressure increases the risk of stroke 2–3-fold.[12,172] AF in patients with diabetes is also associated with a very high risk of stroke. One study in patients with diabetes found that those who also had AF had a more than 60% greater risk of death from all causes than patients without AF; they also had an increased risk of death from stroke and heart failure.[173]

Alternative therapies or strategies are needed for the prevention of stroke in patients with AF

It is therefore clear that conditions that increase the risk of stroke and that coexist with AF must be carefully managed. This approach is known as multidisciplinary patient management.

The outlook for stroke prevention in patients with atrial fibrillation

To summarize, patients with AF should be managed using a multidisciplinary approach and treated with drugs or other strategies that control the abnormal heart rhythm itself, as well as with anticlotting therapy to reduce the risk of blood clots and, hence, stroke. VKAs have been shown to reduce the risk of stroke in patients with AF in both clinical trials and clinical practice. Importantly, VKAs have proven efficacy in reducing the risk of severe, fatal, or disabling strokes. In addition, these agents have been demonstrated to be cost-effective in patients with AF and a moderate to high risk of stroke. However, studies are required to calculate the cost-effectiveness of VKAs in Latin American populations. VKAs are, however, associated with major, well-recognized drawbacks. Nevertheless, they remain frontline therapy in this indication. Thus, in the immediate term, improved detection of asymptomatic AF, and increased use and optimization of VKA therapy are important to reduce the incidence of severe stroke in patients with AF.

In the medium to long term, alternative therapies that combine convenience with a favorable benefit-to-risk profile could help to further improve the prevention of stroke in patients with AF.

The development of effective, fixed-dose therapies with a good safety profile is likely to lead to considerable improvements in the management of patients with AF. Various clinical studies are ongoing, and early indications are that new anticoagulants show promise of providing better stroke prevention in the foreseeable future.

New and emerging anticlotting agents and recently published clinical trial results are discussed in more detail in the chapter ‘New developments for stroke prevention in patients with atrial fibrillation’ (page 62).

Guidelines for stroke prevention in patients with atrial fibrillation

Key points

- Patients at a high risk of stroke should receive anticlotting therapy, such as a VKA
- Aspirin is only recommended in guidelines for patients at a low or moderate risk of stroke
- Although several sets of guidelines exist for preventing stroke in patients with AF, the recommendations are not universally applied
- Studies in Latin America have shown that the percentage of patients with AF receiving adequate guideline-adherent therapy to prevent clots varies greatly
- The drawbacks of current therapies, and a lack of physician and patient education regarding the benefits of therapy, may contribute to this problem

Summary of guidelines

Latin American guidelines for the prevention of stroke in patients with AF for the region as a whole are not available. However, in Latin American countries such as Argentina, Brazil, Venezuela, and Uruguay, internationally endorsed guidelines such as the 2006 ACC/AHA/ESC consensus guidelines,[31] the 2010 ESC guidelines and the newly updated 2011 ACCF/AHA/HRS guidelines[63] are followed. All these guidelines (Table 6) are based on expert consensus by an international faculty, and have been endorsed by major societies in both Europe and North America.

Country-specific guidelines for the management of AF do exist for some Latin American countries such as Argentina, Brazil, and Mexico. These include the Argentinian AF guidelines, the Brazilian guidelines on AF, and the Mexican diagnosis and treatment of AF guidelines.[20,64,65] Summaries of all these guidelines are shown in Appendix 1.

Agreement on specific recommendations between the different guidelines on stroke prevention in patients with AF is difficult to extrapolate because the risk categories used are different in each set of guidelines. However, the majority of the guidelines recommend that patients at low risk of stroke should receive aspirin therapy and those at high risk should receive therapy with oral anticoagulants. Most of the guidelines also agree that patients with AF and at moderate risk of stroke should receive aspirin or oral anticoagulant therapy. However, the ESC 2010 guidelines favor the use of oral anticoagulation rather than aspirin in this patient group.[62]

Guidelines endorsed by major societies exist for the prevention of stroke in patients with AF, and these are used by Latin American countries

Guidelines: theory versus practice

Despite the existence of international and country-specific guidelines for the prevention of stroke in patients with AF, their application varies greatly, and VKA therapy is often underused.[174] In some cases, patients eligible for VKA therapy may receive aspirin therapy instead, or the dose of VKA may be outside the recommended range (Figure 13).[58]

Guideline consensus recommends VKAs for patients at moderate or high risk of stroke

In a study of 53 patients with AF at a private clinic in Brazil, among the patients with an indication for anticoagulant therapy according to

Table 6. Summary of the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2006 and the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) 2011 guidelines for the prevention of stroke in patients with atrial fibrillation, and the European Society of Cardiology (ESC) 2010 guidelines for the management of atrial fibrillation.

Guideline (Reference)	Risk category	Recommendation	Definition of risk factors
ACC/AHA/ESC 2006[31]	No risk factor or contraindication to VKAs	Aspirin, 81–325 mg/day	Less validated/weaker risk factors: • Female gender • Age 65–74 years • Coronary artery disease
	One moderate risk factor	Aspirin, 81–325 mg/day or warfarin (INR 2.0–3.0, target 2.5)	Moderate risk factors: • Age ≥75 years • Hypertension • Heart failure • Diabetes • LV dysfunction
	Any high risk factor or >1 moderate risk factor	Warfarin (INR 2.0–3.0, target 2.5)	High risk factors: • Previous stroke, TIA, or thromboembolism • Mitral stenosis • Prosthetic heart valve
ACC/AHA/HRS 2011[63]	No risk factor or contraindication to VKAs	Aspirin, 81–325 mg/day	Less validated/weaker risk factors: • Female gender • Age 65–74 years • Coronary artery disease
	One moderate risk factor	Aspirin, 81–325 mg/day or warfarin (INR 2.0–3.0, target 2.5)	Moderate risk factors: • Age ≥75 years • Hypertension • Heart failure • Diabetes • LV dysfunction
	Any high risk factor or >1 moderate risk factor	Warfarin (INR 2.0–3.0, target 2.5)	High risk factors: • Previous stroke, TIA, or thromboembolism • Mitral stenosis • Prosthetic heart valve
ESC 2010[62]	One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors CHA_2DS_2-VASc score ≥2	Oral anticoagulation, e.g. VKA (INR 2.0–3.0, target 2.5)	*Risk factors for stroke and thromboembolism* 'Major' risk factors: • Previous stroke, TIA or systemic embolism • Age ≥75 years 'Clinically relevant non-major' risk factors: • Heart failure or moderate to severe LV systolic dysfunction (e.g. LV ejection fraction ≤40%), hypertension, diabetes mellitus, female sex, age 65–74 years, vascular disease *Risk factor-based approach expressed as a point-based scoring system (CHA_2DS_2-VASc)* • 2 points assigned for a history of stroke or TIA, or age ≥75 years • 1 point assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, congestive heart failure, LV dysfunction, vascular disease (myocardial infarction, complex aortic plaque, and peripheral artery disease) and female sex
	One 'clinically relevant non-major' risk factor CHA_2DS_2-VASc score = 1	Either oral anticoagulation or aspirin 75–325 mg/day Preferred: oral anticoagulation rather than aspirin	
	No risk factors CHA_2DS_2-VASc score = 0	Either aspirin 75–325 mg/day or no antithrombotic therapy Preferred: no antithrombotic therapy rather than aspirin	

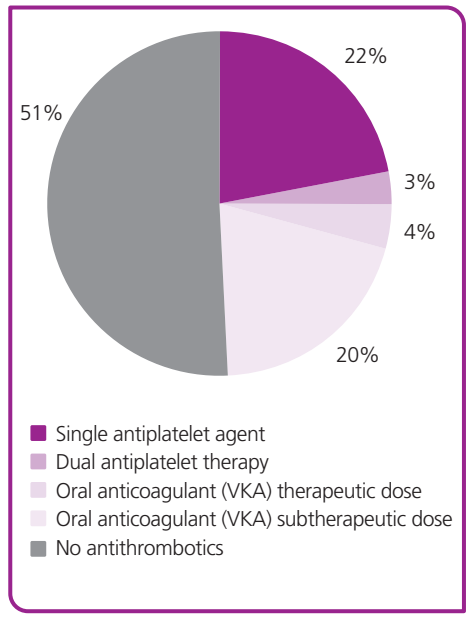
INR, international normalized ratio; LV, left ventricular; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Brazilian guidelines, only 61.7% were using oral anticoagulants. Furthermore, only 65.9% of patients indicated for oral anticoagulation according to American/European guidelines were receiving oral anticoagulants.[56]

In an assessment of 301 patients with AF in a Brazilian University Heart Hospital, only 46.5% of patients who were eligible for anticoagulation were receiving VKA therapy.[59] In another study of 136 patients with AF at a Brazilian tertiary outpatient clinic, only 55% of patients at moderate to high risk for thromboembolism received dose-adjusted VKA therapy. Of the 37 patients who did not receive warfarin, only 7 patients had a contraindication to the drug.[175] Finally, in a Brazilian University Hospital study of 279 patients with AF and other risk factors for thromboembolism (49.1% of patients had ≥3 risk factors), only 24% received a prescription for oral anticoagulation therapy. In addition, almost half of those patients who did receive a prescription did not regularly use the oral anticoagulation therapy.[57] All of these studies highlight the discrepancy between the guideline recommendations and what is happening in clinical practice.

The magnitude of this problem was recently confirmed in a large prospective stroke registry study in Mexico involving 2837 Latin American patients with ischemic stroke and 357 with TIA.[58] Among these patients, 385 had a known history of AF with a prevalence of 12.5% in patients with ischemic stroke and 8.1% in patients with TIA. In patients with a history of AF and a recurrent TIA/ischemic stroke (n=145), only 13.1% were taking VKAs with a therapeutic INR at the time of stroke onset, 22.8% were on VKAs with a subtherapeutic INR (<2), 32.4% were taking antiplatelets, and 31.7% did not receive any anticlotting agents. The anticlotting agents received by patients with known AF and a first-ever ischemic stroke or TIA (n=240), before their admission to hospital, are shown in Figure 13. In this Hispanic population, most of the patients with AF who were admitted with a stroke, and who were candidates for anticoagulation, were not receiving anticlotting therapy or were receiving a subtherapeutic level of oral anticoagulants, or were not taking their oral anticoagulants.[58]

Figure 13. Anticlotting therapies received before admission to hospital by patients in Mexico with known AF who experienced a first-ever ischemic stroke or transient ischemic attack. Only 4% of patients received oral anticoagulation (vitamin K antagonists [VKAs]) at the therapeutic dose.[58] Figure supplied by Dr. Cantù-Brito.



Adherence to guidelines varies greatly, and VKA therapy is often underused

It is worth noting that not all studies on the use of VKAs in patients with AF indicate that they are underused.[176–179] Indeed, the degree of adherence to guidelines reported in different studies varies; a review of the literature from 2000 indicated that, generally, only 15–44% of eligible patients with AF were receiving warfarin.[23]

There is discrepancy between guideline recommendations and clinical practice

Underuse of anticoagulant therapy in patients with AF who are at high risk of stroke is associated with significantly greater risk of thromboembolism and the combined endpoint of cardiovascular death, thromboembolism, or major

bleeding.[60] This was confirmed in a study in Argentina that showed that the risk of death significantly increased in patients with AF who were not receiving anticoagulation therapy. In this study of 615 patients with chronic AF, only 51.4% of patients were receiving anticoagulants on entry to the study.[156] The analysis of the anticoagulated and not anticoagulated patient populations showed a mortality of 17.6% and 29.4%, respectively.

Reasons for poor adherence to guidelines

The need for frequent monitoring and dose adjustment of VKAs contributes to poor adherence to guidelines

Adherence to guidelines for the prevention of stroke in patients with AF may be low for several reasons. These include difficulties in maintaining INR within the therapeutic range,[26] and physicians' concerns about bleeding risk, particularly in the elderly.[53]

Difficulties in maintaining dose of vitamin K antagonist within the therapeutic range

A prospective Peruvian study was carried out in patients with heart disease (AF 38.4%, mechanical valve prostheses 58.8%) who were taking warfarin. On a random day, only 48.2% of patients maintained optimal oral anticoagulant INR protection.[180] The numbers of patients who had under-anticoagulation and over-anticoagulation INR levels were 37.9% and 13.9%, respectively.

The problems associated with the utilization of VKAs are universal. Many patients, both the young and the elderly, find the frequent monitoring and necessary dose adjustments associated with VKAs inconvenient and time consuming, and may miss appointments. Elderly patients particularly may be unwell, become confused or forgetful, or have difficulty with transport, thus causing them to miss appointments. This can be especially true for patients living in the more remote areas of Latin America. Moreover, in some countries there are several formulations of warfarin and irregular drug quality control, which results in patients being switched from one formulation to another. Other challenges associated with VKA therapy include drug–drug interactions, imposed lifestyle restrictions, the need to discontinue therapy for various procedures, variable dose responses, the lack of suitable laboratories to enable adequate anticoagulation monitoring in rural areas, and the fear of increased bleeding for patients during daily activities, accidents, and sporting activities.

In a Brazilian study assessing oral anticoagulation use in clinical practice, patients were asked about their perception of oral anticoagulant use (phenprocoumon 58% of patients, warfarin 42% of patients). Overall, 95% of patients questioned were concerned about the daily use of medication. Furthermore, patients found the need for periodic blood tests (21.4%) and the daily limitations caused by the use of oral anticoagulation (12.8%) as disadvantageous to treatment.[160] A recent comprehensive review of the literature has shown that patients with AF receiving warfarin who were monitored infrequently (defined as representative of routine clinical practice) were within the target INR for a smaller proportion of the time than patients who were monitored frequently, according to strict protocols.[181] The greater the length of time that a patient's INR is within the target range, the lower their risk of a blood clot or of uncontrolled bleeding.

Physicians' concerns about bleeding risk

Some physicians may overestimate the risk of bleeding associated with the use of VKAs and underestimate their benefits in preventing thromboembolism and stroke; conversely, they may underestimate the bleeding risk of aspirin therapy and overestimate its benefits.[53,54,182] As a result, some eligible patients are not receiving optimum

therapy that could prevent strokes.[24] For many physicians, bleeding risk is a particular concern in the elderly, who may become confused and may take more than the recommended dose of warfarin per day. A Chilean study that aimed to determine the effect of a patient's age on the quality of oral anticoagulation reported that older patients (>80 years) were more likely to have occasional INRs >5 than their younger counterparts (patients <60 years).[183] Furthermore, as elderly patients are particularly prone to falls, there is a fear among physicians that elderly patients who fall may suffer a severe hemorrhage if they are taking VKA therapy.[184–186] However, evidence has shown that, in patients with AF who are receiving anticoagulant agents, the risk of a cerebral bleed from falling is so small that the benefits of treatment outweigh the risk.[187] Furthermore, the incidence of stroke among patients aged 75 years or more with AF is lower in those who are receiving VKA therapy than in those taking aspirin, without increasing the risk of hemorrhage.[162]

Bleeding risk during VKA therapy in patients with AF is not homogeneous and a number of clinical factors, including hypertension, older age, and history of bleeding have been identified that are associated with incremental bleeding risk.[188] A number of bleeding risk stratification schemes exist, including a new simple major bleeding risk score known as HAS-BLED,[121] which is used to predict bleeding risk in the ESC guidelines.[62] The HAS-BLED score is described in more detail in the section on detecting AF and stratifying stroke risk (page 31).

Major bleeding events associated with VKA therapy can profoundly influence physicians' prescribing behavior, even when they have evidence that the risk of major bleeding is low. Choudhry *et al.* studied 530 physicians who were treating patients with AF who had bleeding events while receiving VKAs, and who were also treating other patients with AF. Patients treated in the 90 days after the physician had encountered a bleeding event were significantly less likely to receive a prescription for VKA therapy than patients treated before the event.[189] In contrast, patients who experienced an ischemic stroke while not receiving VKA therapy did not influence a physician's prescribing behavior towards subsequent patients.[189] In other words, a bleeding event may make a physician less likely to prescribe VKAs, but a stroke does not increase the likelihood that a physician will prescribe VKAs.

Physicians may overestimate bleeding risk from VKAs and underestimate their benefits in stroke prevention

It has been postulated that the reasons for this phenomenon are twofold. First, Tversky and Kahneman's 'availability heuristic' suggests that assessments of the probability of an event are influenced by the ease with which instances of the event can be recalled.[190] Major bleeding events related to anticoagulation are dramatic and therefore easily remembered and may lead to reductions in VKA prescribing. Secondly, Feinstein's 'chagrin factor' postulates that, when choosing between alternatives, physicians avoid those actions that cause them the most regret.[191] In the case of anticoagulation, physicians may regret acts of commission (i.e. bleeding events associated with the administration of anticoagulation) more than they regret acts of omission (i.e. stroke events associated with withholding anticoagulation). This may be in keeping with one of the principles of the Hippocratic oath, to 'do no harm'.[189]

Discrepancies between patients' and physicians' perceptions of stroke and bleeding risk

Devereaux *et al.* carried out a study of perceptions of risk among patients with AF at high risk of developing stroke versus those among physicians. For both groups, the aim was to identify how big the reduction in risk of stroke should be to justify anticlotting therapy (i.e. VKA or aspirin therapy to reduce

the risk of blood clots) and how much risk of excess bleeding from therapy was acceptable.[192] In order for VKA therapy to be justified, physicians considered that it needed to prevent a significantly higher number of strokes than patients felt acceptable (Table 7). The number of strokes that needed to be prevented to justify aspirin therapy did not differ significantly between patients and physicians.

Patients place more value than physicians do on stroke avoidance and less value on avoidance of bleeding

When perceptions of bleeding risk were evaluated, the maximum number of bleeding events associated with warfarin or aspirin that patients found acceptable was significantly higher than that considered acceptable by physicians (Table 7). Moreover, the results suggest that physicians perceive the risk of bleeding to be higher with VKAs than with aspirin. This perception is at variance with the findings by Mant *et al.* that, compared with aspirin, warfarin decreases stroke risk without increasing the risk of bleeding.[162]

These results indicate that patients place more value than physicians do on the avoidance of stroke, and less value on the avoidance of bleeding.[192] It is important that the views of the individual patient are taken into account when assessing whether to use anticoagulant therapy, even if the physician is risk averse.

To summarize, adherence to guidelines for the prevention of stroke in patients with AF is often suboptimal, largely because of the drawbacks associated with VKA therapy and a lack of physician and patient education regarding the benefit-to-risk ratio of therapy. There is a clear need for improvements in the implementation of, and adherence to, guidelines for AF to improve patient outcomes in stroke for what is a growing burden in Latin America.

Table 7. Hypothetical thresholds among patients with atrial fibrillation at high risk of developing stroke versus those among physicians for how much reduction in risk of stroke is necessary and how much risk of excess bleeding is acceptable over 2 years of anticlotting treatment. Patients place more value than physicians do on stroke avoidance, and less value on avoidance of bleeding.[192]

Scenario	Patients' threshold (mean ± SD)	Physicians' threshold (mean ± SD)	Statistical significance of difference in thresholds
Minimum number of strokes that need to be prevented in 100 patients			
Warfarin	1.8 ± 1.9	2.5 ± 1.6	p=0.009
Aspirin	1.3 ± 1.3	1.6 ± 1.5	NS
Maximum number of excess bleeds acceptable to patients			
Warfarin	17.4 ± 7.1	10.3 ± 6.1	p<0.001
Aspirin	14.7 ± 8.5	6.7 ± 6.2	p<0.001

NS, not significant; SD, standard deviation.

Current challenges for stroke prevention in patients with atrial fibrillation

Key points

A national government-wide commitment within Latin America is needed to reduce AF-related stroke. This could be achieved by:

- Coordinating strategies for early and adequate diagnosis of AF, and promoting the development of relevant research programs
- Raising awareness and understanding of AF and AF-related stroke among patients and caregivers
- 'Empowering' patients and caregivers to take more active roles in determining and evaluating their care
- Encouraging the uptake and use of new therapies and procedures
- Improving knowledge and awareness among physicians involved in AF management
- Optimizing the continuum of care for all patients with AF
- Providing equity of access to AF therapy, and information for all patients across the Latin American region
- Improving the implementation of, and promoting adherence to, guidelines for the management of AF and a collaborative approach to guideline development

It is clear that significant improvements are required in the detection and treatment of AF, in the implementation of, and adherence to, guidelines on the use of existing anticlotting therapies, and in the development of better and more effective strategies to reduce stroke risk. The current challenges in the prevention of stroke in patients with AF are discussed in more detail below.

Improved detection and diagnosis of atrial fibrillation

Awareness of the early signs of AF and common coexisting conditions is required to maximize the opportunity for stroke prevention in patients at risk. Clear strategies are needed that will lead to improved detection and diagnosis of AF by physicians. Part of this involves fostering an increased awareness among the general public that signs such as an irregular pulse and abnormal heart rhythm should be investigated. One such initiative that hopes to achieve this, the 'Know Your Pulse' campaign, will soon be launched by the Arrhythmia Alliance and associated organizations in Argentina, Bolivia, Brazil, Chile, Mexico, and Uruguay.[193,194]

There may be scope for introducing more widespread AF screening programs, after the positive results of the SAFE study.[106] Some of the recommendations for further research put forward by the SAFE study investigators focus specifically on aspects of screening, such as the role of computerized software in assisting with the diagnosis, and how best to improve the performance of healthcare professionals in interpreting the results of ECGs.[106] These recommendations need to be followed up and acted upon.

More widespread screening and awareness-raising would improve detection and diagnosis of AF

Increased awareness among patients

Wider access to information

Many patients with AF do not have sufficient access to information about their condition and its treatment. An international quantitative survey was carried out in 11 countries, including Mexico and Brazil, to analyze understanding, perception, and attitudes towards AF among physicians (cardiologists/electrophysiologists) and patients with AF.[195] Overall, 46% of physicians thought that their patient's ability to explain their condition was poor, and one in four patients surveyed felt unable to explain their condition to another person. Physicians thought that over 50% of their patients with AF had an important need for more and improved information about their condition. In terms of the quality and level of AF information provided to patients, only 35% of physicians found it easy to understand, and only 20% of physicians thought that there was enough of it. From a patient perspective, almost a quarter (23%) did not know where to seek, and who to contact, to get additional information on AF. Results from another recent survey of AF involving over 3700 patients with AF and physicians in 12 countries worldwide, also including Mexico and Brazil, found that people with AF were likely to turn to family and friends (29%), pharmacists (26%), and websites (18%) for information about their condition.[196] Over time, fewer patients with AF were worried as they became more informed. Similarly, in a study of 119 patients with AF in the UK, 37% were unaware of their specific heart condition and 48% did not know the reasons for commencing VKA therapy.[197] Approximately two-thirds of patients were unaware that VKAs had a role in preventing blood clots and stroke, and over 60% felt that their underlying illness (i.e. AF) was not severe.

Many patients do not understand the role of VKAs in preventing blood clots and stroke

A number of organizations are working to improve access to information on AF in Latin America. The Arrhythmia Alliance, a charity set up in the UK to promote greater understanding, diagnosis, treatment, and quality of life for people with cardiac arrhythmias, is now established in Argentina, and will soon extend to Bolivia, Brazil, Chile, Ecuador, Mexico, and Uruguay.[194] The main tasks of the charity are to create awareness about arrhythmias and sudden death, and to promote the creation of a legal framework for a better 'chain of survival'. A number of activities have been undertaken in Argentina including 'World Heart Rhythm Week', the 'Know Your Pulse' campaign, and the 'Campaign for the Prevention of Sudden Death'. 'World Heart Rhythm Week' is an annual international event that aims to raise awareness of heart rhythm disorders and sudden cardiac death.[198] It is organized by the Arrhythmia Alliance and held in partnership with the International Cardiac Pacing and Electrophysiology Society (ICPES).

The 'Know Your Pulse' campaign raises awareness of routine pulse-taking as being one of the easiest ways to pick up an irregular pulse and so prevent potentially fatal cardiac arrhythmias.[193] The 'Campaign for the Prevention of Sudden Death' seeks to address the need to optimize training in cardiopulmonary resuscitation, the availability of external defibrillators and the scarce motivation among witnesses.[199]

The Arrhythmia Alliance in Argentina also aims to interact with individuals and groups involved in this area, provide education materials, and promote volunteering to help disseminate knowledge effectively.[200] In addition to the Arrhythmia Alliance in Argentina, Bolivia, Brazil, Chile, Ecuador, Mexico, and Uruguay, a partnership of the Arrhythmia Alliance and Atrial Fibrillation Association will soon be launched in a

number of other Latin American countries. The Atrial Fibrillation Association is a UK registered charity which focuses on raising awareness of AF by providing information and support materials for patients and medical professionals involved in detecting, diagnosing and managing AF.[201] International patient information on cardiac arrhythmias, prepared with guidance from the International Medical Advisory Committee of the Arrhythmia Alliance, has been translated into many different languages, including Spanish and Portuguese.[202]

StopAfib.org is a worldwide patient-to-patient resource to help patients with AF treat and manage their illness. The mission of the organization is to raise awareness of AF to ensure it gets diagnosed and treated, improve quality of life for those living with AF, support the patient-healthcare provider relationship, and decrease AF-related strokes. Information for patients with AF and their caregivers is accessible from anywhere in the world and the site provides up-to-date content on what AF is, why it is a problem, and how to manage and treat it. It also shares patient stories and provides valuable resources.[203] The patient and caregiver resources section of the site provides general information on AF, as well as information about patient discussion forums, social media, guidelines, medications, and physician resources.[204] StopAfib.org is the most visited arrhythmia site worldwide, with significant traffic from Latin America, and is also HONcode certified by the Health on the Net Foundation.

Recent global campaigns to raise awareness of AF from StopAfib.org have included the 'Take A Stand Against Atrial Fibrillation' campaign, held in conjunction with Atrial Fibrillation Awareness Month in September 2010,[205] and the simultaneous release of an online 'Get Started Learning About Atrial Fibrillation Guide' aimed at educating consumers, patients, and caregivers about the condition.[206] To serve patients and caregivers in Latin America and around the globe, the site is available in a number of languages, including Spanish and Portuguese, and features an International AF Services Locator to help patients find help with their AF. Advice from the StopAfib.org Global Medical Advisory Board ensures that patient and caregiver content is culturally appropriate.

Better adherence to therapy

Without clear information or guidance, patient adherence can be poor, leaving patients at risk of bleeding or stroke

According to AntiCoagulation Europe, adherence to therapy is reliant on the patients understanding of their condition. AntiCoagulation Europe is a registered charity committed to the prevention of thrombosis and the provision of information and support for people already receiving anticoagulant and antiplatelet therapy.[207] Although some patients fully appreciate the need to stay within the therapeutic range – but fail to do so for reasons outside their control (e.g. genetic or metabolic factors) – not all patients have this understanding. Without the proper information or guidance, adherence can be poor, leaving patients at risk of bleeding or stroke. The need for improved understanding is demonstrated by the 'It's About Time' survey. This found that, although just below three-quarters of patients knew their target INR reading, over one-third of patients believed that being outside their target range had no major effect on their health. Only 30% of patients had been in their target INR range in their last 5–10 monitoring sessions, and 7% had not been in their target INR range in any of their last 5–10 sessions.[208] Although there are no similar surveys for Latin American countries, patients do understand the relevance of their INR in general (Dr. Meschengieser, Dr. Reyes, Dr Avezum, personal communications 2011). Patients who do not understand are not good candidates for warfarin therapy and, consequently, may not

receive such medication. The provision of education and guidance has been shown to help patients achieve therapeutic targets of anticoagulation, as demonstrated in a study of 188 patients attending an anticoagulation clinic in Chile. After the implementation of guidance and a patient education program, the number of patients with an INR >5.0 and <1.5 in all age groups studied decreased significantly.[183]

Greater patient 'empowerment'

Educating patients and encouraging them to take a more active role in decision-making, setting goals, and evaluating outcomes is often described as patient 'empowerment', and is associated with improved clinical outcomes.[209] Indeed, patient education and involvement in the management of VKA therapy has been shown to reduce the risk of major bleeding.[210] Thus, patient information should help to empower patients by being consistent and available in formats appropriate for all affected, including people with different native languages and different levels of literacy. However, inconsistencies in the level of education, socioeconomic factors, and local/national provision of services in Latin American countries, as well as other factors such as age and cognitive problems, may lead to inequalities in the uptake of patient information outputs. In Argentina, there are no differences in the uptake of patient information between males and females; however, for older patients, access to the Internet may be limited or non-existent, although printed material is still available to them. Moreover, patients from poorer backgrounds are less informed about their illness and healthcare options.

Patient 'empowerment' is associated with improved clinical outcomes

Provision of new therapeutic options

New strategies for AF treatment may also be helpful in reducing the prevalence of AF and, hence, AF-related stroke. Furthermore, the disadvantages – and resulting poor use – of current anticoagulant therapy have led to the search for new therapies and other strategies that can be used in the prevention of stroke in patients with AF. For example, new anticoagulant drugs that are easier to use and more convenient than VKAs are becoming available. These drugs have more predictable effects and a better safety profile, and thereby have the potential to increase adherence to therapy and improve outcomes for patients. A large multinational survey in collaboration with the patient organization AntiCoagulation Europe found that 68% of patients with chronic AF would be interested in new anticoagulation drugs for which routine monitoring was not needed.[211] Unfortunately, similar data for Latin American populations do not exist.

New anticoagulant drugs are becoming available that should increase adherence to therapy and improve clinical outcomes

Improved knowledge and awareness among healthcare professionals

Benefits of current treatments to prevent stroke

Poor adherence to guidelines may result from underestimation of the efficacy and/or overestimation of the risks of anticoagulation therapy. This highlights the urgent need for improved awareness among physicians of the efficacy of VKAs in preventing stroke in patients with AF. Physicians also need to be reassured that the risk of bleeding is usually small compared with the great benefits that therapy can bring.

Healthcare professionals should be convinced of the importance of communicating the benefits and risks of potential therapy to patients. Patients have a significant amount of information to absorb in one consultation with the physician. Therefore, written information needs to be provided, critical facts and advice repeated and the patient's full understanding confirmed during future consultations. In addition, communication between different

healthcare professionals interacting with the patient needs to be improved to ensure that consistent information and advice is provided. If the patient is overwhelmed by too much information and/or contradictory opinions, they are unlikely to agree to, and subsequently adhere to, therapy.

Healthcare professionals need to communicate, so as to provide consistent information and advice for patients

Management of patients receiving vitamin K antagonists

There is a clear need for a proper infrastructure for the delivery and monitoring of VKAs across all the countries of the Latin American region as well as for better education and support for physicians who manage patients receiving VKAs. Such patients may be managed by the physician who prescribed the therapy, a primary care provider or a dedicated anticoagulation service.[212] In surveys, physicians have reported that increased training and availability of consultant advice or guidelines specifically on managing anticoagulation therapy would increase their willingness to prescribe VKAs.[213] There is general agreement among both primary care physicians and specialists that anticoagulation therapy is best managed in primary rather than secondary care to ensure optimal access and continuity of care.[213] This may prove difficult in some Latin American countries because of the inconsistency in access to healthcare services, which is particularly noticeable in rural and impoverished areas where adequate infrastructure, drugs supply, and staff are lacking.[214]

Increased training and advice on managing anticoagulants would increase the willingness of physicians to prescribe VKAs

Anticoagulation clinics – a potential educational resource

Anticoagulation clinics may be in a hospital or attached to a primary care practice. At times, they have been considered the gold standard of VKA management,[212] helping to increase the time that a patient's INR values are within the target range, improve the overall cost-effectiveness of therapy, increase patient adherence and provide valuable information for both healthcare professionals and patients.[157,215] Anticoagulation clinics are widespread in America and Western Europe. Although anticoagulation clinics are available in some Latin American countries, access to them is variable. Anticoagulation clinics in Mexico are mainly found in the large academic hospitals in the big cities. In Argentina, there are many anticoagulation clinics, private and public. Similarly to Mexico, these clinics also tend to be found in the large cities. Anticoagulation clinics are uncommon in Brazil; however, access to these clinics is available through some academic institutions. Patients in these clinics often have the best INR monitoring available to them, and time within therapeutic range values can reach around 80%. In Uruguay, the majority of public and private hospitals have anticoagulation clinics. Where anticoagulation clinics are unavailable, alternatives have been made in order to provide anticoagulation monitoring services. For example, patients in Brazil who do not have access to anticoagulation clinics have their INR control monitored by their doctor. Where anticoagulation clinics are not available in Mexico, INR monitoring is often carried out by a qualified physician, usually a cardiologist. However, in rural areas in Mexico, anticoagulation therapy tends to be avoided because monitoring is not available. In smaller towns in Argentina, patients who were previously connected to a clinic can have their INR monitoring performed near to their home, with their results and details of their new dose available by phone or fax. Overall, the lack of availability of anticoagulation monitoring facilities for some patients in Latin America means that INR monitoring may be suboptimal, which can lead to reduced levels of anticoagulation control.

If patients are referred to an anticoagulation clinic, communication between all the healthcare professionals involved is crucial: delegation of one

part of the integrated care of a patient to an external clinic can weaken the relationship between the primary care physician and patient, and may lead to disruption of care if communication breaks down.[212] Therefore, healthcare providers may need education and support in ensuring a seamless transition between the different strands in the patient pathway. As management of patients receiving anticoagulants evolves, anticoagulation clinics will change and adapt.[212] The staff that run clinics may have an increasing role as educators and coordinators of anticoagulation therapy, providing support for other healthcare providers.

Healthcare providers may need education and support in ensuring a seamless transition between the different strands in the patient pathway

Awareness of treatment innovations

Novel anticoagulants currently in advanced stages of development may simplify the management of patients with AF. As with any chronic intervention, however, high-quality guidance and education for doctors, patients and their caregivers will be essential. Healthcare professionals will need to identify and manage eligible patients and know how to deal with emergency situations. Increased resources for education and rapid dissemination of information will allow faster introduction and uptake of new therapies.

Patient self-management and computer programs

Patient self-management, or self-testing, has been proposed to reduce the burden of regular INR monitoring. Increased involvement of the patient should improve adherence, and several studies have shown self-monitoring to be an effective and acceptable alternative to management at an anticoagulation clinic.[216,217] A Cochrane analysis of 18 clinical trials highlighted the benefits of patient self-monitoring and self-management in improving the quality of their oral anticoagulation therapy compared with standard monitoring.[218] Although no such data exist for Latin American populations, a study in Germany has also shown self-management to be cost-effective.[219] However, this approach may not be appropriate for all patients as shown in the Cochrane analysis in which self-testing could not be used for up to half of the patients requiring oral anticoagulation therapy.[218] Therefore, support from adequately trained physicians will be needed for self-management to be successful.[220]

Patient self-management of INR monitoring will need the initial support of adequately trained physicians

Computer programs that analyze several variables and recommend the level of adjustment of the VKA dose, if required, have been developed to assist in management. Such computer programs have been shown to perform as well as staff in anticoagulation clinics, and may therefore be a useful tool for optimizing care.[221,222] Here too, healthcare professionals will need specific training to enable them to adjust to these changes in practice, while still retaining an essential supervisory role.

Moves towards patient-centered care

Management of patients with AF is also likely to be greatly improved by a move to more patient-centered care. Various definitions of patient-centered care exist, but common elements include consideration of patients' needs, preferences, and concerns relating to overall health, rather than just to the specific condition in focus.[223] Although a patient-centered approach is widely advocated, it is not always implemented.[223] Instead, health care is typically centered on treating the disorder, rather than considering patients' individual needs.[223,224] There is evidence that anticlotting therapy tailored to patients' preferences is more cost-effective in terms of QALYs than giving the same therapy to every patient.[225] There is therefore a need to provide physicians with further education on the benefits of patient-centered care, with support in implementing this approach locally.

An optimized continuum of care

Continuity of care, involving continuing communication between healthcare providers, is essential for high-quality care. As the provision of health care often involves several different service providers, continuity of care is defined as 'coherent health care with a seamless transition over time between various providers in different settings'.[226]

Biem *et al.* have described seven characteristics (the seven Cs) of optimal continuity of care:[226]

1. Regular *contact* between patients and healthcare providers
2. *Collaboration* between healthcare professionals and patients in educating and "empowering" the patient
3. *Communication* between healthcare providers
4. *Coordination* of the multidisciplinary teams involved, with clear identification of different roles
5. *Contingency* plans in the form of access to healthcare professionals out of hours to answer questions and address concerns
6. *Convenience* – achieved, for example, by avoiding the need for patients to keep repeating information and by considering home monitoring
7. *Consistency* of the advice provided by different professionals and implementation of, and adherence to, clinical practice guidelines

The close monitoring required in patients receiving VKA therapy can be problematic in ensuring continuity of care. When patients are transferred to other healthcare providers or to different settings, such as during hospitalization or at discharge, critical information can be lost. Indeed, transferring patients at night time and at weekends has been reported to increase death rate.[227,228] Comprehensive, timely, and appropriate discharge information is essential – possibly in some portable format[229] – so that the primary care practice has all it needs for appropriate follow-up care. Insufficient discharge information can contribute to hospital readmission.[230] Education of caregivers also plays a key role in the success of therapy, and the availability of a healthcare provider to answer questions and address concerns is likely to improve continuity of care.

Educating physicians on the benefits of patient-centered care will improve the management of patients with AF

The implications of a breakdown in continuity of care are illustrated in the case study on the next page.

Equity of access to health care and information

Exchange of information – a benchmark for management

An example from another area of medicine illustrates how best practice can be exchanged between countries in a given region. For patients with multiple sclerosis (MS), the European Multiple Sclerosis Platform (EMSP) has been set up with the mission of exchanging and disseminating information on all issues relevant to people affected by the disease.[231] The way in which MS is managed varies across Europe; hence, the EMSP has set up an 'MS barometer' to record the experiences of patients with MS with regard to health care and quality of life, and to allow comparisons of these experiences across Europe. The aim is to identify which aspects of the disease are well managed and in which countries, as well as in what areas healthcare providers need to improve their policies and practices.

In addition to providing patients with information, an equivalent organization for AF could serve to collate and compare data from different countries in Latin America, potentially identifying successes and benchmarks for management and helping to drive improvements where necessary. It is hoped that the establishment of the Arrhythmia Alliance/Atrial Fibrillation Association in many Latin American

Comprehensive, timely discharge information is essential for appropriate primary care follow-up

Case study: the importance of continuity of care

A 75-year-old man with a history of diabetes, high blood pressure, and osteoarthritis presented with a cough at a rural healthcare center. Pneumonia and AF were subsequently diagnosed. He received oxygen, cefuroxime (for pneumonia), and digoxin (for AF) and was transferred to a regional care hospital.

In hospital, the patient was seen by a resident in the emergency room and by a senior medical student. After 1 day, he was transferred to a medical ward. His condition improved but the AF persisted. Warfarin therapy was initiated and a pharmacist provided information on the drug. The patient's wife, who managed all of his medications, was unable to travel to visit her husband in this hospital. He was later discharged after an INR measurement of 2.0, with a 1-week course of cefuroxime, and instructed to remain on metformin (for diabetes), enalapril (for high blood pressure), digoxin, and warfarin. He was also told to make an appointment with a physician for INR monitoring the next day.

A weekend locum physician received the discharge letter listing the diagnoses and medications but not the INR measurement. The repeat INR was 2.8. The patient was advised to stay on the same dose and see the family doctor on Monday for repeat INR testing.

At home, the patient took ibuprofen for osteoarthritis and some herbal pills. On Sunday evening, his wife became worried about bleeding after the glucose finger-stick test (used to monitor his diabetes). On Monday, when the patient saw the family doctor, his INR was 4.8. The patient was advised to take acetaminophen instead of ibuprofen, to stop taking the herbal pills and warfarin, and to have his INR tested the next day.

The patient found it difficult to travel to have his INR tested, because of arthritis. His wife thought he was on too many medications. At his next clinic appointment, he refused warfarin but agreed to start taking aspirin.

One year after the initial diagnosis of AF, the patient suffered a stroke which left him with weakness down his right side and speech impairment

Case study adapted from Biem *et al*. 2003[226]

countries will lead to the sharing of best practices, as well as educating and empowering patients and physicians.

An AF patients' platform would make it easier to collate data, identify successes, and drive improvements

Equal access for all

In addition to possible variations in literacy, education, income, and care across countries of the Latin American region, people of different backgrounds may have different access to health care, or their perceptions of the health care they receive may differ. Access to health care is an issue for many countries in the region – population groups most likely to face inequalities when accessing health care including the poor, those who live in rural areas, mothers, children, the elderly, groups at epidemiologic risk, and those from indigenous populations, which has been the case in countries such as Brazil, Costa Rica, Honduras, and Panama.[33] In a Brazilian study that sought to determine if healthcare for older community residents (≥60 years) was based on health-related criteria and not on other patient characteristics, investigators reported that the use of healthcare services did not differ by race, ethnicity, or religion, but that private healthcare insurance facilitated outpatient access and

increased education facilitated hospitalization.[232] Differences were also found as a function of age, sex, and employment status. Under any health system based on personal recognition of a health problem, those with education, a higher income, and better health insurance are more likely to access health care.

All patients have a basic right to equal access to quality medical treatment, regardless of where they live, their status or their income.

We call for equal and timely access to quality health care and better information for all patients

Collaborative approach to guideline development

The efficacy and tolerability of VKAs in the prevention of stroke in patients with AF are well established,[31] but several drawbacks can lead to poor adherence to guidelines, as discussed earlier.

Regular reviews, updates, and endorsement of the guidelines will ensure that these are relevant to current clinical practice and may thereby increase adherence.[53,233] Programs aimed at improving the implementation of existing guidelines into clinical practice would also be of benefit to Latin American countries. 'Get With The Guidelines-Stroke', carried out by the American Heart/Stroke Association, is an example of an initiative aimed at improving adherence to the latest scientific guidelines.[61] Mechanisms to implement a similar program for guidelines in AF should be explored. Furthermore, there is a rationale for providing standardized guidelines for the whole of Latin America, as too many different sets of guidelines can cause confusion and reduce adherence. Guidelines also need to be easy to follow and readily available to all relevant healthcare professionals.

Summary of current challenges

In summary, numerous challenges remain in the prevention of stroke in patients with AF in Latin America. The level and quality of information on AF provided to physicians and patients needs to be improved. Increased detection of AF by physicians is vital, and improved education is needed among patients and healthcare professionals on the benefit-to-risk profile of aspirin and VKAs, and on the optimum management of patients receiving VKAs. Healthcare professionals need to be aware of new anticoagulants and other therapeutic strategies that are emerging, as well as advances in the treatment of AF. It is also important to encourage patient empowerment and patient-centered care and ensure equity of access to health care for all. Finally, improved implementation of, and adherence to, guidelines, development of new guidelines, and implementation of strategies to ensure effective communication between healthcare professionals will improve patient management, as will optimizing the continuum of care. All these factors will contribute to the prevention of stroke in patients with AF.

Regular reviews, updates and endorsement of the guidelines will ensure that they are relevant to current clinical practice

New developments for stroke prevention in patients with atrial fibrillation

Key points

- New anticoagulants in development aim to offer reliable efficacy and tolerability, with the benefit of simplified dosing and no need for frequent monitoring or dose adjustment
- Several new oral anticoagulants directly target key steps in the clotting pathway
- Four oral anticoagulants are in phase III development or have been recently licensed for use in the prevention of stroke in AF
- New antiplatelet agents and drugs for stabilizing heart rhythm are also either in advanced stages of development or have also been approved
- Non-pharmacologic methods for managing abnormal heart rhythm exist, and research is ongoing in this area
- Surgical procedures are being developed to reduce the risk of clots reaching the brain

New anticoagulants are needed that offer reliable efficacy and tolerability, with simplified dosing and no need for frequent monitoring or dose adjustment

Limitations of VKAs and aspirin restrict their use and effectiveness in the prevention of stroke in patients with AF (see chapter on 'Stroke prevention in patients with atrial fibrillation', page 39). These limitations have led to an ongoing search for alternative effective and convenient therapies. In addition, there have been developments in antiarrhythmic drugs used to treat AF. These developments are discussed in more detail in this chapter.

Anticoagulant agents

The characteristics of an ideal anticoagulant for long-term use in a chronic condition such as AF include:[234]

- Effectiveness
- A good safety profile in a wide range of patients, including the elderly
- A low tendency to interact with food and other drugs
- No requirement for regular monitoring
- Oral administration
- Administration of fixed doses without the need for dose adjustment

New oral anticoagulants are in advanced stages of clinical development

VKAs are taken orally but interact with many foods and drugs, have a narrow therapeutic window and require frequent dose adjustment and monitoring, which is often not carried out in practice. They therefore meet few of the criteria for an ideal therapy for stroke prevention in patients with AF.

The search for new anticoagulants has therefore focused on compounds that meet more of the criteria for an ideal anticoagulant. Several new oral anticoagulants are in development: relevant phase III trials (large, late-stage studies) of these drugs – either published or listed on the global clinical trials registry, www.clinicaltrials.gov – are shown in Appendix 2 (page 82). In the coagulation pathway (Figure 10, page 40) there are many potential targets for new anticoagulant agents. The agents that are currently most advanced in their development target single proteins in the coagulation pathway (Factor Xa and thrombin).[234] Those agents that are in phase III development or have been recently licensed are discussed in this chapter.

Oral direct Factor Xa inhibitors

Factor Xa is the primary site for amplification in the coagulation pathway.[235] Inhibition of Factor Xa achieves effective anticoagulation by inhibiting thrombin generation, while allowing the vital functions of existing thrombin to continue, thus potentially maintaining hemostasis at sites of hemostatic challenge.[235] Oral direct inhibitors of Factor Xa include rivaroxaban, apixaban, and edoxaban. Rivaroxaban and apixaban are both licensed for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Rivaroxaban is approved for this indication in more than 100 countries worldwide. Edoxaban is approved in Japan for the prevention of VTE in patients undergoing total knee arthroplasty, total hip arthroplasty, and hip fracture surgery. A press release stated that rivaroxaban has been submitted for EU marketing authorization in stroke prevention in patients with AF, as well as for the treatment of deep vein thrombosis and the prevention of recurrent deep vein thrombosis and pulmonary embolism.[236] Unlike VKAs, rivaroxaban does not require routine coagulation monitoring. Studies of other oral direct Factor Xa inhibitors are underway in different indications, including stroke prevention in patients with AF.

Rivaroxaban

ROCKET AF was a randomized, double-blind phase III study that compared the efficacy and safety of once-daily rivaroxaban (20 mg, or 15 mg for patients with moderate renal impairment) with dose-adjusted warfarin for the prevention of stroke in 14 264 patients with AF. Results from this trial were recently reported at AHA.[237]

Rivaroxaban was superior to warfarin for the primary efficacy endpoint, showing a 21% relative risk reduction (RRR) for stroke and non-CNS systemic embolism in the prespecified on-treatment population (1.7% vs 2.2%, respectively, p=0.015). Additionally, in the intent-to-treat population, which followed all patients randomized in the trial until its completion, whether or not they completed the full course of therapy or switched to other options, rivaroxaban showed comparable benefits to warfarin (2.1% vs 2.4%, p<0.001 for non-inferiority). This result indicates that the treatment benefits compared with warfarin were sustained as long as the patients received rivaroxaban.

Oral direct Factor Xa inhibitors act at a pivotal point in the coagulation pathway to inhibit thrombin generation

For the principal safety measure, rivaroxaban showed similar rates of major and non-major clinically relevant bleeding events, compared with warfarin (14.9% vs 14.5%, p=0.442). Rates of major bleeding were also comparable between rivaroxaban and warfarin (3.6% vs 3.5%, p=0.576). Patients treated with rivaroxaban had fewer intracranial hemorrhages (0.5% vs 0.7%, p=0.019), critical organ bleeding events (0.8% vs 1.2%, p=0.007), and bleeding-related deaths (0.2% vs 0.5%, p=0.003) compared with those treated with warfarin, but showed increased rates of hemoglobin/hematocrit drop (2.8% vs 2.3%, p=0.019) and transfusions (1.7% vs 1.3%, p=0.044), compared with warfarin.

Rivaroxaban-treated patients also had numerically fewer myocardial infarctions (0.9% vs 1.1%, p=0.121), and an observed reduction in rates of all-cause mortality compared with warfarin (1.9% vs 2.2%, p=0.073), though these results were not statistically significantly different.

Apixaban

Phase II studies of apixaban for the prevention of VTE and treatment of symptomatic deep vein thrombosis have been completed,[238,239] and help serve as dose-finding studies for phase III trials of stroke prevention in patients with AF. ARISTOTLE, a randomized, double-blind phase III study, is evaluating the efficacy and safety of apixaban 5 mg twice daily

compared with warfarin for stroke prevention in patients with AF.[240] Results from ARISTOTLE will be presented at the ESC 2011 meeting. Another phase III study (AVERROES) investigated whether apixaban was more effective than aspirin in preventing stroke in patients with AF who had failed or were unsuitable for VKA therapy (Appendix 2, page 82).[167] Apixaban was shown to reduce the risk of stroke or systemic embolism compared with aspirin with no significantly increased risk of major hemorrhage.[166]

Several other anticoagulants are in development

Edoxaban (DU-176b)

Phase II studies have compared the Factor Xa inhibitor edoxaban with warfarin in patients with AF; early results indicate that patients receiving 30 mg or 60 mg once-daily doses of edoxaban had a similar incidence of bleeding to those assigned to warfarin.[241] A phase III study (ENGAGE-AF TIMI 48) has also been initiated to demonstrate the safety and efficacy profile of two doses of edoxaban vs warfarin.[242] Results are expected in March 2012.[243]

Indirect Factor Xa inhibitors

Biotinylated idraparinux is an indirect inhibitor of Factor Xa that acts via antithrombin. Unlike the direct Factor Xa inhibitors in development, biotinylated idraparinux must be administered by subcutaneous injection.[234] A phase III study (BOREALIS-AF) was evaluating whether biotinylated idraparinux, administered subcutaneously once a week, was at least as effective as warfarin for the prevention of stroke and systemic thromboembolic events in patients with AF; however, the trial was discontinued early because of a strategic decision by the sponsor rather than due to any safety concern.[244]

Antiplatelet agents reduce the risk of blood clots forming by inhibiting aggregation of platelets

Oral direct thrombin inhibitors

Dabigatran etexilate is an oral direct thrombin inhibitor. This class of drug blocks the conversion of fibrinogen to fibrin in the coagulation pathway. Dabigatran has been approved in 83 countries for the primary prevention of VTEs in adults who have undergone elective total hip or elective total knee replacement surgery. Dabigatran is approved in at least 14 countries, including the US, Canada, and Japan for stroke risk reduction in patients with AF. Approval was based on RE-LY, a phase III randomized, non-inferiority study, which compared the efficacy and safety of dabigatran at doses of 110 mg or 150 mg twice daily with dose-adjusted warfarin (INR 2.0–3.0) for the prevention of stroke in patients with AF. RE-LY was a blinded study with regards to the dabigatran dose given, and open label with regards to warfarin. Approximately 18 000 patients with AF and at risk of stroke were enrolled in this study and followed up for a median of 2 years.

At a dose of 110 mg twice daily, dabigatran was associated with a similar rate of stroke and systemic embolism to dose-adjusted warfarin (1.53% vs 1.69%, respectively) and a significantly lower rate of major bleeding than warfarin (2.71% vs 3.36%, respectively, p=0.003).[245] At the higher dose of dabigatran (150 mg twice daily), the rate of stroke and systemic embolism was significantly lower than with warfarin (1.11% vs 1.69%, respectively, p<0.001) but the rate of major bleeding was similar to that associated with warfarin (3.11% vs 3.36%, respectively, p=0.31). The rate of intracranial bleeding was significantly lower with both dabigatran doses (110 mg, 0.23%; 150 mg, 0.30%) compared with warfarin (0.74%, p<0.001 for both comparisons).

There were higher rates of myocardial infarction with dabigatran (110 mg, 0.72% [p=0.07 vs warfarin]; 150 mg 0.74% [p=0.048 vs warfarin]) compared with warfarin (0.53%).[245] After the identification of several additional primary efficacy and safety outcome events during routine clinical site closure visits, a post hoc analysis of the RE-LY study was carried out.[246] This involved checking all primary and

secondary efficacy and safety data for consistency and re-evaluating the study database for possible underreporting of events. This analysis led to the identification of 32 new myocardial infarction events (4 clinical and 28 silent myocardial infarctions). Although observed myocardial infarction rates were higher with both dabigatran doses, the statistical significance previously seen with the higher dose was no longer evident.

Rates of dyspepsia were significantly higher with both dabigatran doses (110 mg, 11.8%; 150 mg, 11.3%) compared with warfarin (5.8%, $p<0.001$ for both comparisons).[245] Further studies of dabigatran and other direct thrombin inhibitors are ongoing.[247,248]

Other anticoagulants

There are several other oral anticoagulants in earlier stages of development for stroke prevention in AF. Agents that have been studied in phase II trials include the direct thrombin inhibitor AZD0837, the indirect thrombin inhibitor odiparcil, and the direct Factor Xa inhibitors YM150 and betrixaban.[248–252]

Antiplatelet agents

Clopidogrel is an inhibitor of platelet aggregation. Reduced platelet aggregation reduces the risk of a blood clot forming and helps to prevent another heart attack or stroke. Clopidogrel is currently indicated for the prevention of atherothrombotic events in patients suffering from heart attack, ischemic stroke, or established peripheral arterial disease and in patients suffering from acute coronary syndrome. Studies have assessed the efficacy and safety of clopidogrel for stroke prevention in patients with AF. The ACTIVE-A trial investigated the effects of clopidogrel in combination with aspirin for the prevention of stroke in patients who had an increased risk of stroke and for whom VKA therapy was unsuitable.[253] This study showed that, compared with aspirin and placebo, clopidogrel in combination with aspirin significantly reduced the risk of stroke in patients with AF but was also associated with a significantly greater rate of major bleeding.

Other antiplatelet agents are in phase III clinical trials (ticagrelor) or have recently been approved for clinical use (prasugrel).[254] However, there are no data on the use of these drugs for the prevention of stroke in patients with AF.

Other pharmaceutical agents

The efficacy and safety of agents in other classes, such as thromboxane receptor antagonists (e.g. NCX-4016 and S18886), platelet adhesion antagonists, and thrombin receptor antagonists (e.g. vorapaxar), are being evaluated in phase I and II trials.[254]

Alternative strategies in development

Current strategies are focused on reducing thromboembolic risk with drugs that target the process of clot formation. However, other strategies are emerging for stroke prevention in patients with AF. These include: management of AF itself through the use of drugs to control heart rhythm and/or rate; non-pharmacologic methods that control rhythm and/or rate or prevent blood clots reaching the brain; and surgical interventions to reduce thromboembolic risk.[17]

New pharmacological methods for restoring normal heart rhythm

AF itself can be managed using 'rhythm control' or 'rate control' strategies. In rhythm control, drugs are used to maintain the sinus rhythm of the heart; in rate control, drugs are used to maintain a steady heart rate. Examples of drugs used for rhythm or rate control include amiodarone, digoxin, and β-blockers.

New drugs to treat AF by stabilizing heart rhythm or heart rate are in advanced stages of development

Dronedarone is a new antiarrhythmic drug that is licensed for maintaining normal heart rhythms in patients with a history of AF or atrial flutter in the US, and for use in clinically stable adult patients with a history of, or current, non-permanent AF to prevent recurrence of AF, or to lower ventricular rate in the UK. In a phase III study of 4628 patients with AF (the ATHENA study), dronedarone was shown to reduce the incidence of death or hospitalization due to cardiovascular events compared with placebo.[255] In a post hoc analysis of the ATHENA data, dronedarone administered over a follow-up period averaging 21 months was also associated with a reduced risk of stroke compared with placebo, particularly in patients with multiple risk factors for stroke.[256] Rare but severe cases of hepatic injury have been reported with the use of dronedarone.[257]

Research into non-pharmacologic methods for managing abnormal heart rhythm is also ongoing

Non-pharmacologic methods

Non-pharmacologic interventions for stroke prevention in AF concentrate on eliminating the AF itself or stopping potentially harmful blood clots reaching the brain.

Non-pharmacologic management of abnormal heart rhythm

There are numerous non-pharmacologic methods for the management of abnormal heart rhythm.[17] These include:

- Electrical cardioversion (the process by which an abnormally fast heart rate or disturbance in heart rhythm is terminated by the delivery of an electric current to the heart at a specific moment in the heart cycle)
- Catheter ablation (an invasive procedure used to remove a faulty electrical pathway from the heart)
- Surgical procedures (open-heart surgery or minimally invasive procedures that also serve to remove the faulty electrical pathways from the heart)
- Installation of a device into the wall of the left atrial appendage of the heart (a procedure aimed at closing/occluding the left atrial appendage)

Surgical procedures are being developed to reduce the risk of blood clots traveling from the heart to the brain

Existing data suggest that catheter ablation is more effective than antiarrhythmic drug therapy in maintaining normal heart rhythm.[258] Whether this intervention results in fewer AF-related strokes requires testing in clinical trials. The efficacy of surgery versus antiarrhythmic drug therapy has yet to be assessed in clinical trials.

Surgical interventions to reduce thromboembolic risk

In patients with non-valvular AF, more than 90% of blood clots form in the left atrial appendage (part of the left atrium).[17] Closing the left atrial appendage may therefore be an effective way to reduce the risk of blood clots and stroke. Several new occlusion devices have been developed that allow the left atrial appendage to be blocked off. Such devices are designed to be placed permanently just behind, or at the opening of, the left atrial appendage. Once in place, they should prevent any blood clots of a harmful size from entering the bloodstream and ultimately causing stroke.[259,260] In Latin America, occlusion devices are used in Argentina, Brazil, Chile, and Venezuela. The results of a recently published trial showed that the efficacy of percutaneous closure of the left atrial appendage with an occlusion device was non-inferior to that of warfarin therapy. Although there was a higher rate of adverse events in the intervention group compared with warfarin, the authors concluded that closure of the left atrial appendage might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with AF.[261]

Next steps

To summarize, there are several pharmacologic agents that have been developed for use in patients with AF, including the new oral anticoagulants rivaroxaban, dabigatran, apixaban, and edoxaban. Non-pharmacologic

approaches to the management of arrhythmia and surgical interventions to reduce thromboembolic risk are also being developed.

Valuable insights into the impact of these new therapies on the prevention of stroke in patients with AF can be gained from registries. A number of registries of AF patients are in existence in Latin America, some of which are country specific.

The Board of Electrophysiology and Arrhythmias of the South American Society of Cardiology is currently conducting a registry on the prevalence of AF in the cardiology consultation in South America (REFASUD).[262] The REFASUD is an online-based registry that consists of a questionnaire that physicians complete over a given period (2–4 weeks) for each patient with AF that they encounter. The questionnaire consists of demographic data, types of fibrillation, underlying heart disease, and treatment strategies undertaken.[262] The study will offer a valuable insight into the epidemiology of AF in South America in order to improve intervention strategies for patients with AF.

The First National Registry of Chronic Atrial Fibrillation of Argentina included 945 consecutive patients with chronic AF; of these, 615 were followed up at 2 years.[156] The mortality rate was high, and the lowest survival rate was associated with older age, left ventricular dysfunction, and lack of anticoagulation at admission.

A new global registry of a different magnitude has now been established with a truly international reach. The Global Anticoagulant Registry in the FIELD (GARFIELD) is prospectively following 50 000 patients newly diagnosed with AF and 5000 patients with previously diagnosed AF – all eligible for long-term anticoagulant therapy – over 6 years.[263] Patients are being included and followed, regardless of whether or not they receive appropriate therapy. The GARFIELD registry is documenting details such as the risk factors, treatment patterns and clinical events associated with AF, and will provide a picture of the real-life global burden of the condition. In addition, it will show how the new advances in therapy, particularly new anticoagulants, can contribute to the prevention of stroke in patients with AF.[264]

In addition, a number of hospital-based stroke registries exist.[265] The Luis Vernaza Hospital Stroke registry in Ecuador included 500 Hispanic patients with a first stroke. Results from the registry suggest that the pattern of stroke is different in Hispanics compared with other ethnic groups; the prevalence of cerebral hemorrhage is 2–3 times higher in Hispanics than in whites but is similar to that observed in Chinese.[266]

It is hoped that the availability of new therapy options, together with a greater understanding of their impact on the burden of stroke, will pave the way for better management of patients with AF.

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Appendix 1

Summary of guidelines for the prevention of stroke in patients with atrial fibrillation

Risk category	Recommendation
Internationally used AF guidelines	
European Society of Cardiology (ESC) – Management of atrial fibrillation guideline 2010[62]	
All patients with AF	• Administration of antithrombotic therapy should be based on the presence (or absence) of risk factors for stroke and thromboembolism
Patients with AF and one major risk factor[a] or ≥2 clinically relevant non-major risk factors[b]	• Administer an oral anticoagulant, such as a VKA (target INR 2.5; range 2.0–3.0)
Patients with AF and one clinically relevant non-major risk factor[b]	• Administer either an oral anticoagulant, such as a VKA (target INR 2.5; range 2.0–3.0) or aspirin (75–325 mg/day). However, an oral anticoagulant is preferred over aspirin
Patients with AF and no risk factors	• Administer either aspirin (75–325 mg/day) or no antithrombotic therapy. However, no antithrombotic therapy is preferred over aspirin
Patients with AF in whom oral anticoagulation is appropriate therapy: • Patients at low risk of bleeding (HAS-BLED score 0–2) • Patients with a measureable risk of bleeding (HAS-BLED score ≥3) • Patients with one clinically relevant non-major risk factor[b]	• Dabigatran may be considered as an alternative to dose-adjusted VKA therapy: – Dabigatran 150 mg twice daily – Dabigatran 110 mg twice daily – Dabigatran 110 mg twice daily
American College of Cardiology Foundation, American Heart Association, and Heart Rhythm Society (ACCF/AHA/HRS) – Focused update on the management of patients with atrial fibrillation (updating the 2006 guideline), 2011[63]	
All patients with AF or atrial flutter, except those with lone AF or contraindications	• Antithrombotic therapy is recommended to prevent thromboembolism • Selection of antithrombotic agent should be based on absolute risks of stroke and bleeding and the relative risk and benefit for a given patient
Patients without mechanical heart valves at high risk of stroke (i.e. prior thromboembolism [stroke, TIA, or systemic embolism] and rheumatic mitral stenosis)	• Chronic oral anticoagulant therapy with a dose-adjusted VKA (INR 2.0–3.0) unless contraindicated. INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable
Patients with >1 moderate risk factor (age ≥75 years, hypertension, heart failure, impaired left ventricular systolic function [ejection fraction ≤35% or fractional shortening <25%], or diabetes mellitus)	• VKA is recommended
Low-risk patients or in those with contraindications to oral anticoagulation	• Aspirin 81–325 mg/day is recommended as an alternative to VKAs
Patients with AF who have mechanical heart valves	• Target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR of at least 2.5
For primary prevention of thromboembolism in patients with non-valvular AF who have just one validated risk factor (age ≥75 years [especially in female patients], hypertension, heart failure, impaired left ventricular function, or diabetes mellitus)	• Antithrombotic therapy with either aspirin or a VKA is reasonable, based upon an assessment of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences
For patients with non-valvular AF who have ≥1 less-well-validated risk factor (age 65–74 years, female gender, or coronary artery disease)	Antithrombotic therapy with either aspirin or a VKA is reasonable. The choice of agent should be based upon the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences

continued

Risk category	Recommendation
Latin American country-specific AF guidelines	
Argentine Society of Cardiology (Sociedad Argentina De Cardiología [SAC]) – consensus on atrial fibrillation, 2005[65]	
All patients with AF	• Administration of antithrombotic agent should be based on the absolute risks of cerebrovascular accident or hemorrhage and the relative risk and benefit for each patient
Patients with non-valvular AF who are aged <60 years (except for lone AF)	• Administer oral anticoagulation or aspirin
Patients with a high risk of cerebrovascular accident	• Administer dose-adjusted warfarin (INR 2.0–3.0) unless contraindicated. Assess the need for oral anticoagulation regularly
Patients with a low risk of stroke or strong contraindications for oral anticoagulants	• Aspirin 325 mg/day suggested as an alternative
Patients with AF with mitral valve disease or mechanical or biologic heart valve prosthesis	• Administer oral anticoagulant (INR 2.0–3.0)
Patients with persistent, permanent, or paroxysmal AF	• Administer antithrombotic therapy with the same criteria for each type of AF
Patients with atrial flutter	• Give the same anticoagulation therapy as for patients with AF with similar risk factors
Patients with AF who are aged >75 years with a high risk of hemorrhage and without a clear contraindication for oral anticoagulation	• Maintain INR close to 2.0 for prevention of thromboembolism
Patients with AF and without a prosthetic heart valve	• Interrupt oral anticoagulation for a week for surgery or diagnostic procedures, because of the risk of bleeding, without substituting with heparin • In high-risk elective patients for whom oral anticoagulation is to be discontinued, or discontinued for more than 1 week, administer unfractionated heparin or low molecular weight heparin
Patients with AF who are aged <60 years without heart disease or embolic risk factors	• Administration of aspirin is optional
Patients with AF duration >48 hours or unknown: Before cardioversion After successful cardioversion	 • Maintain on oral anticoagulation for 3 weeks • Maintain on oral anticoagulation (INR >2.0) for 4 weeks
Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia [SBC]) – Brazilian guidelines on atrial fibrillation, 2009[20]	
Patients with AF but no contraindications	• Antithrombotic therapy (INR 2.0–3.0) for an unspecified period of time
Patients requiring secondary stroke prevention for cerebrovascular accident, TIA, prior systemic embolization	• Administration of VKA (INR >2.5)
Patients with rheumatic mitral stenosis or metallic prosthetic valve	• Administration of VKA (INR >2.5)
Patients with AF and ≥2 risk factors (age ≥75 years, hypertension, cardiac insufficiency, LVEF ≤35%, or diabetes mellitus)	• Give VKA, or aspirin (81–325 mg/day) when this is contraindicated
Patients with AF who have anticoagulation interruption due, for example, to surgical procedures with a high risk of hemorrhaging	• Administer heparin, preferentially of low molecular weight
Patients with AF, no valvulopathy, and only one risk factor (age ≥75 years, hypertension, cardiac insufficiency, LVEF ≤35%, or diabetes mellitus)	• Give VKA or aspirin (81–325 mg/day)
Patients with AF, no valvulopathy and ≥1 risk factor (age 60–74 years, female, or coronary artery disease)	• Give VKA or aspirin (81–325 mg/day)

continued

Risk category	Recommendation
Patients with AF who are aged <60 years and have no heart disease or risk of thromboembolic events	• Give aspirin (81–325 mg/day)
Patients with AF duration ≥48 hours or unknown:	
Before cardioversion	• Maintain on oral anticoagulation (INR 2.0–3.0) for 3 weeks
After successful cardioversion	• Maintain on oral anticoagulation (INR 2.0–3.0) for 4 weeks
Patients with AF with metallic valve prosthetics	• Patients must maintain an INR >2.5
Mexican National Center for Health Technology Excellence (Centro Nacional de Excelencia Tecnológica en Salud [CENETEC])– diagnosis and treatment of atrial fibrillation, 2009[64]	
Patients with AF with a low risk of stroke ($CHADS_2$ score 0) with lone AF	• Administer aspirin
Patients with AF who are aged <75 years with a moderate risk of stroke ($CHADS_2$ score 1)	• Administer aspirin or coumarin-derived agents as anticoagulant (maintain INR 2.0–3.0)
Patients with AF who are aged >75 years with a moderate risk of stroke ($CHADS_2$ score 1)	• Administer aspirin or coumarin-derived agents as anticoagulant (maintain INR 1.6–2.5)
Patients with AF who are aged <75 years with a moderate risk of stroke ($CHADS_2$ score 2)	• Administer coumarin-derived agents as anticoagulant (maintain INR 2.0–3.0)
Patients with AF who are aged >75 years with a moderate risk of stroke ($CHADS_2$ score 2)	• Administer coumarin-derived agents as anticoagulant (maintain INR 1.6–2.5)
Patients with AF at high risk of stroke ($CHADS_2$ score >2), patients with valvular heart disease, and patients with hypertrophic cardiomyopathy	• Administer coumarin-derived agent as anticoagulant (maintain INR 2.5–3.5)
Patients with AF at high risk undergoing hemodynamic or surgical intervention	• Treat with intravenous unfractionated heparin or low molecular weight heparin, preoperatively and postoperatively

[a]Prior stroke, TIA, or thromboembolism, older age (≥75 years), and valvular heart disease, including mitral stenosis.

[b]Heart failure (LVEF ≤40%), hypertension, diabetes, female sex, age 65–74 years, and vascular disease (specifically myocardial infarction, complex aortic plaque, and peripheral arterial disease).

AF, atrial fibrillation; INR, international normalized ratio; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; VKA, vitamin K antagonist.

Appendix 2

Phase III studies of new pharmaceutical agents for stroke prevention in atrial fibrillation

Data obtained from searching www.clinicaltrials.gov using the term 'stroke prevention atrial fibrillation' (last accessed June 2011). In total, 72 studies were obtained with this search term; 26 of these are phase III studies, and those relevant to new agents or methods of stroke prevention in patients with AF are listed.

Drug or intervention	Study acronym	Study title (ClinicalTrials.gov identifier)	Estimated completion date
Oral direct thrombin inhibitor			
Dabigatran etexilate	RE-LY	Randomized Evaluation of Long-term anticoagulant therapY (RELY) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open-label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multicenter, parallel-group, non-inferiority trial (NCT00262600)	**Completed and published:** Connolly SJ *et al. N Engl J Med* 2009;361:1139–51 **Update published:** Connolly SJ *et al. N Engl J Med* 2010;363:1875–6
Direct Factor Xa inhibitors			
Apixaban	ARISTOTLE	A phase III, active (warfarin) controlled, randomized, double-blind, parallel arm study to evaluate efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with non-valvular atrial fibrillation (NCT00412984)	**April 2011** http://clinicaltrials.gov/ct2/show/NCT00412984
	AVERROES	Apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment: a randomized double-blind trial (NCT00496769)	**Published:** Connolly SJ *et al. N Engl J Med* 2011;364:806–17
Rivaroxaban	ROCKET AF	A prospective, randomized, double-blind, double-dummy, parallel-group, multicenter, event-driven, non-inferiority study comparing the efficacy and safety of once-daily oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and non-central nervous system systemic embolism in subjects with non-valvular atrial fibrillation (NCT00403767)	**Completed:** Results presented at the AHA scientific sessions: 12–16 November 2010
Edoxaban	ENGAGE-AF TIMI-48	A phase III, randomized, double-blind, double-dummy, parallel-group, multicenter, multinational study for evaluation of efficacy and safety of edoxaban versus warfarin in subjects with atrial fibrillation – effective anticoagulation with Factor Xa next generation in atrial fibrillation **(ENGAGE-AF TIMI-48)** (NCT00781391)	**March 2012** http://www.clinicaltrials.gov/ct2/show/NCT00781391
Antiplatelet agents			
Clopidogrel	ACTIVE A	A parallel randomized controlled evaluation of clopidogrel plus aspirin, with factorial evaluation of irbesartan, for the prevention of vascular events, in patients with atrial fibrillation (NCT00249873)	**Published:** Connolly SJ *et al. N Engl J Med* 2009;360:2066–78
	ACTIVE I	A parallel randomized controlled evaluation of clopidogrel plus aspirin, with factorial evaluation of irbesartan, for the prevention of vascular events, in patients with atrial fibrillation (NCT00249795)	**Published:** Yusuf S *et al. N Engl J Med* 2011;364:928–38
	ACTIVE W	A parallel randomized controlled evaluation of clopidogrel plus aspirin, with factorial evaluation of irbesartan, for the prevention of vascular events, in patients with atrial fibrillation (NCT00243178)	**Published:** Connolly S *et al. Lancet* 2006;367:1903–12

Glossary

1 billion	1000 million
Anticoagulant	A type of drug that reduces the ability of the blood to clot by inhibiting any step in the coagulation pathway, thereby resulting in impaired formation of fibrin (the end result of the clotting pathway)
Antiplatelet agent	A type of drug that inhibits the formation of blood clots by inhibiting activation of blood platelets
Antithrombotic therapy	Any therapy that interferes with the formation of blood clots (thrombi)
Asymptomatic	Showing or causing no symptoms
Atherothrombotic event	An ischemic event triggered by platelet activation following disruption of plaque or fatty deposits in the arteries
Atrial fibrillation	A heart rhythm abnormality, characterized by rapid, disorganized electrical signals, which cause the atria to contract quickly, irregularly (known as fibrillation), and inefficiently
Cardioembolic stroke	A stroke caused by a blood clot originating in the heart
Cardioversion	The process by which an abnormally fast heart rate or disturbance in heart rhythm is terminated by the delivery of an electric current to the heart at a specific moment in the heart cycle (electrical cardioversion) or injection of anti-arrhythmic agents (pharmacologic cardioversion)
Coagulation	The process by which a blood clot is formed; essential for the arrest of bleeding
Coagulation pathway	The pathway of chemical reactions that results in the formation of a blood clot
Direct thrombin inhibitor	A class of anticoagulants that act by binding directly to thrombin and blocking interaction with its substrate fibrinogen, thus inhibiting the generation of fibrin and clot formation
Embolize	The process of forming an embolus
Embolus/embolism	A blood clot, air bubble, piece of fatty deposit, or other object that has been carried in the bloodstream, which lodges in a vessel and impedes the circulation
Epidemiology	The study of the occurrence and distribution of disease
Factor Xa inhibitor	A class of anticoagulants that inhibit Factor Xa in the coagulation cascade either by binding directly to Factor Xa, or indirectly through antithrombin. Inhibition of Factor Xa reduces the production of thrombin
Fibrinogen	A soluble plasma protein. In the final phase of the coagulation process, thrombin converts fibrinogen to insoluble fibrin, which polymerizes and forms the fibrous network base of a clot
Hemorrhagic stroke	A stroke caused by leakage from a blood vessel in the brain
Heart attack	An ischemic event in a section of heart after interruption of its blood supply (also known as myocardial infarction)
Incidence	The number of new cases of a disease or condition in a population over a given period of time
International normalized ratio (INR)	Prothrombin time test results vary according to the activity of the thromboplastin used. The INR conversion normalizes results for any thromboplastin preparation but is valid only with vitamin K antagonists
Ischemic stroke	Stroke caused by a blood clot or embolus blocking a blood vessel in the brain

Morbidity	The state of having a disease; ill health
Platelet	A very small, disc-shaped component of the blood that forms a significant part of a blood clot, particularly in the arteries
Prevalence	The total number of cases of a disease or condition in a population at any given time
Prothrombin time	The prothrombin time measures clotting time in the presence of tissue factor (thromboplastin). It is used to assess the overall functioning of the extrinsic and common pathways
QALY (quality-adjusted life-year)	A measure that represents the composite of several outcomes affecting quality of life; 1 year in perfect health is considered to be equal to 1.0 QALY; 1 year in less than perfect health would have a QALY <1
Stroke	A condition caused by disruption of the blood supply to part of the brain, or leaking of blood from a blood vessel into the brain, which may result in damage or death of brain cells
Subarachnoid hemorrhage	Bleeding between the surface of the brain and the skull
Therapeutic range	The interval between the lowest dose of a drug that is sufficient for clinical effectiveness and the higher dose at which adverse events or toxicity become unacceptable
Thrombin	Thrombin (Factor IIa) is the terminal enzyme of the coagulation cascade and converts fibrinogen into fibrin, which forms clot fibers. Thrombin also activates several other coagulation factors, in addition to protein C
Thromboembolism	The process by which a blood clot becomes detached from its place of formation and circulates in the blood
Thrombolytic	Having the ability to break up a blood clot
Thrombus	A blood clot
Transient ischemic attack	A brief disruption of the blood supply to part of the brain
Vitamin K antagonist	A class of compounds that inhibit the vitamin K-dependent formation of specific coagulation factors. This results in decreased levels of the affected coagulation factors, leading to anticoagulation
Warfarin	A vitamin K antagonist that is currently the most commonly used oral anticoagulant

Abbreviations

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
AF	Atrial fibrillation
AHA	American Heart Association
$CHADS_2$	Congestive heart failure; Hypertension; Age >75 years; Diabetes; Stroke or transient ischemic attack (a system for scoring risk factors for stroke, assigning 1 point each to C, H, A and D, and 2 points to S)
CHA_2DS_2-VASc	Congestive heart failure or left ventricular dysfunction; Hypertension; Age ≥75 years; Diabetes; Stroke, TIA, or thromboembolism; Vascular disease; Age 65–74 years; Sex category female (a system for scoring risk factors for stroke, assigning 1 point each to C, H, D, V, A, Sc, and 2 points to A, S)
CT	Computed tomography
CV	Cardiovascular
ECG	Electrocardiogram
EMSP	European Multiple Sclerosis Platform
ESC	European Society of Cardiology
HAS-BLED	Hypertension (uncontrolled, >160 mmHg systolic); Abnormal renal/liver function; Stroke (previous history, particularly lacunar); Bleeding history or predisposition (e.g. anemia); Labile INR (unstable/high INRs or in therapeutic range <60% of time); Elderly (>65 years); Drugs/alcohol (concomitant use of drugs such as antiplatelet agents and non-steroidal anti-inflammatory drugs or alcohol) (a system for scoring risk factors for bleeding, assigning 1 point each)
HRS	Heart Rhythm Society
INR	International normalized ratio
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MS	Multiple sclerosis
PAHO	Pan American Health Organization
QALY	Quality-adjusted life-year
STEPS	Stepwise Approach to Risk-Factor (RF) Surveillance
TIA	Transient ischemic attack
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WHO	World Health Organization

Every year hundreds of thousands of people in Latin America experience a stroke, and the number of strokes per year is predicted to rise dramatically as the population ages. This is an epidemic already beginning to happen, and prompt action is required to avoid a crisis.

Many of these patients die from stroke; others are left with severe disabilities, which devastate not only their lives but also the lives of their families and caregivers. Unsurprisingly, the economic implications of stroke are huge for both individuals and healthcare systems.

Atrial fibrillation (AF) – the most common sustained abnormality of heart rhythm – affects millions of people in Latin America. For example, in Brazil, it has been estimated that there are approximately 1.5 million patients living with AF. Individuals with AF are at a fivefold increased risk of stroke compared with the general population. Furthermore, strokes related to AF are more severe, have poorer outcomes, and are more costly than strokes in patients without AF. Patients with AF are therefore an important target population for reducing the overall burden of stroke.

This report aims to raise awareness among policy makers and healthcare professionals that better knowledge and management of AF, and better prevention of stroke are possible. However, greater investment in preventing stroke is needed, particularly in patients with AF. Coordinated action by national governments of Latin American countries is urgently required to achieve earlier diagnosis and better management of AF, and to reduce the risk of stroke in patients with AF. Implementation of the recommendations detailed in this report, at regional and national level, will be crucial.