How Can We Avoid a Stroke Crisis in the Asia-Pacific Region?

Working Group Report:
Stroke Prevention in Patients with Atrial Fibrillation

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Endorsements

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

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

Anticoagulation Europe – www.anticoagulationeurope.org

Arrhythmia Alliance – www.heartrhythmcharity.org.uk

Arrhythmia Alliance China – www.a-a-international.org

Arrhythmia Alliance Japan – www.a-a-international.org

Asian Pacific Society of Cardiology – www.apscardio.org

Atrial Fibrillation Association – www.atrialfibrillation.org.uk

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

Cardiac Society Myanmar Medical Association – www.myanmarcardiac.org

Chinese College of Cardiovascular Physician – www.drheart.cn

Chinese Society of Cardiology – www.cscnet.org.cn

Chinese Society of Pacing and Electrophysiology – www.cspe-cma.org

Clinical Research Center for Stroke, Korea – www.stroke-crc.or.kr

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

European Primary Care Cardiovascular Society – www.epccs.eu

European Stroke Conference – www.eurostroke.eu

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

Heart Association of Thailand – www.thaiheart.org

Hong Kong College of Cardiology – www.hkcchk.com

Indonesian Heart Association – www.inaheart.org

Japanese Organization of Clinical Research Evaluation and Review – www.j-clear.jp

Korean Stroke Society – www.stroke.or.kr

Lao Cardiac Society

Malaysian Medical Association – www.mma.org.my

National Heart Association of Malaysia – www.malaysianheart.org

National Heart Foundation of Australia – www.heartfoundation.org.au

National Stroke Foundation of Australia – www.strokefoundation.com.au

Philippine Heart Association – www.philheart.org

StopAfib.org – www.stopafib.org

Taiwan Stroke Association – www.strokecare.org.tw

Taiwan Stroke Society – www.stroke.org.tw

World Stroke Organization – www.world-stroke.org

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Foreword

Millions of people are affected by stroke in the Asia-Pacific region. For example in 2004, in South East Asia and the Western Pacific Region, 1.8 and 3.3 million people, respectively, suffered a first-ever stroke. In the same year, 1 816 000 people in China and 727 900 in India died from a stroke. In China, the overall mean cost of hospitalization for stroke in 2010 equated to more than half the annual wage. For many sufferers, death is the first and last manifestation of stroke, and for stroke survivors the effect on their life can be drastic. Some stroke victims are left severely disabled, lacking in bowel and bladder control, and with speech and cognitive difficulties. Not surprisingly, the economic implications of stroke are huge, both for the individual and communities as a whole. Moreover, the cost of stroke in the Asia-Pacific region is likely to increase dramatically in the coming years, as the age of the population increases, and survival from stroke – and the conditions predisposing to stroke – improves.

There are simple actions, which if taken now, could prevent a large number of the deaths, disabilities and costs that result from stroke. If we do not carry these out, we will face a stroke epidemic in the Asia-Pacific region.

In this report, there are recommendations that are particularly significant for patients with atrial fibrillation (AF), which is the most common sustained abnormality of heart rhythm. AF increases the risk of stroke fivefold and is responsible for 15–20% of all strokes caused by blood clots. Significantly more patients with AF are likely to have a severe stroke than those who do not have AF, and AF increases the risk of remaining disabled after a stroke by almost 50%. Moreover, patients with AF who have a stroke have a 50% risk of death within 1 year. Patients with AF are therefore at high risk of stroke and, in particular, severe stroke. They are an important target population for reducing the overall burden of stroke.

Despite being a common condition, AF is often underdiagnosed. The recommendations in this report seek to draw attention to the poor understanding of AF, which consequently is undertreated, resulting in inadequate stroke prevention. More specifically, these recommendations aim to help patients, policy makers, healthcare professionals and the general public to gain better knowledge and management of AF. This report contains a clear Call to Action – I urge you to give this your full attention.

What can be done? Even though healthcare delivery continues to be the responsibility of national governments, cooperation at a regional level could bring great benefits to both individuals and the healthcare systems of each country. Stroke prevention in patients with 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 early detection of AF is mandatory. In this report, the main aim is to raise awareness of the need for greater investment in the prevention of AF-related stroke. The countries of the Asia-Pacific region will need a clear strategy to help coordinate the various domains of policy development, awareness-raising, research and educational activities to focus them on the improvement of AF management and effective stroke prevention.

It is a privilege for me, as President of the Asian Pacific Society of Cardiology, to participate actively in an initiative that will help to push forward this important work. I firmly believe that only through the coordinated actions of all participants – both on a national and regional level – will we see the highest number of strokes avoided and the greatest improvements in quality of life achieved. I will seek to set these changes in motion with the support of my colleagues from other Asia-Pacific countries, and look forward to your support in driving this important initiative.

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May 2011

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 the countries of the Asia-Pacific region, China and India have the largest populations and the highest numbers of deaths from stroke with 1 816 000 and 727 900, respectively.[3]

Surviving a stroke can often be worse than dying from one. Patients can be left immobile, incontinent and unable to speak.[1] The consequences of stroke can devastate not only the patient's quality of life,[4] but also the lives of their family and carers.[5] Furthermore, the economic burden of stroke is huge. In a country such as Australia, the total lifetime cost for strokes was estimated at AU$2 billion (US$2 billion).[6]

In the South East Asia and Western Pacific territories, which form the Asia-Pacific region, 1.8 and 3.3 million people, respectively, suffered a first-ever stroke, and the number of strokes per year is predicted to rise dramatically as the population ages.[2] This is an epidemic already beginning to happen, and prompt action is required to avoid a crisis.

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.[7] An important risk factor for stroke, AF is responsible for 20% of ischaemic strokes (strokes caused by a blood clot blocking a blood vessel in the brain).[8] 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).[9]

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 ischaemic attack. More recently, additional risk factors have been included – such as vascular disease, age 65–74 years and female gender.[10]

Furthermore, AF-related strokes are more severe, cause greater disability and have a worse outcome than strokes in people without AF. An Australian analysis of 7784 patient records showed that a history of AF increased the risk of death by 29% in patients with an ischaemic stroke and by 42% in those with an intracerebral haemorrhage.[11]

There are a large number of people in the Asia-Pacific region living with AF. For example, in China, up to 8 million people suffer from AF.[12] Studies have shown that across the Asia-Pacific region, the prevalence of AF in adults ranges from 770 per 100 000 population in China[13] to 1634 per 100 000 in Japan.[14]

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

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 countries in the Asia-Pacific region.

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

Stroke risk is increased fivefold in patients with AF

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

Anticlotting therapy reduces stroke risk in patients with AF. When appropriately used and properly monitored, it lowers stroke risk by about two-thirds.[15] 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[16–18] associated with both vitamin K antagonists[19,20] and aspirin.[21–24]

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

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.

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.[25,26] 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 countries in the Asia-Pacific region where there is a high level of out-of-pocket expenditure on healthcare.[27]

The incidence and prevalence of AF and AF-related stroke in many countries of the Asia-Pacific region is not known and further research is required

Currently, data on the incidence and prevalence of AF and AF-related stroke are unavailable for many countries of the Asia-Pacific region. Continued research is recommended to provide further insights and improve 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 the countries of the Asia-Pacific region to promote the recommendation for the 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 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 the Asia-Pacific region to ensure better detection and management of atrial fibrillation (AF) and more effective measures to prevent AF-related stroke. Through this, we will be able to reduce the major social and economic burden of a largely preventable condition: AF-related stroke.

The Asia-Pacific region needs a clear policy on stroke prevention in patients with atrial fibrillation

The Asia-Pacific region is vast and diverse, encompassing both small and large countries, with developed and emerging economies. While each nation faces unique health challenges, they share a common need to turn the tide on the growing burden of cardiovascular diseases, particularly as more than half the world's population lives in the Asia-Pacific region.[28]

The consequences of cardiovascular diseases are immense – they are the leading cause of death globally.[2] Moreover, they are on the increase, and are expected to account for 23.6 million deaths by 2030.[29] Cardiovascular disease has no geographic, gender or socioeconomic boundary, and accounts for approximately a third of all deaths in the world. Of these, 80% occur in low- and middle-income countries.[30]

In 2004, 3 875 000 patients from South East Asia and 4 094 000 from the Western Pacific Region died as a result of cardiovascular disease.[2] The rate of cardiovascular mortality varies across the region. Death rates, as a proportion of total deaths from all causes, were <20% in Thailand, Philippines and Indonesia; 20–30% in urban China, Hong Kong, Japan, Korea and Malaysia; and 30–35% in New Zealand, Australia and Singapore.[31]

The rate of cardiovascular mortality is on the rise in several countries in the region, including urban China, Malaysia, Korea and Taiwan. In China, cardiovascular mortality increased as a proportion of total deaths from 12.8% in 1957 to 35.8% in 1990.[31] These countries are undergoing a rapid pace of urbanization and industrialization with major technological and lifestyle changes, and it is important to monitor the impact of these changes on cardiovascular risk factors.

Cardiovascular disease has an enormous impact on a country's economy. For example, it has been estimated that over a 10-year period to 2015, China will lose US$558 billion in foregone national income because of the combination of heart disease, stroke and diabetes.[29]

The most prevalent cardiovascular disorders are coronary heart disease and stroke. Asia-Pacific countries bear a disproportionate share of the burden of stroke – a burden that will grow as life expectancy rises.[32] China and India have the highest number of deaths from stroke in the region, with 1 816 000 and 727 900, respectively.[3]

Asia-Pacific countries bear a disproportionate share of the burden of stroke which will grow as their populations' life expectancies rise

AF is a major cause of severe, disabling stroke

AF is the most common type of sustained abnormal heart rhythm and a major cause of stroke – in particular 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 cardiovascular diseases.

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%.[33–35] However, some of the drugs that help to prevent unwanted clotting, such as warfarin, 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 risks of therapy may outweigh the benefits.[16–18]

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

Furthermore, AF is often not diagnosed until the patient suffers a first stroke. This increases the size of the problem – many potentially preventable strokes are occurring each 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 AF increase, so do the prevalence and incidence of AF.[36] 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 the Asia-Pacific region 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

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 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 Asia-Pacific region
- Advocate adherence to guidelines to improve management of AF
- Exchange best practice between countries in the Asia-Pacific region
- Boost research into the causes, prevention and management of AF and address paucity of information around epidemiology

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.[7,37] There are a large number of people in the Asia-Pacific region living with AF, with prevalence in adults ranging from 770 per 100 000 in China[13] to 1634 per 100 000 in Japan.[14] However, these numbers only reflect those who have been diagnosed and do not take into account those with AF who remain undiagnosed. In China, the overall mean cost of hospitalization for stroke in 2010 was ¥11 216 (US$1706) per patient (based on an average length of stay of 20 days), which equates to more than half the average annual wage in China.[38] In Taiwan in 2003, the overall median cost for acute care for first-ever stroke was 26 326 New Taiwan Dollars (NTD) per patient (US$891), based on a median length of stay of 7 days.[39] This suggests that across the region, the economic impact of AF and AF-related stroke is likely to be considerable.

Despite the high cost of stroke, appropriate management can substantially reduce the risk of stroke in patients with AF. There is a critical need across the Asia-Pacific region 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 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.

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 disorder. A simple, inexpensive procedure such as routine pulse-taking (which is not always carried out as a matter of principle) followed by electrocardiographic monitoring can play a crucial role in helping to improve detection of AF in patients at risk. 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 ischaemic attack. 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 reduce the need for specific stroke prevention treatment.

We call on the national governments of the Asia-Pacific region to drive policy initiatives to improve early detection and management of AF and to prevent stroke in patients with AF

We advocate a campaign of routine pulse-taking across the countries of the Asia-Pacific region, to promote better early detection of AF

3. Improve education of patients and carers 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

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

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

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 Asia-Pacific 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 countries in the Asia-Pacific region. 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 for a coordinated Asia-Pacific effort to initiate appropriate physician education and awareness strategies, supported by adequate resources

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 ageing process, are not modifiable, so it will not be possible to eliminate AF entirely.[40]

We call on national governments of the Asia-Pacific region to promote equal access to all diagnostic, treatment and monitoring services for AF, supported by clear information

Thus, other important areas of focus are early diagnosis of AF – before 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 favourable 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 anticlotting therapy that they underestimate its benefits in reducing stroke risk.[41–43] 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 equality of access to therapy, monitoring services and information for all patients across the Asia-Pacific region

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 countries of the Asia-Pacific region, to ensure clear and relevant communication with patients, so that they are partners in determining their care.

7. Advocate adherence to guidelines to improve management of AF

Several sets of guidelines exist for the management of AF. Their recommend - ations largely overlap, but the degree to which they are properly implemented varies widely between and within countries. This can be demonstrated when the use of anticlotting therapy is analysed in large cohorts of patients with AF. For example, according to recent surveys in Tasmania and China, the proportion of patients with AF at risk of stroke not receiving anticlotting therapy was 24.6% and 35.5%, respectively.[44,45] Moreover, in Taiwan, the proportion of patients with AF receiving guideline-adherent anti-clotting therapy for stroke prevention was 28.3% for warfarin and 37.9% for aspirin; even with the combination of these two regimens, only 62.0% of patients received anticoagulant or aspirin prophylaxis.[46] In Korea, up to 73.9% of patients with AF receive guideline-adherent prophylaxis.[47] There is therefore a need across much of the Asia-Pacific region to improve adherence to guidelines for the prevention of stroke in patients with AF, because non-adherence is associated with poor outcomes.[48]

All the governments of the Asia-Pacific countries can encourage guideline adherence by calling for better implementation of the existing guidelines such as those by the American College of Cardiology, American Heart Association and European Society of Cardiology (ACC/AHA/ESC),[25] the American College of Chest Physicians (ACCP),[49] and the recently released ESC guidelines.[50] All the guidelines are based on expert consensus by an international faculty. Alongside these guidelines, country-specific ones are used, such as the Singapore Ministry of Health Clinical Practice guidelines for the Management of Atrial Fibrillation,[51] the New Zealand 'Management of people with atrial fibrillation and flutter',[52] Chinese AF guidelines,[53] and the Japanese Guideline for Pharma-cotherapy of Atrial Fibrillation.[54] We call on national governments in the Asia-Pacific region to raise awareness of the existing guidelines – improved adherence to these will help 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 adherence, and the timely updating of guidelines as appropriate, would also enhance patient safety.

We call on national governments of the Asia-Pacific region to support initiatives to raise awareness of existing relevant guidelines for the management of AF

8. Facilitate exchange of best practice between countries in the Asia-Pacific region

An Asia-Pacific initiative to harmonize existing national guidelines into one set of unified Asia-Pacific 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. A tactical approach such as this would help directly in the sharing of best practice and the development of a focussed policy on stroke prevention in patients with AF extending to all countries in the region. It would also help to ensure that the principle of healthcare equality across the countries of the Asia-Pacific region is implemented and individual patients receive similar (and the best possible) care. It would be beneficial if there could be a better alignment between the countries of the region, to identify key areas where the guidance is being overlooked or where agreement is required on divergent advice.

We advocate an Asia-Pacific 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

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

We call on national governments of the Asia-Pacific region to support a coordinated research initiative to increase understanding of AF and improve the prevention of AF-related stroke

and the development of strategies for its prevention and treatment through research.

The countries of the Asia-Pacific region could provide funding to boost research into these areas, via a coordinated research strategy. Research topics that Asia-Pacific 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
- Asia-Pacific studies monitoring the effect of interventions to manage AF and prevent AF-related stroke

Countries within the Asia-Pacific region already acknowledge the importance of stimulating cardiovascular disease research activities at the regional level by providing direct financial support for research projects and meetings. However, an Asia-Pacific coordinated research initiative 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 4.4 million people in South East Asia and 9.1 million in the Western Pacific Region who had survived an episode of stroke at some time in their life
- In 2004, about 1.8 million people in South East Asia and 3.3 million in the Western Pacific Region 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
- The total lifetime cost for all ischaemic and intracerebral haemorrhagic stroke in Australia has been estimated at about AU$2 billion (US$2 billion)

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: haemorrhagic and ischaemic. A haemorrhagic stroke is caused by bleeding from a blood vessel in the brain. Ischaemic strokes are more common, accounting for approximately 85% of all strokes,[1] and are caused by a blood clot in the brain. This blood clot may have developed in the brain, or it may have formed elsewhere in the body and travelled to the brain (in this case, the blood clot is said to have 'embolized'). For example, an ischaemic stroke caused by a blood clot that formed in the heart is known as a cardioembolic stroke.

A transient ischaemic attack (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%.[55,56] Studies have shown that in the 90 days after a TIA, the risk of stroke exceeds 10%.[56]

Prevalence and incidence of stroke in countries in the Asia-Pacific region

Every year, 15 million people worldwide experience a stroke. Approximately 5 million of these suffer permanent disabilities and over 5 million more die.[57] In 2004, stroke accounted for 9.7% of all deaths worldwide.[2]

In 2004, the World Health Organization (WHO) estimated that the prevalence (i.e. total number of cases) of patients surviving a stroke in countries in the Asia-Pacific region was 4.4 million in South East Asia and 9.1 million in the Western Pacific Region.[58]

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

In 2004, 4.4 million people in South East Asia and 9.1 million people in the Western Pacific Region survived a stroke, while about 1.8 and 3.3 million, respectively, had a first-ever stroke

In the same year, the incidence (i.e. number of new cases) of first-ever stroke was 1.8 million in South East Asia and 3.3 million in the Western Pacific Region,[2] compared with an estimated incidence of cancer cases of 1.7 million and 3.2 million, respectively.[2]

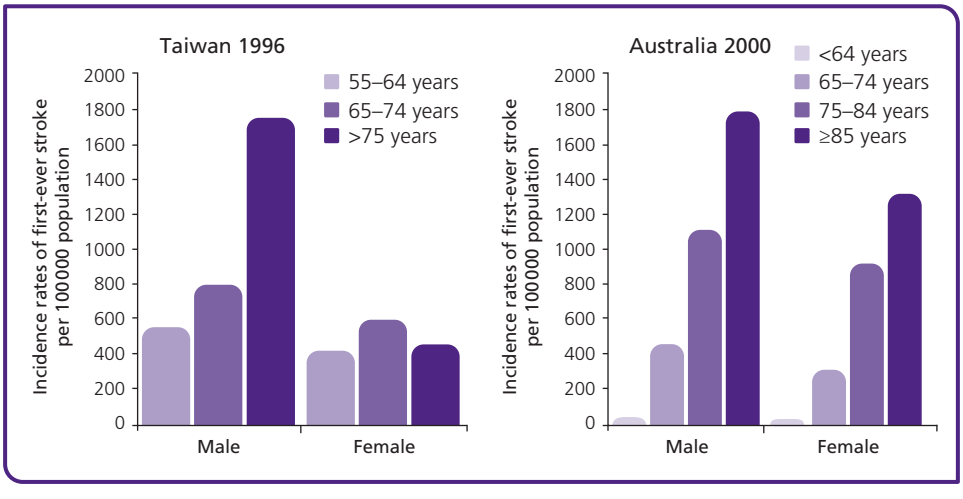
There are no data from the WHO for the incidence and prevalence of stroke by country in 2004; however, data from a review in 1998 showed that the incidence and prevalence of stroke in Asia-Pacific populations were not dissimilar to those in Caucasian populations.[59] In this review, the incidence of stroke in Caucasian populations ranged from 100 to 500 per 100 000 population. Incidence data from Asia-Pacific countries are rare; however, data from South Vietnam show an incidence of 161 per 100 000, with higher rates in rural areas than urban areas.[59]

The prevalence of stroke in Caucasian populations ranged from 500 to 600 per 100 000, while in Asia-Pacific countries it ranged from 415 per 100 000 in South Vietnam to 690 per 100 000 in Thailand.[59]

The world population is ageing rapidly and as a result it has been predicted that stroke incidence will increase in the future. In Australia and New Zealand, the proportion of people aged ≥60 years is expected to rise from 16.2% in 2000 to 28.4% in 2050.[60] In addition, the number of men and women experiencing stroke has been shown to increase substantially with age, except in females in a Taiwanese study (Figure 1).[61,62] For example, in Australia, the incidence of first-ever stroke in men ≥85 years of age is almost 4 times that of men aged 65–74 years; in women aged ≥85 years, it is nearly 4.5 times that of women aged 65–74 years.[62] Furthermore, these studies show that stroke incidence is higher in men than in women irrespective of age.[61,62] Therefore, the expected rise in the ageing population of the Asia-Pacific region will further increase the incidence and socioeconomic burden of stroke and limit the medical resources available to provide for the needs of stroke sufferers and their families.

Some ethnic differences in stroke epidemiology exist, reflecting differences in the predisposition to some of the risk factors associated with stroke. For example, the frequency of haemorrhagic stroke is thought to be approximately 29.6% in Asian populations compared with 15% in Caucasian populations.[1,63] Conversely, cardioembolic stroke has been shown to be less frequent in Asian populations compared with Caucasian populations (10.9% vs 20.8%,

Figure 1. Estimates of stroke incidence per 100 000 men and women at selected ages in studies from Taiwan and Australia. Data taken from Fuh *et al*. 2000 and Islam *et al.* 2008.[61,62]



respectively).[64] In addition, the optimal international normalized ratio (INR – a measure of how long it takes the blood to clot in a patient receiving vitamin K antagonist therapy) for Asians is thought to be lower than the INR range of 2.0–3.0, determined mainly in Caucasians. Studies have shown that INR intensities of 1.5–2.1 might be more appropriate in Asian populations.[65–67]

Although strokes in young adults are relatively uncommon, approximately 25% of strokes occur in people aged below 65 years,[68] and a national survey of stroke in the USA estimated that 3.7% of strokes occurred in patients aged 15–45 years.[69] 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 the countries in the Asia-Pacific region.

Death and poor health in patients with stroke

Stroke accounts for nearly 10% of all deaths worldwide.[1,2] 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 12.3 per 100 000 for South East Asia and 19.0 per 100 000 in the Western Pacific Region.[70] This figure rises substantially in individuals aged 60 years or over: 698.4 per 100 000 in South East Asia and 919.6 per 100 000 in the Western Pacific Region.[70]

Stroke death rates vary between countries of the Asia-Pacific region. For example, stroke death rates ranged from 43.2 per 100 000 in Malaysia to 138.4 per 100 000 in China.[3]

Additionally, stroke is a major cause of long-term disability worldwide – each year, 5 million stroke sufferers are left permanently disabled.[1] The young are not exempt from the devastating effects of stroke. A long-term study assessing outcomes in young adults aged 15–45 years following stroke 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.[71]

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,[1] stroke can adversely affect mental health.[72]

Because its onset is sudden, affected individuals and their families are often poorly prepared to deal with the consequences of stroke.[72] The development of chronic disability can severely affect quality of life of both the

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

Illustrative example

"It was very hard for me when the doctor told me I couldn't go back home after my stroke. While I was in rehabilitation I became very low. I felt like I was taking one step forwards and three steps back. I can no longer walk and my right arm is still weak. It was so difficult for me to accept having to go into a nursing home when I've always been an independent, active person. I feel hugely frustrated by not being able to do everything for myself and being so reliant on the care and support of my family and the nursing home staff. My family has found some games and activities to help with my memory, speech and general brain activity, so we can communicate better, as sometimes I get my words confused. The effects of stroke mean that you must change, relearn and redefine how you live."

patient and their relatives. It is also important to consider the role of carers 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 countries in the Asia-Pacific region

Although data are not available on the financial cost of stroke for many countries of the Asia-Pacific region, information can be sourced from some specific countries. New evidence derived from the North East Melbourne Stroke Incidence Study (NEMESIS) was used to estimate the cost of first-ever stroke in 27 291 patients with ischaemic stroke and 4291 with intracerebral haemorrhagic stroke (haemorrhagic stroke within the brain).[6] For 2004, the mean annual cost of resource, excluding carer cost, was AU$6022 (US$5941) for ischaemic stroke and AU$3977 (US$3927) for intracerebral haemorrhagic stroke.[6] Total lifetime cost for all ischaemic and intracerebral haemorrhagic strokes, based on data from this study, was estimated at about AU$2 billion (US$2 billion).[6] Total outpatient and community costs were greater than costs of inpatient hospital care for both ischaemic and intracerebral haemorrhagic strokes.

Estimates from the Korea National Health Insurance Claims Database for 2005 have shown the total cost for the treatment of stroke in the nation was 3737 billion Korean won (KRW) (US$3.3 billion) which included direct costs of 1130 billion KRW (US$1.0 billion) and indirect costs of 2606 billion KRW (US$2.3 billion).[73] The per capita cost of stroke was 3 million KRW (US$2648) for men and 2 million KRW (US$1765) for women.[73] Costs per patient for haemorrhagic and ischaemic stroke were estimated at 6 million KRW (US$5295) and 2 million KRW (US$1765), respectively.[73]

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

It is therefore evident that stroke is a costly health problem in countries in the Asia-Pacific region, 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 carers, families, 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 countries in the Asia-Pacific region. Furthermore, the prevention of stroke with pharmacological or non-pharmacological therapies in patients at high risk has the potential to reduce this economic burden significantly.[74] The cost-effectiveness of anticlotting treatments for patients with AF is discussed further in the section 'Cost of vitamin K antagonist therapy in stroke prevention in atrial fibrillation' (page 42).

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 the Asia-Pacific region 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, ischaemic 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 Asia-Pacific populations are unavailable
- The present and future impact of AF on Asia-Pacific populations is currently unknown; further studies are urgently needed in order to provide these data

AF is the most common sustained heart rhythm abnormality[75] and is a major risk factor for ischaemic stroke and death in the general population.[8,75] 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.[76] The five major modifiable risk factors – the 'big five' – that merit targeting in the prevention of stroke have been identified as:[77]

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

Owing to its high prevalence, high blood pressure is the leading modifiable risk factor for stroke,[57] accounting for approximately 40% of all strokes.[1,57,78] AF, by comparison, is estimated to be responsible for approximately 15–20% of all strokes[79] and patients with AF have a 3–4% risk per year of developing stroke.[80] 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 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 2).[7,37] Moreover, many patients with AF also have high blood pressure, so a holistic approach to management is required (see section on 'Management of other conditions that increase stroke risk: a holistic approach', page 43).

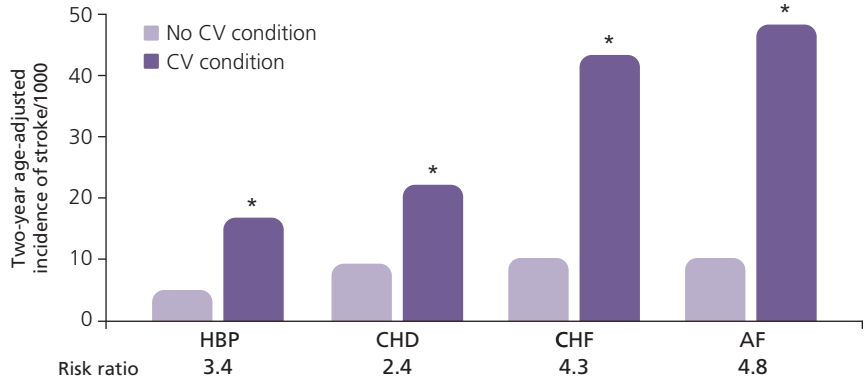
AF is responsible globally for about 15–20% of all strokes

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

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

Figure 2. Two-year age-adjusted incidence of stroke in the presence and absence of cardiovascular (CV) conditions. AF confers a fivefold increase in the risk of stroke; in patients with high blood pressure, stroke risk is increased threefold. Adapted from Wolf *et al.* 1991.[7]



*p<0.001.
AF, atrial fibrillation; CHD, coronary heart disease; CHF, congestive heart failure; HBP, high blood pressure.

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 and travel to vessels in the brain and cause an ischaemic stroke.[81]

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

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, ischaemic heart disease (reduced blood supply to the heart muscle) and diabetes.[82,83] 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;[25] the majority of studies discussed in the following chapters involve patients with non-valvular, rather than valvular, AF. In a study of 9297 patients from 41 hospitals in China, rheumatic heart disease was a cause/factor for non-valvular AF in 23.9% of patients. Other causes and associated factors for AF were advanced age (58.1% of patients), hypertension (40.3%) and coronary heart disease (34.8%).[45]

The likelihood of developing AF increases with advancing age. 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.[40,84] In addition, there are limited data suggesting that the incidence of AF is higher than normal in athletes.[85,86] 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.[85] Therefore, AF is not just a condition of the elderly.

Signs and symptoms of atrial fibrillation

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.[87] However, many people with AF have no symptoms, or vague, non-specific symptoms.[25] 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 ischaemic 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.[88] 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.[89] 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 pharmacological management of AF are available in New Zealand, Singapore, China and Japan.[51–54] The Singapore guidelines for the management of AF recommend that all patients, whether symptomatic or asymptomatic, should be evaluated and the initial evaluation should include a confirmation of their diagnosis.[51] In addition, the Japanese guidelines state that the duration of AF should be comprehensively determined based on the history and symptoms of AF and electrocardiogram (ECG) findings.[54] In addition, the UK National Institute for Health and Clinical Excellence (NICE) guidelines, which are used along with the American College of Cardiology, the American Heart Association and the European Society of Cardiology (ACC/AHA/ESC) guidelines by Asian-Pacific countries that have not yet developed their own guidelines, recommend further assessment for the presence of AF in individuals with breathlessness, palpitations, fainting/dizziness, chest discomfort, stroke or TIAs.[90]

Management of AF is discussed in more detail in the chapter 'Stroke prevention in patients with atrial fibrillation', page 37. NICE has produced some useful information on AF for patients and their carers, which gives a brief overview of the main treatments used for the condition.[87] This document is due to be reviewed in June 2011 and updated if necessary.

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 coexist with AF, but there are differences in the mechanisms of the two rhythm disturbances.[25] Atrial flutter will not be discussed further in this document.

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

Prevalence and incidence of atrial fibrillation

A large number of people in the Asia-Pacific region live with AF. The prevalence of AF in adults ranges from 770 per 100 000 in China[13] to 1634 per 100 000 in Japan.[14] However, the prevalence and incidence of AF in many countries of the Asia-Pacific region is currently unknown, and further research is urgently needed to address this.

Increase over time

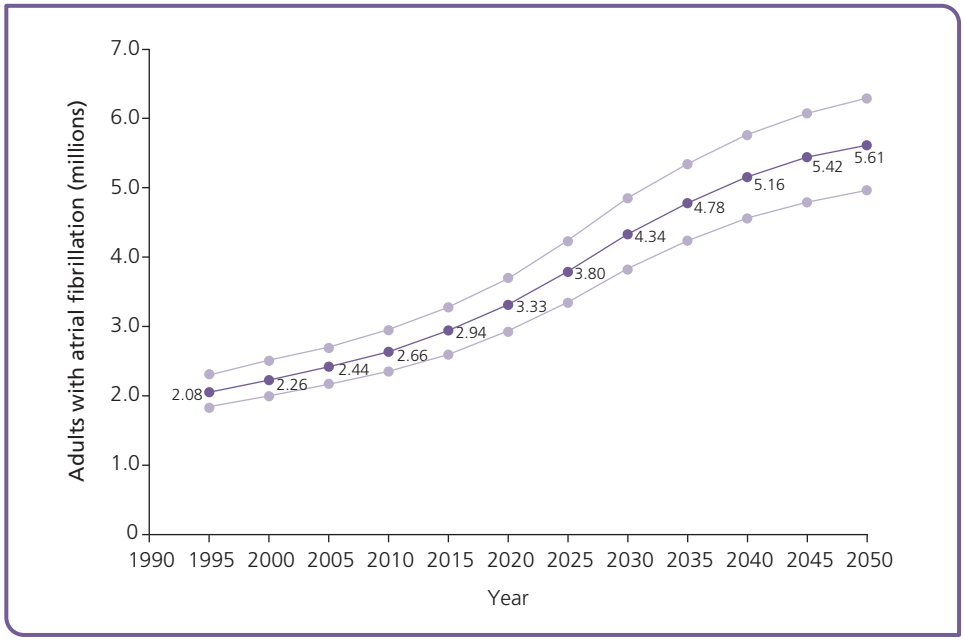
The prevalence of AF worldwide appears to be increasing over time. In one cross-sectional study of almost 18 000 adults with AF diagnosed between July 1996 and December 1997 in California, USA, it was estimated that approximately 2.1 million people in the USA had AF.[91] By 2001, this number was thought 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 3).[91] 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.[36]

The prevalence and incidence of AF in many countries of the Asia-Pacific region is currently unknown

Increase with age

The prevalence of AF has also been shown to increase with each advancing decade beyond the age of 50 years, and the incidence of AF has been found to increase with each decade of age. In a

Figure 3. The number of people with atrial fibrillation is expected to continue rising: projected number of adults with the condition in the USA between 1995 and 2050. Upper, middle and lower curves represent upper, middle and lower boundaries of estimate. Adapted from Go *et al*. 2001[91] with permission from the American Medical Association.



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

community-based prospective cohort study, among 3560 participants of Chinese ethnicity, the overall prevalence rates of AF were 14 per 1000 person-years in men and 7 per 1000 person-years in women and increased with each advancing decade beyond the age of 35 years.[92] Using these prevalence rates in the context of China's predicted population for 2026 of 1.4 billion,[93] approximately 1.96 million men and 0.98 million women would have AF by this time. The incidence rates of AF also increased appreciably with increasing age; the highest rates were 4.3 and 1.7 per 1000 person-years for men aged 65–74 years and women aged ≥75 years, respectively.[92] Overall, the incidence of AF was higher in men than in women – 1.68 and 0.76 per 1000 person-years, respectively.[92]

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

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.[94] 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 Asia-Pacific populations.

This statistic underscores the important public health burden posed by AF – 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;[95] for breast cancer, the remaining lifetime risk was 1 in 8 for women aged 40 years.[94]

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 countries of the Asia-Pacific region to get a better understanding of the patterns of incidence and prevalence of AF throughout the Asia-Pacific 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 or TIA 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 countries in the Asia-Pacific region 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 22), it is commonly without symptoms and may have been so for an unknown period.[25] 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.[25] Often though, AF is not detected until an individual presents with a serious complication such as stroke or heart failure.[88]

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. Episodes of AF may be transient, and Singapore guidelines for the management of AF suggest that documentation during symptoms may be needed – using an ECG, transtelephonic ECG monitoring or 24-hour ambulatory Holter ECG recordings.[51] Similarly, Japanese guidelines recommend that the duration of AF should be comprehensively determined based on the history, symptoms and ECG findings.[54] Given that some patients with other risk factors for stroke, such as high blood pressure, diabetes and ischaemic 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 multicentre 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.[96] 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$2865) compared with £363 (US$582) 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.[96]

Conversely, in Japan the total medical cost for general patients over a 1-year period was greater in those patients who did not receive routine health screening including ECGs (Figure 4), which highlights the cost benefits of routine health screening, as well as the health benefits for patients.[97]

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 programme implemented through primary care.[96] Several recommendations are made for future research that could help further define the optimum patient pathway (Table 1).

Figure 4. Medical cost of general population who underwent regular health status checks by GPs and those who did not: Kumamoto Prefecture – 1-year healthcare costs by age group. Image adapted from www.mhlw.go.jp (Japanese Ministry of Health, 2011).[97]

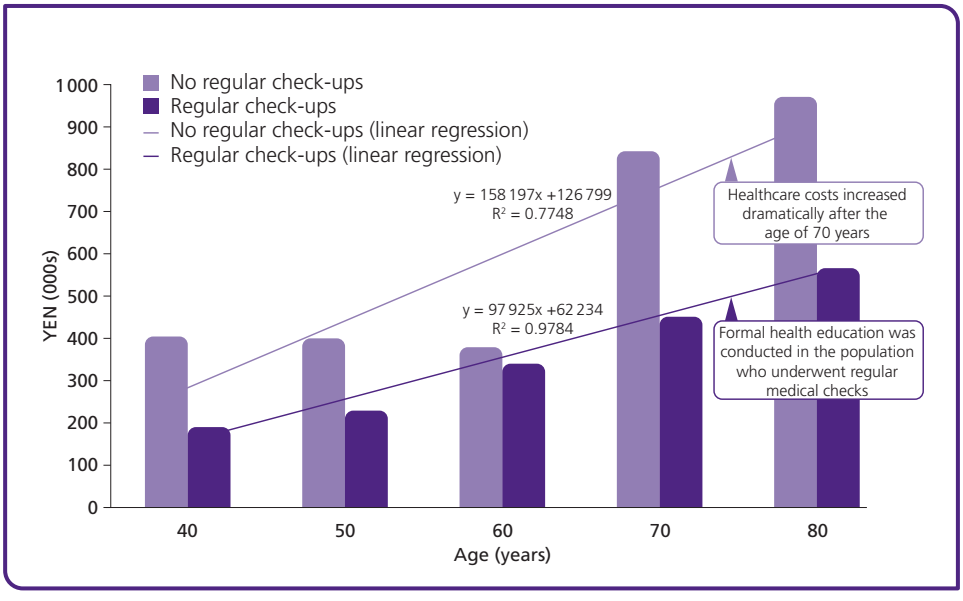


Table 1. Some of the recommendations for further research, based on the findings of the Screening for AF in the Elderly (SAFE) study.[96]

- How the implementation of a screening programme 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

Additional risk factors for stroke in patients with atrial fibrillation

Factors reported to further increase the risk of stroke in patients with AF include:[25,36,90,98]

- 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,[99–101] the literature shows that death rate from stroke is increased fourfold in women with AF compared with twofold in men with AF.[102] However, not all studies have demonstrated such a significant difference between the genders.[102,103]

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.[25] 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.[104] High blood pressure increases the risk of stroke approximately threefold in patients with AF.[105] However, it should be borne in mind that neither of these studies report data specific to particular countries within the Asia-Pacific region.

Previous stroke or TIA increases the risk of another stroke threefold 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 sex.[10] Risk stratification systems currently used are summarized in Table 2.

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

Among patients not receiving anticoagulant therapy, the $CHADS_2$ scheme has been found to be a more accurate stroke predictor than AFI[106] and SPAF[107] – two pre-existing schemes.[9] In patients receiving therapy, three schemes have predicted stroke significantly better than chance: Framingham, $CHADS_2$ and SPAF.[108] 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 and SPAF.[108,109] Few models so far have addressed the cumulative nature of risk factors, whereby a combination of factors would confer a greater risk than any factor alone.[102]

Table 2. Risk stratification schemes used to predict thromboembolism in atrial fibrillation. Adapted from Lip *et al.* 2010.[10]

Reference	Stroke risk strata		
	High	**Intermediate**	**Low**
$CHADS_2$ Classical*[9]	Score 3–6	Score 1–2	Score 0
$CHADS_2$ Revised[10]	Score 2–6	Score 1	Score 0
ACC/AHA/ESC[25]	Previous stroke, TIA or embolism; 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)
NICE[90]	Previous stroke/TIA or thromboembolic event; age ≥75 years with hypertension, diabetes or vascular disease; clinical evidence of valve disease or heart failure or impaired left ventricular function	Age ≥65 years with no high-risk factors; age <75 years with hypertension, diabetes or vascular disease	Age <65 years with no moderate/high risk factors
ACCP[49]	Previous stroke, TIA or embolism; or ≥2 moderate risk factors (age ≥75 years; moderate or severely impaired LVEF and/or heart failure; hypertension or diabetes)	Age >75 years, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes	No risk factors
CHA_2DS_2-VASc[10]	One 'major' risk factor (previous stroke, TIA or embolism, 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

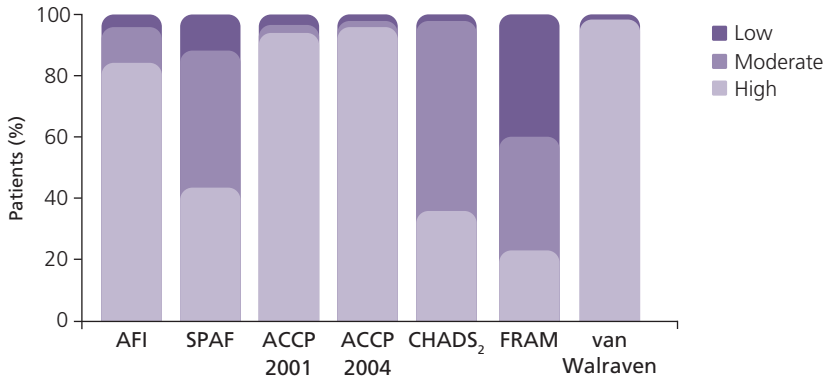
*Secondary prevention study. $CHADS_2$ score is a sum of numerical scores assigned to five risk factors: Congestive heart failure (1 point); Hypertension (1 point); Age ≥75 years (1 point); Diabetes (1 point); and Stroke or transient ischaemic attack (2 points). For definition of CHA_2DS_2-VASc see below.
ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; ESC, European Society of Cardiology; ACCP, American College of Chest Physicians; LVEF, left ventricular ejection fraction; NICE, National Institute for Health and Clinical Excellence; TIA, transient ischaemic attack.

In light of the variable understanding and use of risk stratification schemes, the $CHADS_2$ scheme has been expanded and clarified.[10] 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[10] and in several other studies.[110–112]

CHA_2DS_2-VASc denotes:

- Congestive heart failure/left ventricular dysfunction: 1 point
- Hypertension: 1 point
- Age ≥75 years: 2 points
- Diabetes: 1 point

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.[108]



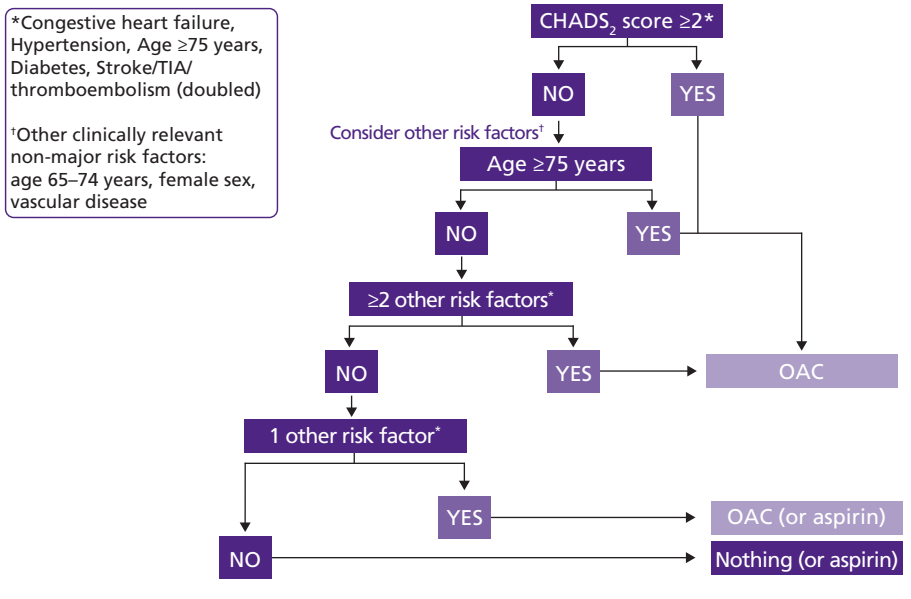
ACCP, American College of Chest Physicians; AFI, Atrial Fibrillation Investigators; SPAF, Stroke Prevention in Atrial Fibrillation; SPORTIF, Stroke Prevention using a ORal Thrombin Inhibitor in atrial Fibrillation; FRAM, Framingham.

- Stroke, TIA or thromboembolism: 2 points
- Vascular disease: 1 point
- 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.[10]

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 6).

Figure 6. Clinical flow chart for the use of oral anticoagulation for stroke prevention in atrial fibrillation. Adapted from Camm *et al*. 2010[50] with permission from Oxford University Press.



OAC, oral anticoagulant; TIA, transient ischaemic attack.

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:[113]

- 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. anaemia): 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

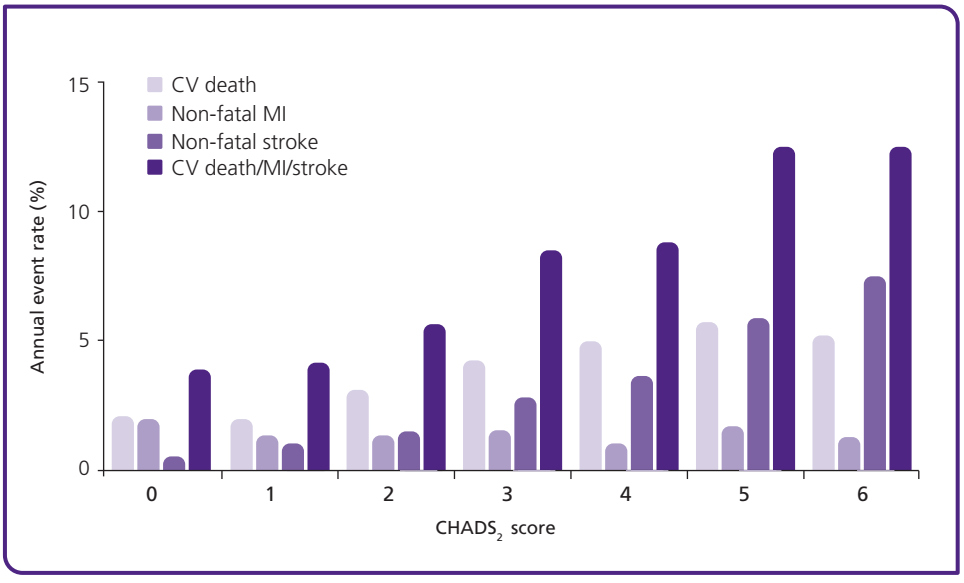
Predictions from risk stratification models may be inconsistent, which could result in inequality of advice and therapy

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,[113] the recent ESC guidelines state 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'.[50] In addition, some caution and regular review of the patient would be needed following the initiation of anticlotting therapy.[50]

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 7).[114]

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 the Asia-Pacific region may receive inconsistent advice and therapy, depending on local choices.

Figure 7. Annual cardiovascular (CV) event risk in patients with atrial fibrillation with various $CHADS_2$ scores. Annual event rates of CV death, non-fatal stroke, and combined CV 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[114] with permission from Elsevier.



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

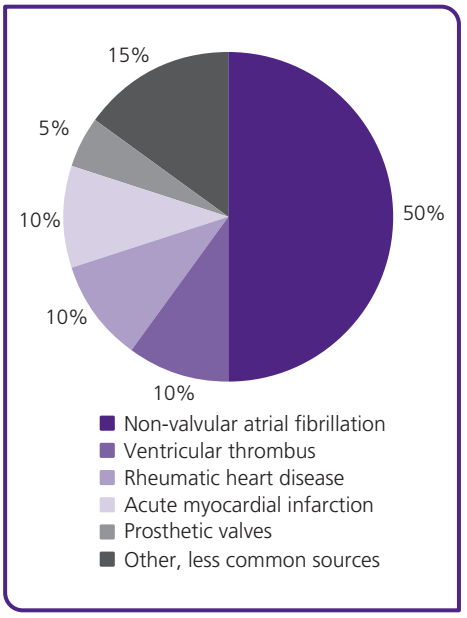
In addition to a high risk of stroke, patients with AF suffer from more severe strokes and have a poorer prognosis after the event than those without AF.[103] The increased severity of strokes in patients with AF is thought to be because such strokes are predominantly cardioembolic.[103] A cardioembolic stroke is caused by a blood clot in the heart, part of which breaks away and becomes trapped in large arteries in the brain.[103] 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).[115]

In a Japanese hospital-based prospective registration study, the outcomes of 16 922 consecutive patients with acute ischaemic stroke and TIA who presented to hospital within 7 days of onset were analysed.[116] Frequency of good outcome at discharge was highest for lacunar stroke (blockage of a small artery deep in the brain; 76.3%), followed by other stroke (60.9%) and atherothrombotic (51.7%), and lowest in cardioembolic stroke (36.6%).[116]

Although mean cost data for stroke in patients with AF in countries in the Asia-Pacific region are not available, cost data from Europe may offer an indication of the cost spread across the countries of the Asia-Pacific region. The total mean cost of acute hospital care has been shown to be higher for cardioembolic stroke (€4890 per patient; US$6802) than for non-cardioembolic stroke (€3550; US$4938) in a study of more than 500 patients in Germany.[117] In addition to being more severe, cardioembolic strokes are associated with a higher risk of recurrence than other types of stroke.[118]

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

Figure 8. The main cause of cardioembolic stroke is non-valvular atrial fibrillation (Schneck and Lei 2008).[115] Image reprinted with permission from eMedicine.com, 2011. Available at: http://emedicine.medscape.com/article/1160370-overview.



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

In an estimated expenditure report prepared by PricewaterhouseCoopers on the economic cost of AF in Australia, the annual cost resulting from AF to the Australian economy in 2008–2009 was at least AU$1.25 billion (US$1.23 billion), which equates to AU$5200 (US$5137) per annum for every person with AF.[119] This estimate included medical costs, costs of long-term care for those with a disability, and lost productive output. The authors stated they had been conservative when estimating individual component costs and did not include other costs such as reduced quality of life.

In addition to increasing stroke risk, AF is also known to have an impact on quality of life[120] and all-cause mortality, with a relative risk of 1.87 compared with those without AF.[121]

The increased severity of strokes in patients with AF compared with other strokes suggests that these people will experience a greater impairment in quality of life than those without AF. Patients with AF are therefore a key target population for reducing the overall burden of stroke on society.

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

Increased death rate

The death rate from stroke is significantly higher in patients with AF than in those without AF. In an Australian analysis of linked hospitalization and death records of 7784 patients with first-ever stroke or TIA, 2360 (30%) of the patients died.[11] Of these, 1049 (44%) died during their index hospitalization. A history of AF increased the risk of death by 29% in patients who had an ischaemic stroke and by 42% in those who had an intracerebral haemorrhage.[11] Similarly, in a large-scale Italian study of patients who had suffered a first-ever stroke, AF was found to increase the 5-year death rate from stroke almost twofold (Table 3) and to be an independent predictor of death rate even after adjusting for other outcome predictors, such as age, sex and vascular risk factors.[8]

Table 3. 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.[8]

	Annual death rate (%)	
Year	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

A trend towards an increase in the overall early death rate in patients with AF over the past 20 years has been reported,[122] which may reflect the increasing age of the population. With both its prevalence[91] 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%).[114] This higher mortality in patients with AF was observed across all subgroups with established atherothrombosis or at risk for atherothrombosis.[114]

Increased disability and poor health

AF-related stroke is more severe and is associated with more ill health than stroke unrelated to AF.[8,18,82,103]

At present there are no data for the Asia-Pacific region to indicate the increased risk of disability that the presence of AF confers on stroke patients; however, data from European studies 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%.[18]

Data from the Copenhagen Stroke Study were used to investigate the impact of stroke on morbidity. Loss of ability to perform normal daily activities following stroke, and decline in neurological 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.[103] 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.

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

While data regarding the impact of AF-related stroke exist in a limited number of countries in the Asia-Pacific region, in much of the region there is still work to be done.

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 carers, family members, and health and social services
- European studies have shown that healthcare costs associated with stroke are higher for patients with AF than for those without AF. Similar studies are needed in the Asia-Pacific region

Significant impact on quality of life

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

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 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).[123] This indicates that AF-related strokes, which are more severe than strokes in patients without AF,[103] 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.[124]

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 neurological function). Some quality-of-life scores for patients with and without AF who experience stroke are shown in Table 4. Like the utility scores discussed above, the scores given in the table indicate that AF-related stroke has a more negative impact on quality of life than non-AF-related stroke.

Table 4. Outcome of stroke in patients with and without atrial fibrillation (AF). Adapted from Jørgensen *et al.* 1996.[103]

	Patients with AF	Patients without AF
Initial stroke severity (SSS* score; lower score = greater neurological impairment)	30	38
Neurological 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]

AF also increases the risk of medical complications following stroke. Patients with AF suffer more frequently from pneumonia, pulmonary oedema (accumulation of fluid in the lungs) and bleeding in the brain after stroke than those without AF.[127]

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.[1] They then rely on informal carers, 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, carers have to manage the often considerable cognitive, behavioural and emotional changes in the patient. These changes include mood swings, personality changes, irritability, anxiety, memory loss and depression.[1,128] Carers can therefore experience a loss of identity, independence and social life, and extreme tiredness and depression. Carers also report fears regarding the safety of the patient and distress at not having time to attend to all of the patient's needs.[1,128]

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

Illustrative example: a carer's perspective

"Over the past year I have been caring for my wife after she had a stroke. She is slowly making progress and can now take a few steps using a walking frame but she has trouble communicating and needs virtually 24-hour care. I love her very much; it is so hard to see her like this. I worry about her all the time and feel guilty, as though I'm not doing enough. I miss the life we used to have together. Caring for someone after a stroke is a serious undertaking; sometimes it overwhelms me and I feel quite depressed. Although I want to be there for her, I don't feel like I have a life of my own anymore."

Illustrative example: a child's perspective

"After my father had a stroke, I didn't see him for a couple of days until I visited the hospital. When we got to his room, he was leaning sideways in his wheelchair and tried to say hello to me, but I couldn't understand what he said. I hated seeing him like this; I was scared. It's as if he wasn't my father any more … luckily he has no recollection of being like that but I will never forget it."

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.[1,129] Together with loss of time in employment and contribution to the community of the patient – and most probably also the carer – this amounts to a significant overall burden on society.

High economic cost

The economic cost of stroke for the entire Asia-Pacific region is unknown. However, data from individual countries attest to the high cost of stroke in many countries in the Asia-Pacific region. For example, data from the North East Melbourne Stroke Incidence Study (NEMESIS) estimated the total lifetime costs for all first-ever strokes, including ischaemic and intracerebral haemorrhagic strokes, for 2004 at AU$2 billion (US$2 billion);[6] a significant increase from the 1997 estimate of AU$1.3 billion (US$1.3 billion).[130] Similarly, data from

AF increases the risk of medical complications following stroke

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

the Korea National Health Insurance Claims Database for 2005 have shown that the total national costs for haemorrhagic and ischaemic stroke were 1323 billion and 1553 billion KRW, respectively (US$1.2 billion vs US$1.4 billion).[73] In 2009, the cost of stroke to the Japanese healthcare system was ¥1786 billion (US$22 billion).[131]

The share of government expenditure on healthcare in countries in the Asia-Pacific region can affect the financial burden of stroke imposed on patients and their families. In 2004, the government share of total expenditure on healthcare was over 50% in Japan, DPR Korea, Australia, Thailand, Bhutan and Malaysia. Globally, government share is at least 40% in many countries; however, in China, Indonesia, Cambodia and Lao PDR it was below this level. Therefore, the financial burden of stroke is likely to be higher for patients with AF and their families in countries such as China where there is a high level of out-of-pocket expenditure on healthcare.[27] This out-of-pocket spending in China is a major source of financing of healthcare, and is estimated to push 32.4 million people below the poverty line.[27] A nationwide 62-hospital registry study of 3-month stroke survivors in China involving 4739 patients, highlighted the significant cost burden of stroke in this country.[132] The average hospital and medication costs following acute stroke in China were US$2361, and out-of-pocket costs were US$2038. Overall, 71% of patients in China had experienced catastrophic out-of-pocket expenditure (defined as ≥30% of total household income). In Indonesia, Thailand and Vietnam more than 20% of household expenditure is spent on healthcare. At a subnational level, inequalities also exist in the level of government expenditure on healthcare (e.g. in rural areas and disadvantaged provinces in China).[27] Overall, the financial hardship associated with stroke, in particular the cost of after-stroke care, is a heavier burden for some patients and their families than others because of the unbalanced distribution of healthcare in certain countries in the Asia-Pacific region.

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

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.[133] The total economic cost of stroke is probably even greater, because these calculations largely omit costs incurred by the patient and carers, which 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$53 billion).[134]

Because stroke in patients with AF is more severe than stroke in those without AF,[103] it is likely to incur greater costs. A Japanese study also showed the presence of AF to be associated with an increased risk of severe stroke and length of hospital stay – a mean of 40.5 days compared with 34.0 days for patients without AF.[135] This in turn has been shown to be associated with increased costs.[136] More detailed cost studies are required in countries in the Asia-Pacific region 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 those without AF. Thus, AF-related stroke imposes an even greater burden on individuals, carers, families, society and healthcare resources than stroke in patients without AF. This provides 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-pharmacological 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 a target INR range for VKA therapy is difficult in some countries in the Asia-Pacific region because of the lack of access to INR monitoring facilities and problems associated with INR blood testing in remote/rural areas
- Currently available anticlotting therapies, such as warfarin 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 in the management of AF 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 more detail 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 help to prevent stroke. AF is most commonly managed using 'rhythm control' or 'rate control' strategies.[82] In rhythm control, drugs are used to maintain the heart's rhythm (these are known as anti-arrhythmic drugs); in rate control, the drugs are used to maintain a steady heart rate.[82] Examples of drugs used for rhythm or rate control include amiodarone, digoxin and β-blockers. Non-pharmacological 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 the patient 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 anticlotting therapy (see 'Guidelines for stroke prevention in patients with atrial fibrillation', page 45).[25]

Patients receiving treatment for AF should also receive anticlotting therapy

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 9)
- 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

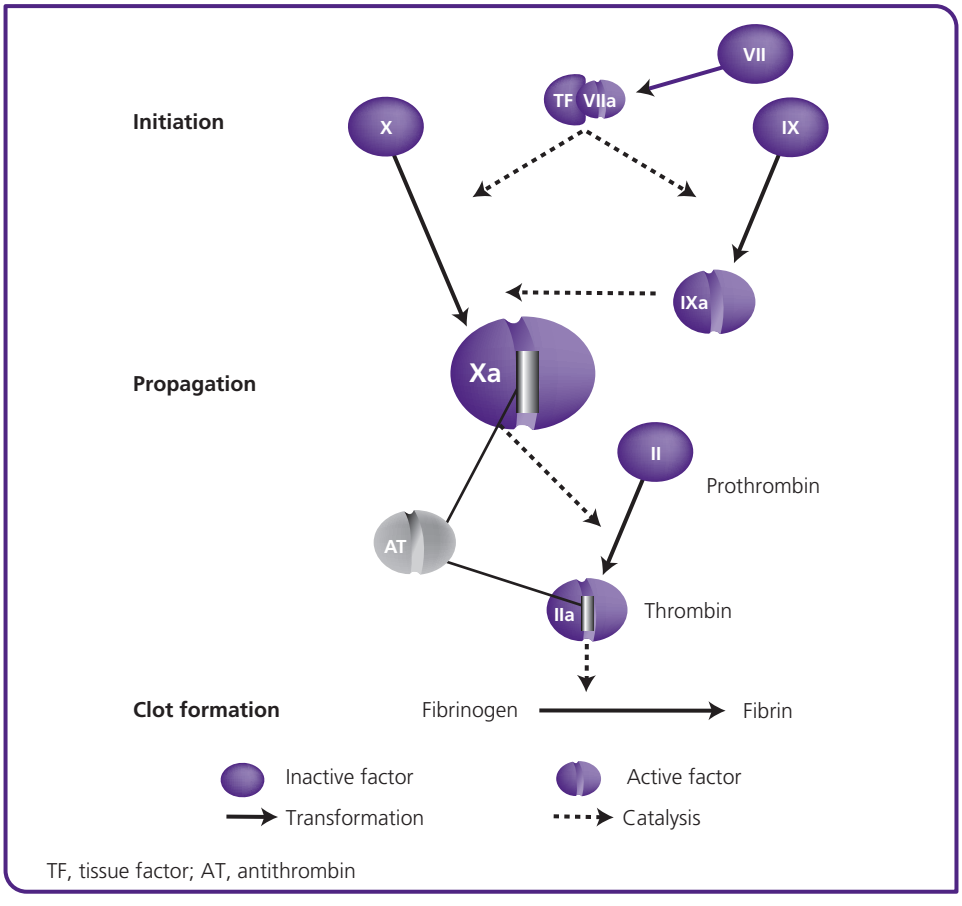
VKAs, which are oral anticoagulants, and acetylsalicylic acid (or aspirin), an antiplatelet agent, are currently the most widely used drugs in the prevention of stroke in patients with AF.

Vitamin K antagonists

VKAs, such as warfarin, exert their anticoagulant effects by inhibiting the production of four vitamin K-dependent proteins that play key roles in the coagulation pathway.[8,19] This series of enzyme reactions ultimately produces fibrin, an insoluble protein that combines with platelets to form blood clots. The effects of VKAs can be significantly modified by genetic factors[137] and interactions with other drugs and food.[20] 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).

Thus, the management of patients receiving VKAs may be challenging, and frequent monitoring is required.

Figure 9. 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.



TF, tissue factor; AT, antithrombin

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.[25,76] 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. However, recent data have demonstrated that warfarin therapy is associated with a higher incidence of intracranial bleeding in Asian patients than in Caucasians.[138] Therefore, the optimal INR intensity may be lower for Asians than the recommended target range, which was determined mainly in Caucasians. Indeed, studies have shown optimal INR intensities of 1.8–2.4 and 1.5–2.1 in Chinese and Japanese patients, respectively, receiving warfarin therapy.[66,67] The findings of a retrospective cohort study of 555 Chinese patients with AF taking warfarin supported a lower INR range of 1.5–3.0 for stroke prevention in a Chinese population.[65] This range was achieved 75.1% of the time,[65] which is in broad agreement with a study in Japan, and suggested that a benefit from anticoagulant therapy was achieved with a time in therapeutic range of over 68%.[139]

VKAs interact with food and other drugs – including amiodarone, an anti-arrhythmic drug used in the treatment of AF.[140] In addition, some herbal products that are commonly used in the Asia-Pacific region have been shown to interact with warfarin. There is an increased risk of bleeding when warfarin is combined with some of these, including ginkgo and garlic.[141] Maintaining the INR within a target range can therefore be very challenging, and the resulting need for frequent monitoring and dose adjustment is a significant barrier to effective anticoagulation in everyday practice. This is a particular challenge for some countries in the Asia-Pacific region because of the limited access that some patients have to healthcare resources,[27] including to INR monitoring facilities. 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 blood testing. This has been evidenced in Malaysia, and attempts have been made to provide INR monitoring facilities to smaller rural centres, with the growing use of reliable point-of-care INR devices.

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

Efficacy of vitamin K antagonists in clinical trials

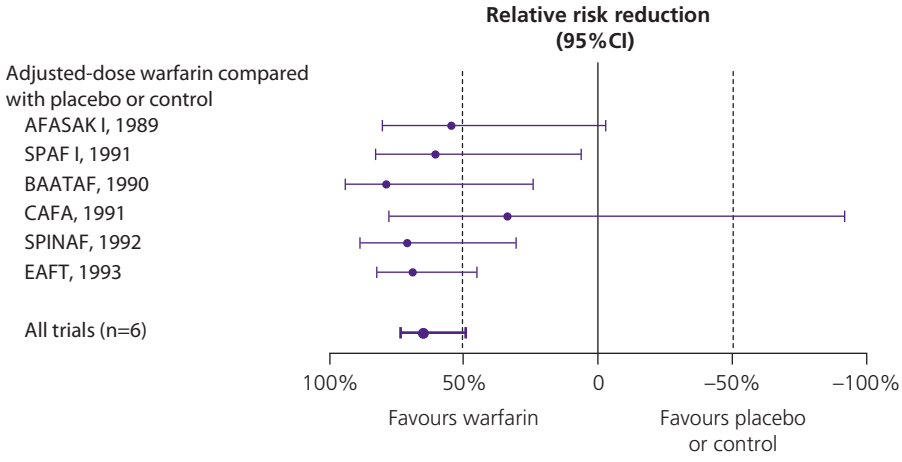
Systematic reviews of clinical trials in patients with AF have shown that, compared with no therapy, warfarin (with close monitoring and dose adjustment if necessary) provides a 62–68% reduction in the risk of stroke (Figure 10) and a 26–33% reduction in death rate[33–35,106] without significantly increasing the risk of major bleeding. The implication is that for every 1000 patients treated with warfarin, 31 ischaemic strokes will be prevented each year.[35] VKA therapy has not been well studied in Asian populations – this could be addressed by carrying out subset analyses in studies involving Asian patients who have been given warfarin.

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.[147,148]

VKAs are therefore currently recommended as first-line therapy in patients with AF and a moderate or high risk of developing stroke.[25,76] This is despite the major drawbacks associated with VKA therapy, including

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

Figure 10. 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[34] with permission from the American College of Physicians.



AFASAK I, Atrial Fibrillation, Aspirin, and Anticoagulation study;[142] SPAF I, Stroke Prevention in Atrial Fibrillation Study;[107] BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation;[143] CAFA, Canadian Atrial Fibrillation Anticoagulation Study;[144] SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation;[145] EAFT, European Atrial Fibrillation Trial.[146]

Patient populations in clinical trials may not reflect normal clinical practice

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.[117] Thus, many patients with AF and a moderate to high risk of stroke do not receive appropriate anticoagulant therapy and therefore remain unprotected.[48,149] 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 45).

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.[150] 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.[35,150]

Retrospective studies and cohort studies with an observational design have shed more light on this matter. In a large-scale cohort of over 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.[151] Overall, there were 148 cases of ischaemic 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 bleeding in the brain

was almost doubled with warfarin, but still remained low, and there was no significant association between warfarin and bleeding outside the brain. 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.

A retrospective review of the medical records of consecutive patients with documented AF in Australia demonstrated a 51% reduction in the risk of stroke in patients treated with warfarin compared with those who did not receive warfarin. The authors concluded that the reduction in the risk of stroke observed in this study was broadly similar to that reported in clinical trials.[44] Despite this, the annual overall incidence of bleeding complications was higher in patients taking warfarin than in those who were not (14.2% vs 8.4%). Thus, patient outcomes with VKA therapy do appear to be somewhat less favourable in clinical practice than in clinical trials. Overall, however, the benefits of VKA therapy 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.[152] It is most effective in the prevention of blood clots that are rich in platelets, such as those that form in arteries.

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%).[34] In addition, aspirin was associated with a non-significant 19% reduction in stroke compared with no treatment.[34] 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.[153,154] 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.[21–24] Therefore, aspirin is not the preferred option for any patient at risk of stroke.

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

Patient outcomes following oral anticoagulation therapy may be less favourable in clinical practice than in clinical trials

Illustrative example: an elderly patient receiving warfarin

A 68-year-old female patient with AF, who had recently started warfarin therapy, was admitted to hospital after an episode of pneumonia. Despite it being standard procedure to complete a separate warfarin chart, given the requirements of administering and monitoring warfarin, this was not done. The patient was started on antibiotics for her pneumonia but these interacted with the warfarin, resulting in an INR of 6.0. Following complicating empyema (pus within the lining surrounding the lung), a chest drain needed to be inserted. Given her raised INR, the warfarin was stopped and she was given vitamin K. The chest drain was removed, but it was only at discharge that the issue of restarting her warfarin therapy was raised. The patient was reluctant to restart warfarin because of the frequent blood testing required, but being unwilling to continue taking warfarin put the patient at risk of stroke. Although the patient did not suffer any immediate life-threatening problems in this case, the existence of an oral anticoagulant that could be given at a fixed daily dose, required infrequent monitoring, and would be unaffected by changes in diet or other medications would have been of great benefit.

Clinical trials have shown VKAs to be cost-effective compared with no therapy or aspirin in the prevention of stroke in AF

The ESC guidelines state that patients with one clinically relevant non-major risk factor, including hypertension, age 65–74 years and female sex, should receive an oral anticoagulant in preference to aspirin.[50] In addition, no treatment with anticlotting therapy should be considered over aspirin in patients without any stroke risk factors.[50] It should be noted that there is some doubt about the real benefit of aspirin in low-risk patients.[155,156] Similar advice is given in local Asia-Pacific guidelines such as the Singapore, New Zealand and Chinese guidelines.[51–53] Summaries of these guidelines are given in Appendix 1.
In a recent study, the investigational oral anticoagulant apixaban was shown to be superior to aspirin for the prevention of stroke in patients with AF who either had been found to be unsuitable for VKA therapy and it had been discontinued, or had not been previously prescribed VKA therapy but in whom it would be expected to be unsuitable.[157,158] 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. 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 VKAs.[158]

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

The cost of preventing AF-related stroke using VKA therapy compared with the cost of treating stroke has not been assessed for countries in the Asia-Pacific region. However, data from Europe suggest that the cost of prevention appears to be favourable compared with the average direct per capita cost for treatment. The cost of preventing one AF-related stroke per year using VKA therapy was estimated to be £5260 (US$8441) in a UK study, with regular INR monitoring and hospital admissions for bleeding complications being the major cost drivers.[159] In contrast, the average direct per capita cost for treating stroke in the EU was €11 799 (US$16 432) (see section on ‘High economic cost’, page 35).[160] While 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 over a 10-year period after a stroke was estimated to be almost fourfold greater than the estimated 10-year direct costs of anticoagulation,[161] indicating that prevention is as important as treatment.

Numerous other studies have provided further evidence that anticoagulation with VKAs is cost-effective in patients with AF at moderate or high risk of stroke, compared with no therapy or aspirin.[102,162] Management of complications following suboptimal anticoagulation is the major driver of cost.[162]

Little is known about the cost-effectiveness of VKA therapy for countries in the Asia-Pacific region. Furthermore, in some countries such as China, the relevance of assessing the cost-effectiveness of VKAs is questionable due to the unbalanced distribution of healthcare across the Asia-Pacific region.[27] In other countries such as Australia, cost-effectiveness of VKA therapy is very relevant and measured in incremental cost-effectiveness ratio per QALY. A review of US-based studies in patients with

AF showed VKA therapy to be cost-effective, particularly in patients considered to be at moderate to high risk of stroke.[162] Despite the questions over their relevance for some countries, similar country-specific studies are needed in the Asia-Pacific region, particularly because of the growing burden of stroke in the region. Small investigator-initiated studies are currently underway in Malaysia to assess the cost-effectiveness of VKA therapy.

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, carer and society, which are not captured in cost-effectiveness studies. Results from a study in Hong Kong have shown that spending longer within a target INR range correlates favourably with direct health costs for anticoagulation therapy.[163] Further data are needed about the cost of attending anticoagulation clinics in other countries in the Asia-Pacific region. However, as previously highlighted, access to INR monitoring facilities is disparate in some countries in the Asia-Pacific region. This issue needs to be addressed in these countries before cost-effectiveness of attending anticoagulation clinics can be addressed.

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 favourable efficacy and safety profiles.

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

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

Blood pressure control is particularly important in the management of AF, and uncontrolled blood pressure increases the risk of stroke 2–3-fold.[7,164] 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.[165]

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

The outlook for stroke prevention in patients with atrial fibrillation

To summarize, patients with AF should be managed holistically 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

Studies assessing the cost-effectiveness of VKA therapy are needed for countries in the Asia-Pacific region

Further data are needed regarding the cost of attending anticoagulation clinics in countries in the Asia-Pacific region

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

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

cost-effective in patients with AF and a moderate to high risk of stroke, but further studies are required to calculate these costs in Asia-Pacific 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 is 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 favourable 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 59).

Guidelines for stroke prevention in patients with atrial fibrillation

Key points

- Patients at a high risk of stroke should receive anticlotting therapy, such as warfarin
- Aspirin is only recommended in guidelines for patients at a low or moderate risk of stroke, although the Japanese guidelines do not recommend aspirin as a first line treatment because of the risk of increased bleeding
- Although several sets of guidelines exist for preventing stroke in patients with AF, the recommendations are not universally applied
- Up to 36% of at-risk patients do not receive guideline-adherent therapy for clot prevention in the Asia-Pacific region, according to data from countries where these data are available (China and Taiwan). This is similar to the situation on a global scale (in Europe, North and South America, and Asia as a whole)[114]
- 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

Internationally endorsed Asia-Pacific guidelines for stroke prevention in patients with AF are not available. Therefore, many countries in the Asia-Pacific region such as Australia, Malaysia and the Philippines, use the internationally endorsed ACC/AHA/ESC and NICE guidelines, although guidelines for stroke prevention in patients with AF are in preparation in these countries. The ACC/AHA/ESC guidelines represent American–European consensus guidelines,[25] and the ESC has recently published its own guidelines on the management of AF.[50] The ACCP produces international guidelines that are regularly updated; the current 8th edition was published in 2008[49] and an updated version is expected soon. As with ACC/AHA/ESC, the ACCP guidelines (Table 5) are based on expert consensus by an international faculty, and have been endorsed by major societies in both Europe and North America. The UK guidelines from NICE are based on systematic reviews and cost-effectiveness analysis[90] in contrast to the methodology of expert consensus that is used to produce the ACC/AHA/ESC and ACCP guidelines.[166]

Country-specific guidelines for stroke prevention in patients with AF do exist for some countries in the Asia-Pacific region. These include the Singapore 'Management of atrial fibrillation' guidelines,[51] the New Zealand 'Management of people with atrial fibrillation and flutter' guidelines,[52] the Chinese 'Current knowledge and management recommendations in AF' guidelines[53] and the Japanese 'Guidelines for pharmacotherapy of atrial fibrillation'.[54] In addition, sections on stroke prevention in patients with AF are included in the country-specific guidelines for stroke, such as the Korean 'Clinical practice guidelines for stroke'[167] and the Taiwan management of stroke guidelines.[168] Summaries of these guidelines are given in Appendix 1.

Guidelines endorsed by major societies exist for the prevention of stroke in patients with AF, and these are used by many countries in the Asia-Pacific region

Table 5. Summary of the American College of Chest Physicians (ACCP) 2008 guidelines (8th edition), the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2006 guidelines for the prevention of stroke in patients with atrial fibrillation, and the ESC 2010 guidelines for the management of atrial fibrillation.

Guideline (Reference)	Risk category	Recommendation	Definition of risk factors
ACCP 2008[49]	No risk factor (low risk)	Long-term aspirin, 75–325 mg/day	Low risk factor: • Age ≤75 years
	One risk factor (intermediate risk)	Long-term oral VKA (e.g. warfarin) (INR 2.0–3.0, target 2.5), or aspirin, 75–325 mg/day Preferred: VKA rather than aspirin	Increased risk and intermediate risk factors: • Age >75 years • History of hypertension • Diabetes mellitus • Moderately or severely impaired left ventricular systolic function and/or heart failure
	Two or more risk factors (increased risk)	Long-term oral VKA (e.g. warfarin) (INR 2.0–3.0, target 2.5)	
	High risk	Long-term oral VKA (e.g. warfarin) (INR 2.0–3.0, target 2.5)	High risk factors: • Prior ischaemic stroke, TIA or systemic embolism
ACC/AHA/ESC 2006[25]	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 embolism • Mitral stenosis • Prosthetic heart valve
ESC 2010[50]	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 daily Preferred: oral anticoagulation rather than aspirin	
	No risk factors CHA_2DS_2-VASc score = 0	Either aspirin 75–325 mg daily 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.

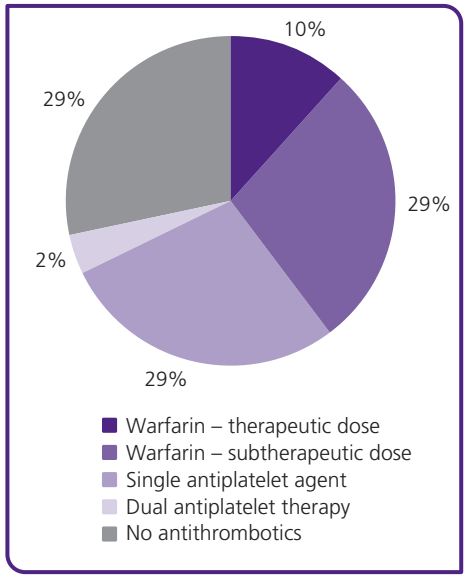
It is difficult to extrapolate agreement on specific recommendations between the different guidelines on stroke prevention in patients with AF because the risk categories used are different in each set of guidelines. However, there is general agreement that patients at low risk of stroke should receive 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 favour the use of oral anticoagulation rather than aspirin in this patient group.[50]

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

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.[169] 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 11).[17]

Figure 11. Medications received before admission to hospital by patients with known atrial fibrillation who suffered an acute ischaemic stroke: only 10% of patients had received warfarin at a therapeutic dose. Adapted from Gladstone *et al*. 2009.[17]



A survey at the annual meeting of the Japanese Society of General Medicine, which received 139 replies, showed that only 26% of respondents preferred to use anticoagulant therapy in patients with AF. Physicians with longer clinical experience or responsibility at a teaching hospital had a negative attitude towards anticoagulant therapy in patients with chronic AF. An advanced age and the risk of bleeding complications were the main reasons given for not prescribing anticoagulant therapy.[170] Even in a study of risk factors based on the database of the Japan Thrombosis Registry for AF, Coronary, or Cerebrovascular Events (J-TRACE), approximately one-quarter of patients with AF who had $CHADS_2$ scores ≥2 did not receive treatment with an oral anticoagulant.[171]

It is worth noting that not all studies into the use of VKAs in patients with AF indicate that they are underused.[172–175] 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.[16] In a Taiwanese study of 39 541 patients with AF, which assessed guideline-adherent anticlotting therapy, only 24.7% received the appropriate anticlotting therapy and 29.0% of high-risk patients did not receive any anticlotting medication at all.[176] In a Chinese retrospective study of hospitalized patients with AF, 35.5% had not received any anticlotting treatment.[45] In another study of 207 patients with AF admitted to acute internal medicine wards in Hong Kong, only 44% of patients who had no contraindications to warfarin received the drug, while 22% of patients did not receive any anticlotting therapy.[177] In the Japanese J-TRACE study (n=2242), 58.9% of low-risk patients and only 75.4% of high-risk patients were treated with warfarin.[171]

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

There is discrepancy between guideline recommendations and clinical practice

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

Underuse of anticoagulant therapy in patients with AF and a high risk of stroke are associated with a significantly greater risk of thromboembolism.[48] In a Japanese study of 288 patients with AF, who were followed up for an average of 7.2 years, the incidence of thromboembolic complications was examined retrospectively.[178] Overall, thromboembolic complications occurred in 33 patients (11.5%). The anticlotting therapy for these patients before embolism was warfarin and antiplatelets (18.2% of patients), warfarin only (12.1%), antiplatelets only (42.4%), and no therapy (22.6%). In all patients with thromboembolic complications who were receiving anticlotting therapy during follow-up, the anticoagulant effect just before the embolic attack was found to be insufficient.[178]

Reasons for poor adherence to guidelines

Adherence to guidelines for the prevention of stroke in patients with AF may be low for several reasons, including difficulties in maintaining INR within the therapeutic range (see section on 'Anticlotting therapies for preventing stroke', page 37)[20] and physicians' concerns about bleeding risk, particularly in the elderly.[41]

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

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

In a Korean study of 1502 patients with non-valvular AF without previous stroke, the anticlotting regimens of 422 patients with a $CHADS_2$ score of 1 were reviewed.[47] Anticlotting regimens used were warfarin for 143 patients (33.9%), aspirin for 124 patients (29.4%), clopidogrel/ticlopidine for 45 patients (10.7%) and none for 110 patients (26.1%). In the patients who were taking warfarin, the average INR was 2.00±0.48, and only 66 (46.2%) of the 143 patients maintained their INR within an optimal range between 2.0 and 3.0.[47] As previously discussed, lower INR ranges have been recommended for use in Chinese and Japanese patients with AF based on the results of other studies.[65–67]

Many patients find the frequent monitoring and necessary dose adjustments associated with VKAs inconvenient and time consuming, and may miss appointments. This can be especially true for patients living in the more remote areas of countries in the Asia-Pacific region. 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.[179] The longer 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.[41,43,180] As a result, some eligible patients are not receiving optimum therapy that could prevent strokes.[17] For many physicians, bleeding risk is a particular concern in the elderly, who are liable to become confused and may take more than the recommended dose of warfarin in a day. Furthermore, since elderly patients are particularly prone to falls, physicians fear that elderly patients who fall may suffer a severe haemorrhage if they are taking VKA therapy.[170,181,182] 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.[183] Furthermore, the incidence of stroke among patients aged 75 years or over with AF is lower in those who are receiving VKA therapy than in those taking aspirin, without the risk of haemorrhage being increased.[153]

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.[184] A number of bleeding risk stratification schemes exist, including a new simple major bleeding risk score known as HAS-BLED,[113] which is used to predict bleeding risk in the ESC guidelines.[50] The HAS-BLED score is described in more detail in the section on 'Detecting atrial fibrillation and stratifying stroke risk' (page 25).

Major bleeding events associated with VKA therapy can profoundly influence physicians' prescribing behaviour, 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.[185] In contrast, patients who experienced an ischaemic stroke while not receiving VKA therapy did not influence a physician's prescribing behaviour towards subsequent patients.[185] 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.

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.[186] Major bleeding events related to anticoagulation are dramatic and therefore easily remembered and may lead to reductions in VKA prescribing. Second, Feinstein's 'chagrin factor' postulates that, when choosing between alternatives, physicians avoid those actions that cause them the most regret.[187] 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'.[185]

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.[188] For VKA therapy to be justified, physicians considered that it needed to prevent a significantly higher number of strokes than patients felt acceptable (Table 6). The number of strokes that needed to be prevented to justify aspirin therapy did not differ significantly between patients and physicians.

When perceptions of bleeding risk were evaluated, the maximum number of bleeds associated with warfarin or aspirin that patients found acceptable was significantly higher than that considered acceptable by physicians (Table 6). Moreover, the results suggest that physicians perceive the risk of bleeding to be higher with VKAs than with aspirin. This perception is at

Table 6. 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 on stroke avoidance, and less value on avoidance of bleeding.[188]

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 in 100 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.

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

variance with the findings by Mant *et al.* that, compared with aspirin, warfarin decreases stroke risk without increasing the risk of bleeding.[153]

These results indicate that patients place more value than physicians on the avoidance of stroke, and less value on the avoidance of bleeding.[188] 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 on the benefit-to-risk ratio of therapy. There is a clear need for improvements in adherence to guidelines for AF to improve patient outcomes in stroke for what is a growing burden in Asia-Pacific countries.

Current challenges for stroke prevention in patients with atrial fibrillation

Key points

A commitment by countries within the Asia-Pacific region to reducing AF-related stroke is needed. This could be achieved by:

- Coordinating strategies for early and adequate diagnosis of AF, and promoting the development of relevant research programmes
- Raising awareness and understanding of AF and AF-related stroke among patients and carers
- 'Empowering' patients and carers 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 Asia-Pacific region
- 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 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 in this chapter.

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 China, Japan and Australia[189,190] (see later in this chapter for more information).

There may be scope for introducing more widespread AF screening programmes following the positive results of the SAFE study.[96] 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.[96] 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 survey was carried out in 11 countries, including China and Australia, to analyse understanding, perception and attitudes towards AF among physicians (cardiologists/electrophysiologists) and patients with AF.[191] Overall, 46% of physicians thought that their patients' ability to explain their condition was poor, and 25% of patients surveyed felt unable to explain their condition to another person. Physicians felt that over 50% of their patients had an important need for more, improved information. In terms of the information provided to patients, only 35% of physicians agreed that the information provided on AF was easy to understand, but 20% did feel there was enough educational information on AF for patients. From a patient perspective, 23% did not know where to seek, or whom to contact, for additional information.[191]

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

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.[192] 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. A subgroup analysis of different ethnic populations in the study revealed that Indo-Asians appeared to be less aware of the association of stroke and thromboembolic events to AF compared with White and Afro-Caribbean populations. Indo-Asians also appeared to be less aware of the fact that warfarin prevents stroke and blood clots.[192] A cross-sectional questionnaire in a wider, multi-ethnic population receiving anticoagulation therapy also revealed gaps in the knowledge of patients from ethnic minorities and deficiencies in the provision of patient information.[193]

A number of organizations are working to improve access to information about AF in countries in the Asia-Pacific region. 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 China, Japan, Australia and New Zealand.[194,195] Activities have been undertaken by this organization to raise awareness of heart rhythm disorders in countries in the Asia-Pacific region. The *Know Your Pulse* campaign, soon to be launched by the Arrhythmia Alliance and associated organizations in China, Japan and Australia, is an international initiative that aims to raise awareness of the pulse as being one of the easiest ways to detect potentially fatal cardiac arrhythmias.[189,190] The Arrhythmia Alliance has also organized *World Heart Rhythm Week*, an annual international event that aims to raise awareness of heart rhythm disorders and sudden cardiac death.[196]

Information for patients with AF and their carers is also available from websites, which are accessible anywhere in the world and can provide up-to-date content. StopAfib.org is the most popular arrhythmia site worldwide and the traffic to this site from the Asia-Pacific region exceeds that from Europe.[197] The patient and carer webpage from this site provides general information on AF, as well as patient discussion forums, social media, guidelines, medications and physician resources.

As well as activities, patient information leaflets on AF, such as the one produced by the New Zealand Guidelines Group, help to inform patients on the causes, symptoms and management of AF.[198] International patient information on

cardiac arrhythmias, prepared with guidance from the International Medical Advisory Committee of Arrhythmia Alliance, has been translated into many different languages, including Chinese and Japanese, but much more needs to be done.[199]

Better adherence to therapy

According to AntiCoagulation Europe, adherence to therapy is reliant on the patient's understanding of their condition. While 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, while 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 all of their last 5–10 monitoring sessions, and 7% had not been in their target INR range in any of their last 5–10 sessions.[200] Although there are no published data from similar surveys in countries of the Asia-Pacific region, surveys among urban health centres are underway in Malaysia. When asked, physicians from Asia-Pacific countries were of the opinion that while some patients did not understand the relevance of their target INR, most of them did and that a lower INR target range was now better appreciated and acceptable to patients.

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.[201] Indeed, patient education and involvement in the management of VKA therapy have been shown to reduce the risk of major bleeding.[202] Thus, patient information should help to empower patients if it is consistent and available in formats appropriate for all those affected – including people with different native languages and different levels of literacy. However, differences in the level of education and standards of living in some countries within the Asia-Pacific region may lead to inequalities in the provision of patient education. Factors such as a young age, low income, living in a rural habitat and availability of education providers have a particular impact on the level of education of patients in countries such as China and Malaysia. This was confirmed in a study carried out to determine factors associated with knowledge of warfarin therapy and anticoagulation control in 52 patients at a warfarin clinic in Malaysia.[203] This study showed that a patient's age, income, level of education and literacy in various languages was significantly associated with their knowledge of warfarin therapy.

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

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 are becoming available that are easier to use and more convenient than VKAs, with more predictable effects and a better safety profile; they 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

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

found that 68% of patients with chronic AF would be interested in new anticoagulation drugs for which routine monitoring was not needed.[204] Unfortunately, similar information is not available for Asia-Pacific populations.

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 or overestimation of the risks of anticoagulation therapy, highlighting 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 need to communicate, so as to provide consistent information and advice for patients

Healthcare professionals should be convinced of the importance of communicating the benefits and risks of a potential therapy to patients. Patients have to absorb a significant amount of information in one consultation with the physician; therefore, information needs to be provided in written, diagrammatic and verbal form. Critical facts and advice need to be 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 are 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.

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

Management of patients receiving VKAs

There is a clear need for a proper infrastructure for the delivery and monitoring of VKAs across countries in the Asia-Pacific 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.[205] 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.[206] 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.[206] However, this may be difficult in some countries in the Asia-Pacific region because of the disparity in access to primary care services – a particular problem in rural and impoverished areas lacking an adequate healthcare infrastructure, drugs and staff.[27]

Anticoagulation clinics – a potential educational resource

Anticoagulation clinics may be run from a hospital or attached to a primary care practice. They have sometimes been considered the gold standard of VKA management,[205] 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.[207,208] Anticoagulation clinics are common in America and Western Europe; however, this is not always the case for countries in the Asia-Pacific region. For example, in China and Taiwan most patients with AF who take warfarin usually attend an outpatient cardiology or neurology clinic. Furthermore, in some countries in the region where anticoagulation clinics are available, there are disparities in the level of access to these clinics. For example, in Malaysia and Korea, anticoagulation clinics tend only to be found in the large

city hospitals as opposed to rural areas. Both of these issues mean that INR monitoring may be suboptimal for some patients, which can lead to reduced levels of anticoagulation control.

A number of studies have shown the benefits of anticoagulation clinic care versus routine medical care in countries in the Asia-Pacific region. A study involving 204 patients with AF who were on warfarin therapy was carried out to assess the level of anticoagulation control in an outpatient cardiology clinic versus an anticoagulant clinic in China.[209] Overall, the quality of anticoagulation control was significantly better for those patients who attended the anticoagulant clinic compared with those who attended the outpatient cardiology clinic. Significantly more patients attending the anticoagulation clinic had INRs within the therapeutic range, and significantly fewer were below the lower limit of 1.8. The time interval for testing INR levels was also significantly shorter for those patients who attended the anticoagulation clinic (34.1 days vs 56.8 days for patients attending the outpatient cardiology clinic). There was also a significantly lower incidence of thrombosis during anticoagulation therapy in the group of patients who attended the anticoagulation clinic.

The first pharmacist-run anticoagulation clinic was set-up in South Korea in 1995, and a 1-year pilot study was initiated to assess the use of the clinic compared with the usual physician-managed medical care for patients receiving warfarin therapy.[210] After 1 year, the percentage of INRs maintained within the therapeutic range in the anticoagulation clinic group was 82% compared with 66% in the usual medical care group. Furthermore, INR testing was more frequent in the anticoagulation clinic than in the usual care group.

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.[205] 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 need to change and adapt.[205] The staff that run the 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 carers 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.[211,212] Although there are no similar data for the Asia-Pacific region, a study in Germany has also shown self-management to be cost-effective.[213] However, this approach may not be appropriate for

all patients; therefore, adequately trained physicians will be needed for support if self-management is to be successful.[214]

Computer programs have been developed to assist in management – these analyse several variables and recommend the level of adjustment of the VKA dose if required. Such computer programs have been shown to perform as well as staff in anticoagulation clinics, and may be a useful tool for optimizing care.[215,216] 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.

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

Moves towards patient-centred care

Management of patients with AF is also likely to be greatly improved by a move to more patient-centred care. Various definitions of patient-centred 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.[217] Although a patient-centred approach is widely advocated, it is not always implemented.[217] Instead, healthcare is typically centred on treating the disorder, rather than considering patients' individual needs.[217,218] Anticlotting therapy tailored to patients' preferences has been shown to be more cost-effective in terms of QALYs than giving the same therapy to every patient.[219] Therefore, physicians need further education on the benefits of patient-centred care and support in implementing this approach locally.

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

An optimized continuum of care

Continuity of care, involving continuing communication between healthcare providers, is essential for high-quality care. The provision of health care often involves several different service providers, therefore continuity of care is defined as 'coherent health care with a seamless transition over time between various providers in different settings'.[220]

Biem *et al.* have described seven characteristics (the seven Cs) of optimal continuity of care:[220]

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 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.[221,222] Comprehensive, timely and appropriate discharge information is essential – possibly in some portable format[223] – so that the primary care practice has all it needs for appropriate follow-up care. Insufficient discharge information can contribute to hospital readmission.[224] Education of carers 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.

The implications of a breakdown in continuity of care are illustrated in the case example below.

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.[225] 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

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

Case example: The importance of continuity of care

A 75-year-old man with a history of high blood pressure, diabetes and osteoarthritis presented with a cough at a rural healthcare centre. AF and pneumonia were subsequently diagnosed. He received oxygen, digoxin (for AF) and cefuroxime (for pneumonia) 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. Although the AF persisted, his condition improved. Warfarin therapy was initiated and information on the drug was provided by a pharmacist; however, the patient's wife, who managed all 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 enalapril (for high blood pressure), metformin (for diabetes), 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, his INR was 4.8 when the patient visited the family doctor, and he was advised to take acetaminophen instead of ibuprofen, to stop taking warfarin and the herbal pills, and to have his INR tested the next day.

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

Twelve months after the initial diagnosis of AF, the patient suffered a stroke that left him with weakness down his right side and speech impairment.

Case study adapted from Biem *et al*. 2003[220]

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

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 the Asia-Pacific region, potentially identifying successes and benchmarks for management, and helping drive improvements where necessary.

Equal access for all

In addition to possible variations in literacy, education, income and care across countries of the Asia-Pacific 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 include the poor, those who live in rural areas, women, children, the disabled and migrants.[27]

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

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

Collaborative approach to guideline development

The efficacy and tolerability of VKAs in the prevention of stroke in patients with AF are well established[25] but several drawbacks can lead to poor adherence to guidelines, as discussed earlier.

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

Regular reviews, updates and endorsement of guidelines will ensure that they are relevant to current clinical practice and may thereby increase adherence.[41,226] Furthermore, there is a rationale for providing standardized guidelines for the whole of the Asia-Pacific region, because too many different sets of guidelines can cause confusion and reduce adherence – a study evaluating the different guidelines used in the UK reported that the proportion of patients with AF for whom VKAs were recommended varied from 13% to 100%.[227] 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 to the prevention of stroke in patients with AF in the Asia-Pacific region. 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-centred care and ensure equity of access to health care for all. Finally, improved 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 of these factors will contribute to the prevention of stroke in patients with AF.

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 have been developed for use in the prevention of stroke in AF
- New antiplatelet agents to reduce blood clotting and drugs for stabilizing heart rhythm are also in advanced stages of development
- Non-pharmacological 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

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 37). 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:[228]

- Effectiveness
- A wide therapeutic window (i.e. a wide separation between the dose level that reduces the risk of a blood clot and that which substantially increases the risk of bleeding)
- 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 INR monitoring
- Convenient administration
- Administration of fixed doses

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.

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

The search for new anticoagulants has therefore focussed 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, which are either published or included on the global clinical trials registry, www.clinicaltrials.gov, are listed in Appendix 2 (page 79). In the coagulation pathway (Figure 9, page 38) there are many potential targets for new anticoagulant agents; agents that are currently most advanced in development target single proteins in the coagulation pathway (Factor Xa and thrombin).[228] Those agents that are in

New oral anticoagulants are in advanced stages of clinical development

phase III development or recently licensed are discussed in this chapter.

Oral direct Factor Xa inhibitors

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

Factor Xa is the primary site for amplification in the coagulation pathway.[229] Inhibition of Factor Xa achieves effective anticoagulation by inhibiting thrombin generation, while allowing the vital functions of existing thrombin to continue, thus potentially maintaining haemostasis at sites of haemostatic challenge.[229] Oral direct inhibitors of Factor Xa include rivaroxaban, apixaban and edoxaban. The only direct Factor Xa inhibitor currently approved in any territory is rivaroxaban, which is 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. 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.[230] Unlike VKAs, rivaroxaban does not require routine monitoring. Studies of oral direct Factor Xa inhibitors are underway in other indications, including stroke prevention in patients with AF.

Rivaroxaban

ROCKET AF, a randomized, double-blind phase III study compared the efficacy and safety of rivaroxaban 20 mg once daily with dose-adjusted warfarin for the prevention of stroke in AF.[231] Results from this trial were recently reported at AHA (Chicago, 2010). Patients with AF receiving active treatment with rivaroxaban had a significantly reduced risk of stroke and non-CNS systemic embolism compared with warfarin, with similar rates of bleeding.[232]

The J-ROCKET trial was a prospective, randomized, double-blind study examining the safety and efficacy of rivaroxaban in 1280 Japanese patients with AF within the unique context of Japanese clinical practice. Specifically, Japanese guidelines for stroke prevention in AF recommend a target INR of 2–3 for patients younger than 70 but a lower target INR range, 1.6–2.6, for patients 70 or older. The dose of rivaroxaban used in this trial, 15 mg once daily (10 mg in patients with moderate renal impairment), was selected on the basis of phase I/II studies, the lower level of anticoagulation in the warfarin comparator arm, and the characteristics of the patient population. The primary objective of the trial was to establish the non-inferiority of rivaroxaban versus warfarin with respect to major or non-major clinically relevant bleeding events. The primary efficacy endpoint was the composite of all-cause stroke and non-CNS systemic embolism, although the trial was not powered for efficacy. Presentation of the trial results is expected in 2011.[233]

Apixaban

Phase II studies of apixaban for the treatment of acute symptomatic deep vein thrombosis have been completed. These also served 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.[234] Results are expected in April 2011. 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 79).[158] Results were presented at the ESC 2010 scientific sessions. Apixaban was shown to reduce the risk of stroke or systemic embolism with no significantly increased risk of major haemorrhage.[157]

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.[235] A phase III study (ENGAGE-AF TIMI 48) has also been initiated to demonstrate the safety and efficacy profile of edoxaban. High- and low-dose regimens of edoxaban are being compared with warfarin[236] and results are expected in March 2012.[237]

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.[228] 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.[238]

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 is approved in the US, Canada and Japan for the prevention of stroke and systemic embolism in patients with AF in whom anticoagulation is appropriate. 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. Approximately 18 000 patients with AF who were 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, and a significantly lower rate of major bleeding than warfarin.[239] At the higher dose of dabigatran (150 mg twice daily), the rate of stroke and systemic embolism was significantly lower than with warfarin, but the rate of major bleeding was similar to that associated with warfarin. The rates of myocardial infarction and dyspepsia were higher with dabigatran than with warfarin. Further studies of dabigatran and other direct thrombin inhibitors are ongoing.[240,241]

Indirect Factor Xa inhibitors act via antithrombin and are administered subcutaneously

Other anticoagulants

There are several other anticoagulants in earlier stages of development. Agents that are being studied in phase II trials include the direct thrombin inhibitor AZD0837, the indirect thrombin inhibitor SB424323, and the direct Factor Xa inhibitors YM150 and betrixaban.[241–245]

Several other anticoagulants are in development

Antiplatelet agents

Clopidogrel is an inhibitor of platelet aggregation. Reduced platelet aggregation lowers 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 myocardial infarction, ischaemic 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 for whom VKA therapy was unsuitable. This study showed that, compared with aspirin and placebo, clopidogrel in combination with aspirin significantly reduced the risk of stroke in patients

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

with AF but was also associated with a significantly greater rate of major bleeding.[246]

Other antiplatelet agents are in phase III clinical trials (ticagrelor) or have recently been approved for clinical use (prasugrel).[247] 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, are being evaluated in phase I and II trials.[247]

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

Alternative strategies in development

Current strategies are focussed 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 or rate; non-pharmacological methods that control rhythm or rate or prevent blood clots reaching the brain; and surgical interventions to reduce thromboembolic risk.[82]

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.

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

Dronedarone is a new anti-arrhythmic 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.[248] 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.[249] Rare but severe cases of hepatic injury have been reported with the use of dronedarone.[250]

Non-pharmacological methods

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

Non-pharmacological management of abnormal heart rhythm

There are numerous non-pharmacological methods for the management of abnormal heart rhythm. 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)

The existing data suggest that catheter ablation is more effective than anti-arrhythmic drug therapy in maintaining normal heart rhythm.[251] Whether this intervention results in fewer AF-related strokes requires testing in clinical trials. The efficacy of surgery versus anti-arrhythmic 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).[82] 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 causing a stroke.[252,253] 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.[254]

Next steps

To summarize, there are several pharmacological agents that have been developed for use in patients with AF, including the new oral anticoagulants rivaroxaban, dabigatran and apixaban. Non-pharmacological 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 by the use of registries. J-TRACE is a registry of 8093 Japanese patients with non-valvular AF or a history of stroke and/or myocardial infarction, which includes information on their medical history, risk factors, medication use and demographics collected at baseline; patients will be followed for 2–3 years.[255] The registry aims to provide information on the incidence of cardiovascular ischaemic events and current medical treatment for Japanese patients at high risk of thromboembolic events.[255]

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

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.[256] 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.[257]

In addition, a number of country-specific stroke registries exist in the Asia-Pacific region. The Korean Stroke Registry includes 18 634 patients with ischaemic stroke or TIA.[258] This registry demonstrated that, although stroke mortality was higher among Korean men than women, stroke in women was associated with longer length of hospital stay and greater disability.[258] The Hunter Region Heart and Stroke Register tracked all hospital stroke

admissions in residents of a region of New South Wales, Australia and showed that the rate of stroke attacks was highest in the winter and lowest in the summer.[259] The China Ischaemic Stroke Registry Study has collated data on 1951 post-ischaemic stroke patients and confirmed the association between antiplatelet therapy and the reduced risk of death and recurrent cerebrovascular events in this patient population.[260]

Another Chinese-based registry collected data on acute stroke and highlighted the significant cost burden of stroke from 62 hospitals across the country.[132]

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 country-specific 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[50]	
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 daily). However, an oral anticoagulant is preferred over aspirin
Patients with AF and no risk factors	• Administer either aspirin (75–325 mg daily) 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 adjusted dose VKA therapy: – Dabigatran 150 mg bid – Dabigatran 110 mg bid – Dabigatran 110 mg bid
National Institute for Health and Clinical Excellence (NICE) – Management of atrial fibrillation guideline 2006[90] **Patients with persistent AF**	
Before cardioversion	• Maintain patients on warfarin (INR 2.5, range 2.0–3.0) for ≥3 weeks
After successful cardioversion	• Maintain on warfarin (INR 2.5, range 2.0–3.0) for ≥4 weeks
If cardioversion cannot be postponed for 3 weeks	• Give heparin before cardioversion • Give warfarin for ≥4 weeks after cardioversion
After cardioversion when risk of recurrence is high	• Continue anticoagulation long term (e.g. in patients with previous failed cardioversion attempts, mitral valve disease or where recommended by stroke risk stratification)
When cardioversion restores sinus rhythm in a patient with AF of confirmed duration <48 hours	• Anticoagulation not needed
Patients with atrial flutter or asymptomatic AF	• Give same anticlotting therapy as for symptomatic AF
Patients with permanent AF	• Perform risk–benefit assessment in discussion with the patient when deciding whether to give anticlotting therapy • Adjusted-dose warfarin (target INR 2.5, range 2.0–3.0) is the most effective treatment • Give aspirin (75–300 mg/day) if warfarin is inappropriate • If warfarin is appropriate, do not co-administer aspirin purely for thromboprophylaxis because it provides no additional benefit
Patients with paroxysmal AF	• Do not base decisions regarding the need for anticlotting therapy on the frequency or duration of symptomatic or asymptomatic paroxysms. Perform risk stratification as for permanent AF

continued

Risk category	Recommendation
Acute onset AF	
If patient is on no or subtherapeutic anticoagulation therapy	• Start heparin at initial presentation (unless contraindicated) and continue until a risk assessment has been made and appropriate anticlotting therapy started
If diagnosis of acute AF is confirmed (<48 hours since onset)	• Use oral anticoagulation if stable sinus rhythm not restored within the 48 hours since onset, if there are other risk factors for AF recurrence or if recommended by the algorithm
When the precise time since onset of acute AF is uncertain	• Use oral anticoagulation for acute AF as for persistent AF
If patient is haemodynamically unstable	• Start emergency treatment as soon as possible. Do not delay emergency treatment in order to begin anticoagulation treatment first

Asia-Pacific country-specific AF guidelines

Chinese Society of Pacing and Electrophysiology – Current knowledge and management recommendations in AF 2010[53]

All patients with AF with no contraindication to anticoagulation	• Patient's individual risk for stroke and bleeding should be assessed and the appropriate anticoagulation treatment given
Patients with non-mechanical valvular AF with high[c] and intermediate[d] level risk factors	• Administer warfarin (target INR 1.6–2.5) on a long-term basis
Patients with AF who are at low risk[e] of stroke or have contraindications to warfarin	• Administer aspirin (80–300 mg daily)
Patients with non-valvular AF with 1 intermediate level risk factor[d] or ≥1 low-level risk factor[e]	• Administer warfarin or aspirin. Take into consideration patient's preference, individual risk of bleeding during anticoagulation, and feasibility of maintaining a stable anticoagulation intensity with warfarin
Patients with non-mechanical valvular AF who are about to receive surgical or diagnostic procedures that may pose haemorrhagic risks	• Discontinue anticoagulation temporarily. If discontinuation is for >1 week, substitute with heparin
Patients with mechanical valvular AF/AFL	• Maintain target INR ≥2.5

Japanese Circulation Society – Guidelines for pharmacotherapy of atrial fibrillation 2008[54]

Patients with AF, and one high risk factor[f] or ≥2 moderate risk factors[g]	• Administer warfarin (target INR 2.0–3.0). Monitor INR at least weekly during the induction period and at least monthly after achieving a stable INR
Patients with one moderate risk factor[g], with cardiomyopathy, or with unproven risk factors[h]	• Administer warfarin (target INR 2.0–3.0)
Patients with non-valvular AF who are ≥70 years of age and indicated for warfarin therapy	• Control patients at a lower target INR of 1.6–2.6
Patients with lone AF who are <60 years of age	• Antithrombotic therapy with warfarin or aspirin. When antithrombotic therapy is administered, monitoring is required for the development of bleeding complications
Patients with AFL	• Administer anticoagulation therapy as for patients with AF
Patients with CAD preparing for PTCA or surgical revascularization	• Add aspirin (≤100 mg) or clopidogrel (75 mg)
• During PTCA	• Discontinue warfarin to avoid access-site bleeding. Following procedure, resume warfarin promptly to maintain the INR within the appropriate therapeutic range

continued

Risk category	Recommendation
Patients in whom ischaemic cerebrovascular disease or systemic embolism develops during anticoagulation	• Add antiplatelet drugs and control warfarin with a target INR of 2.5–3.5 to achieve an INR of 2.0–3.0
Patients with contraindications to warfarin	• Administer antiplatelet drugs
Patients with AF lasting ≥48 hours or of unknown duration who are using warfarin 3 weeks before and 4 weeks after cardioversion	• Anticoagulation therapy with a target INR of 2.0–3.0 for patients <70 years and 1.6–2.6 for patients ≥70 years
Patients with AF lasting ≥48 hours and haemodynamic instability who require immediate cardioversion	• Administer i.v. heparin. Following cardioversion, administer warfarin (target INR 2.0–3.0 for patients <70 years and 1.6–2.6 for patients ≥70 years for at least 4 weeks)
New Zealand Ministry of Health – The management of people with atrial fibrillation and flutter guideline 2005[52]	
Patients with AF/AFL, except those with lone AF[i]	• Antithrombotic treatment with oral anticoagulation or aspirin
Patients with AF at high or very high risk of stroke	• Long-term anticoagulation with adjusted-dose warfarin (target INR 2.5, range 2.0–3.0) unless there are clear contraindications
Patients with AF at intermediate risk of stroke	• Patients should discuss their individual risk, the potential benefits and their preferences relating to anticoagulant or aspirin treatment, with their doctor
Patients with AF at low risk of stroke or with contraindications to warfarin	• Aspirin (recommended dose 300 mg)
Patients with previous AF, or paroxysmal AF who have converted to sinus rhythm	• Patients should be assessed for thromboembolic risk and treated with warfarin or aspirin as above
Patients with AF and ischaemic stroke or TIA	• Unless contraindicated, and once intracranial haemorrhage has been excluded, all patients should receive anticoagulation
Singapore Ministry of Health – Management of atrial fibrillation guideline 2004[51]	
All patients with AF/AFL being considered for anticoagulant treatment	• The risk of bleeding needs to be assessed and periodically reassessed
All patients with AF	• Patient's individual risk for stroke and bleeding should be assessed and the appropriate antithrombotic treatment given
Patients with AF and additional risk factors	• Long-term anticoagulation with adjusted-dose warfarin unless they are at low risk of stroke or have a contraindication to warfarin
Patients with AF and any high risk factor[j]	• Long-term anticoagulation with adjusted-dose warfarin (target INR 2.5; range 2.0–3.0) unless contraindicated
Patients with AF who are 60–75 years of age and with any one of the other moderate risk factors[k]	• Long-term anticoagulation with adjusted-dose warfarin (target INR 2.0–3.0)
Patients with non-valvular AF who are at intermediate risk of stroke, i.e. <60 years of age with one moderate risk factor[k] or 60–75 years of age with no other risk factors	• Either aspirin (100 mg daily) or warfarin may be appropriate. Patient's preference, individual risk of bleeding during anticoagulation, and access to anticoagulation monitoring are crucial to the decision as to which antithrombotic treatment to use
Patients with AF who are at low risk of stroke or have contraindications to warfarin[l]	• 100–300 mg aspirin daily. Alternative antiplatelet agents for patients unable to take aspirin include ticlopidine, 250 mg bid; clopidogrel, 75 mg daily; or dipyridamole, up to 75 mg tid
Patients with lone AF, i.e. patients with no risk factors who are <60 years of age	• Long-term aspirin may be used if needed

continued

Risk category	Recommendation
Patients with AF who are older (>75 years of age) or judged to be at an increased risk of bleeding complications but expected to benefit from anticoagulation therapy	• Patients should receive anticoagulation with warfarin at a lower target INR of 1.6–2.5
Patients with AF who have mechanical prosthetic heart valves, antiphospholipid antibody syndrome or recurrent stroke despite anticoagulation	• Patients may receive anticoagulation with warfarin at a higher target INR of 3.0 (range 2.5–3.5)

Asia-Pacific country-specific stroke guidelines with references to AF

Korean Clinical Research Centre for Stroke – Clinical Practice Guidelines for Stroke 2010[167]

Patients with AF who are ≥75 years of age	• Administer warfarin (target INR 2.0–3.0)
Patients with AF with valvular heart disease (particularly those with mechanical heart valves)	• Administer anticoagulation
Patients with AF with an annual risk of stroke of 4%	• Administer warfarin (target INR 2.0–3.0)
Patients with non-valvular AF and:	
• ≥3 major risk factors[m]	• Administer warfarin (target INR 2.0–3.0)
• A history of stroke or TIA or 2 major risk factors[m]	• Administer warfarin (target INR 2.0–3.0)
• A history of stroke or TIA and ≥1 major risk factor[m]	• Administer warfarin (target INR 2.0–3.0)
• 1 major risk factor[m]	• Antithrombotic treatment with either warfarin (target INR 2.0–3.0) or aspirin (75–325 mg daily)
Patients with non-valvular AF with a history of stroke or TIA	• Administer warfarin (target INR 2.0–3.0)
Patients with ischaemic stroke or TIA coexisting with sustained or paroxysmal AF	• Administer warfarin (target INR 2.0–3.0) • If anticoagulants can not be used, administer aspirin (325 mg daily; a dose of 300 mg may be considered)
Patients with AF with recurrent ischaemic stroke or TIA, who are already receiving adequate coagulation therapy	• Increase the therapeutic target to INR 2.5–3.5 or initiate a combination with antiplatelets

Taiwan Stroke Society – Guidelines for the General Management of Patients with Acute Ischaemic Stroke 2008[168]

Patients with non-valvular AF who are at medium risk of cardiac embolism, i.e. 60–75 years of age with no other risk factors	• Administer aspirin or warfarin
Patients with non-valvular AF who are at low risk of embolism, i.e. <60 years of age with no other risk factors	• Administer aspirin or no treatment
Patients with non-valvular AF who have a contraindication to anticoagulation	• Administer aspirin

[a]Prior stroke or transient ischaemic attack (TIA) or thromboembolism; older age (≥75 years); and valvular heart disease, including mitral stenosis; [b]Heart failure (left ventricular ejection fraction [LVEF] ≤40%), hypertension, diabetes, female sex, age 65–74 years, and vascular disease (specifically, myocardial infarction, complex aortic plaque and peripheral arterial disease); [c]Rheumatic mitral stenosis or prior thromboembolism (stroke, TIA or non-central thromboembolism); [d]Age ≥75 years, hypertension, cardiac failure, left systole dysfunction and diabetes; [e]65–74 years of age, female, coronary heart disease; [f]History of cerebral infarction, TIA or systemic embolism; mitral valve stenosis; and use of prosthetic valve; [g]Age ≥75 years of age, hypertension, heart failure, left ventricular systolic dysfunction (LVEF ≤35% or fractional shortening ≤25%) and diabetes mellitus; [h]65–74 years of age, female, coronary artery disease; [i]People <60 years with no hypertension or heart disease; [j]Prior stroke/TIA/systemic embolism, prosthetic heart valve, rheumatic mitral stenosis, age >75 years; [k]History of hypertension, congestive heart failure, poor left ventricular function (LVEF ≤35%), diabetes mellitus, coronary artery disease, thyrotoxicosis; [l]Significant bleeding or fall risks, thrombocytopenia, recent surgery or trauma active peptic ulcer disease, or patients unlikely to comply with the diet and monitoring regimens required in warfarin therapy; [m]Congestive heart failure, hypertension, age >75 years, diabetes.

AF, atrial fibrillation; AFL, atrial flutter; bid, twice daily; tid, thrice daily; CAD, coronary artery disease; INR, international normalized ratio; i.v., intravenous; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischaemic 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 March 2011). In total, 70 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	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, multicentre, parallel-group, non-inferiority trial	**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	**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	**Completed and published:** Connolly SJ *et al. N Engl J Med* 2011;364:806–17
Rivaroxaban	J-ROCKET	Evaluation of the efficacy and safety of rivaroxaban (BAY 59-7939) for the prevention of stroke and non-central nervous system systemic embolism in subjects with non-valvular atrial fibrillation	**Completed**
	ROCKET-AF	A prospective, randomized, double-blind, double-dummy, parallel-group, multicentre, event-driven, non-inferiority study comparing the efficacy and safety of once-daily oral rivaroxaban (BAY 59-7939) with adjusted-dose oral warfarin for the prevention of stroke and non-central nervous system systemic embolism in subjects with non-valvular atrial fibrillation	**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, multicentre, multinational study for evaluation of efficacy and safety of DU-176b versus warfarin in subjects with atrial fibrillation – effective anticoagulation with factor Xa next generation in atrial fibrillation **(ENGAGE-AF TIMI-48)**	**March 2012** http://www.clinicaltrials.gov/ct2/show/NCT00781391
Indirect Factor Xa inhibitors			
Biotinylated idraparinux	BOREALIS-AF	A multicentre, randomized, double-blind, assessor-blind, non-inferiority study comparing the efficacy and safety of once-weekly subcutaneous biotinylated idraparinux (SSR126517E) with oral adjusted-dose warfarin in the prevention of stroke and systemic thromboembolic events in patients with atrial fibrillation	**Terminated** http://www.clinicaltrials.gov/ct2/show/NCT00580216
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	**Completed and 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	**Completed:** http://www.clinicaltrials.gov/ct2/show/NCT00249795

Glossary

1 billion	1000 million
Anticoagulant	A type of drug that reduces the ability of the blood to clot by inhibiting fibrin formulation
Antiplatelet agent	A type of drug that reduces the ability of the blood to clot by inhibiting aggregation of blood platelets
Antithrombotic therapy	Any chemical therapy that interferes with the formation of blood clots (thrombi)
Asymptomatic	Showing or causing no symptoms
Atherothrombotic event	Stroke (or heart attack) caused by a blood clot that has formed because of narrowing of the arteries due to build up of cholesterol and fat (atherosclerosis)
Atrial fibrillation	A heart rhythm abnormality that occurs when the upper chambers of the heart (known as the atria) tremble irregularly rather than beating regularly and effectively
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
Coagulation	The process by which a blood clot is formed; essential for the arrest of bleeding
Coagulation pathway	The pathway of chemical reactions that result in the formation of a blood clot
Embolize	The process of forming an embolus
Embolus/embolism	Part of a blood clot that has broken away from the main clot and is circulating in the blood
Epidemiology	The study of the occurrence and distribution of disease
Fibrin	An insoluble protein that combines with platelets to form a blood clot
Haemorrhagic stroke	A stroke caused by leakage from a blood vessel in the brain
Heart attack	Death of a section of heart following 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)	A measure of how long it takes the blood to clot in a patient receiving vitamin K antagonist therapy
Ischaemic stroke	Stroke caused by a blood clot blocking a blood vessel in the brain

Morbidity	The state of having a disease; ill health
Platelet	A 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
Prothrombin time	A measure of the time it takes for blood to clot
QALY (quality-adjusted life-year)	A measure that represents numerous outcomes affecting quality of life; 1 year in perfect health is considered to be equal to 1.0 QALY
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
Therapeutic range	The range of doses of a particular drug in which both efficacy and safety are acceptable
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 ischaemic attack	A brief disruption of the blood supply to part of the brain
Vitamin K antagonist	A type of oral anticoagulant
Warfarin	A type of vitamin K antagonist

Abbreviations

ACC	American College of Cardiology
ACCP	American College of Chest Physicians
AF	Atrial fibrillation
AHA	American Heart Association
$CHADS_2$	System for scoring risk of stroke for patients assigning the following points to the risk factors: Congestive heart failure (1 point); Hypertension (1 point); Age >75 years (1 point); Diabetes (1 point); Stroke or transient ischaemic attack (2 points)
CHA_2DS_2-VASc	Refined version of $CHADS_2$. Cardiac failure (1 point); Hypertension (1 point); Age ≥75 years (2 points), Diabetes (1 point); Stroke (2 points); Vascular disease (1 point), Age 65–74 years (1 point); Sex category (female) (1 point)
ECG	Electrocardiogram
EMA	European Medicines Agency
EMSP	European Multiple Sclerosis Platform
EPF	European Patients' Forum
ESC	European Society of Cardiology
ESN	European Stroke Network
EU	European Union
INR	International normalized ratio
LV	Left ventricular
MS	Multiple sclerosis
NICE	National Institute for Health and Clinical Excellence
QALY	Quality-adjusted life-year
TIA	Transient ischaemic attack
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WHO	World Health Organization

Every year millions of people in the Asia-Pacific region suffer 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 carers. 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 the Asia-Pacific region. For example, in China alone up to 8 million people suffer from 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 the countries of the Asia-Pacific region 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.