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Atrial Fibrillation-Related Stroke across the Asia-Pacific Region: A Preventable Problem

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Strike Out Stroke in Atrial Fibrillation
Action for Stroke Prevention

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

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ADKA – German Association of Hospital Pharmacists	www.adka.de
AntiCoagulation Europe (ACE)	www.anticoagulationeurope.org
Arrhythmia Alliance – International	www.aa-international.org
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Taiwan Stroke Society	www.stroke.org.tw
The International FH Foundation	www.fh-foundation.org
World Stroke Organization (WSO)	www.world-stroke.org

Atrial fibrillation-related stroke: a global but preventable problem

- A stroke occurs when a blood vessel becomes blocked and the supply of blood to the brain becomes interrupted (ischaemic stroke), or when blood from a ruptured vessel leaks into the brain (haemorrhagic stroke). Both can cause significant brain damage
- Approximately 15% of all strokes are associated with atrial fibrillation (AF),[1] an abnormal heart rhythm. The condition occurs with increasing frequency as people get older and is the most common heart rhythm disorder[2]
- AF causes a stroke when the abnormal heart rhythm leads to the formation of a blood clot in the heart that is then transported to the brain. Patients with AF are *five times* more likely to experience a stroke than those without AF,[3] and AF-related strokes are more severe than strokes unrelated to AF[4,5]
- Globally, approximately 15 million people suffer a stroke each year.[6] The costs associated with stroke are also considerable and have been estimated previously at approximately 3% of total healthcare expenditure for some countries[7]
- In this booklet, we look at key facts concerning the human and economic cost of this preventable type of stroke in the Asia-Pacific region, and how best to prevent it

AF-related stroke is a major problem in the Asia-Pacific region today. However, it is a problem that can be overcome

Atrial fibrillation-related stroke in the Asia-Pacific region: the avoidable burden

The clinical burden

- 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.[8] 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.[9] In Malaysia, the Ministry of Health listed stroke as the most common cause of death in 2009, accounting for 8.4% of total deaths in Ministry of Health Hospitals[10]
- Stroke survivors often have permanent physical and cognitive disabilities; family members can also experience depression and a loss of independence[11,12]
- AF is the most common sustained abnormal heart rhythm (arrhythmia) and occurs with increasing frequency as people get older[2]
- AF is believed to affect a large number of people in the Asia-Pacific region; although the exact incidence and prevalence of AF in Asian populations are not known, they are thought to be slightly lower than in Western populations, with a reported prevalence of AF in adults ranging from 770 per 100 000 in China[13] to 1634 per 100 000 in Japan.[14] However, with an increasingly ageing population, the prevalence of AF in Asia is expected to rise substantially[15]
- Despite differences in incidence and prevalence, the associated relative risk of AF with respect to stroke and mortality is thought to be similar in both Asian and Western populations[15]
- Because of the larger size of the clot, AF-related stroke is more severe than non-AF-related stroke. It is associated with a higher risk of in-hospital death, greater disability, longer hospital stays, a reduced likelihood of patients returning to their own home and increased risk of recurrent stroke[4,5]
- As a result, AF-related stroke imposes a much greater burden on patients and their families than non-AF-related stroke

The financial burden

- The financial burden placed on countries in the Asia-Pacific region by stroke is believed to be immense. Although data on the financial cost of stroke are not available for the Asia-Pacific region as a whole, information can be sourced from individual countries in the region
  - Total lifetime cost for all ischaemic and haemorrhagic strokes, based on data from the North East Melbourne Stroke Incidence Study (NEMESIS), was estimated at approximately AU$2 billion (US$2 billion)[16]

- Estimates from the South Korea National Health Insurance Claims Database for 2005 show that the total cost for the treatment of stroke in the nation was 3737 billion Korean won (KRW) (US$3.3 billion), including direct costs of 1130 billion KRW (US$1.0 billion) and indirect costs of 2606 billion KRW (US$2.3 billion)[17]
- In 2003, the direct medical cost for ischaemic stroke in China was calculated as ¥23,732 billion (US$3787 billion)[18] and in 2009, the cost of stroke to the Japanese healthcare system was calculated as ¥1786 billion (US$22 billion)[19]
- In Malaysia, a retrospective analysis found that the mean cost of care per patient for each admission to hospital was MYR 3696 with an average length of stay of 6.5 days[20]

♦ Because stroke in patients with AF is more severe than stroke in those without AF,[4] it is likely to incur greater costs

- A Japanese study showed the presence of AF to be associated with an increased risk of severe stroke and an increased length of hospital stay – a mean of 40.5 days compared with 34.0 days for patients without AF.[21] This, in turn, has been shown to be associated with increased costs[22]

♦ Stroke is clearly a costly health problem in countries in the Asia-Pacific region, although further research is required to provide a more comprehensive picture of the economic burden of stroke across a wider selection of countries. Early diagnosis and effective management of AF would help to reduce the burden of stroke in countries in the Asia-Pacific region. Furthermore, greater use of pharmacological or non-pharmacological therapies for the prevention of AF-related stroke in patients with AF, particularly those at high risk, has the potential to reduce this burden significantly[23]

Improving stroke prevention: diagnosing atrial fibrillation earlier

♦ Although AF itself can be simple to diagnose, in many cases it goes undetected

♦ One major problem with AF is that it is often asymptomatic.[24] As a result, many patients are not diagnosed and do not receive the anticoagulation that they need

♦ In recent years, strategies have been developed to improve detection of AF: a first step towards providing therapy for the prevention of AF-related stroke

♦ Checking patients aged ≥65 years for an irregular pulse at their next visit and referring them for an electrocardiogram was an effective way of screening patients for AF in one UK-based primary care study.[25] The annual detection rate for new cases of AF in centres where patients were screened in this way was 1.64% per year, compared with 1.04% per year in centres that did not have an active screening programme

♦ Based on these figures, if such a screening programme was adopted in a primary care centre that previously had none, the centre could expect to see an approximate increase of 60% in the annual detection rate (e.g. approximately 1600 vs 1000 new cases per 100 000 patients per year), i.e. a 60% increase in the number of patients who could receive therapy for prevention of AF-related stroke

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

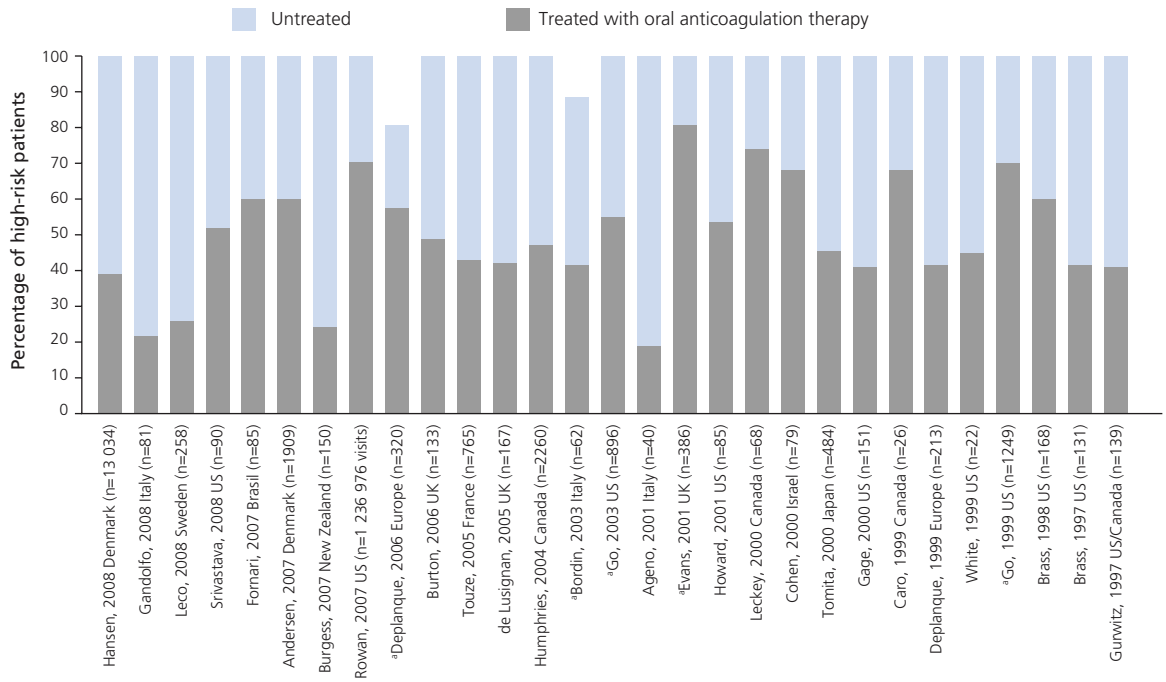
♦ For many years, oral anticoagulation with vitamin K antagonists (VKAs), such as warfarin, has been the 'gold standard' therapy for long-term stroke prevention in patients with moderate to high risk of stroke. In clinical studies, VKAs reduce stroke risk by an average of 64% compared with no therapy and by 38% versus aspirin[26]

♦ However, clinical trials are 'controlled' environments with strict trial conditions and careful anticoagulation monitoring.[27,28] In real-life, VKAs are underused; several studies report anticoagulant use in <50% of patients with AF who are at high risk of stroke (Figure 1)[29]

♦ Patients on VKAs may also spend much of their time (perhaps 45% on average) outside the 'target' therapeutic range for optimal therapy (referred to as the 'international normalized ratio' [INR] of 2.0–3.0).[30] Based on these numbers, perhaps 25–30% of patients with AF receive optimal VKA therapy at any one time

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

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



Adapted from *Am J Med*, vol. 123, Ogilvie IM *et al*. Underuse of oral anticoagulants in atrial fibrillation: a systematic review, 638–645.e4, copyright 2012, with permission from Elsevier.[29]

[a]Contraindications taken into account.

Why is optimal prevention not achieved in practice?

- Successful VKA therapy requires frequent monitoring and dose adjustment to keep the patient within the INR range of 2.0–3.0.[31] VKAs also have an unpredictable and variable dose-response and interact with many different foods, alcohol and drug classes[32]
- Many physicians overestimate the risk of bleeding associated with VKAs and underestimate their benefits, particularly in elderly individuals.[33] Patients themselves may also be unwilling to use them because of fears of side-effects[34]
- Physicians are often concerned about a patient's ability to comply with VKA therapy because of the requirement for regular monitoring and dose adjustment, especially if the patient is elderly, lives alone or has cognitive impairment[35,36]

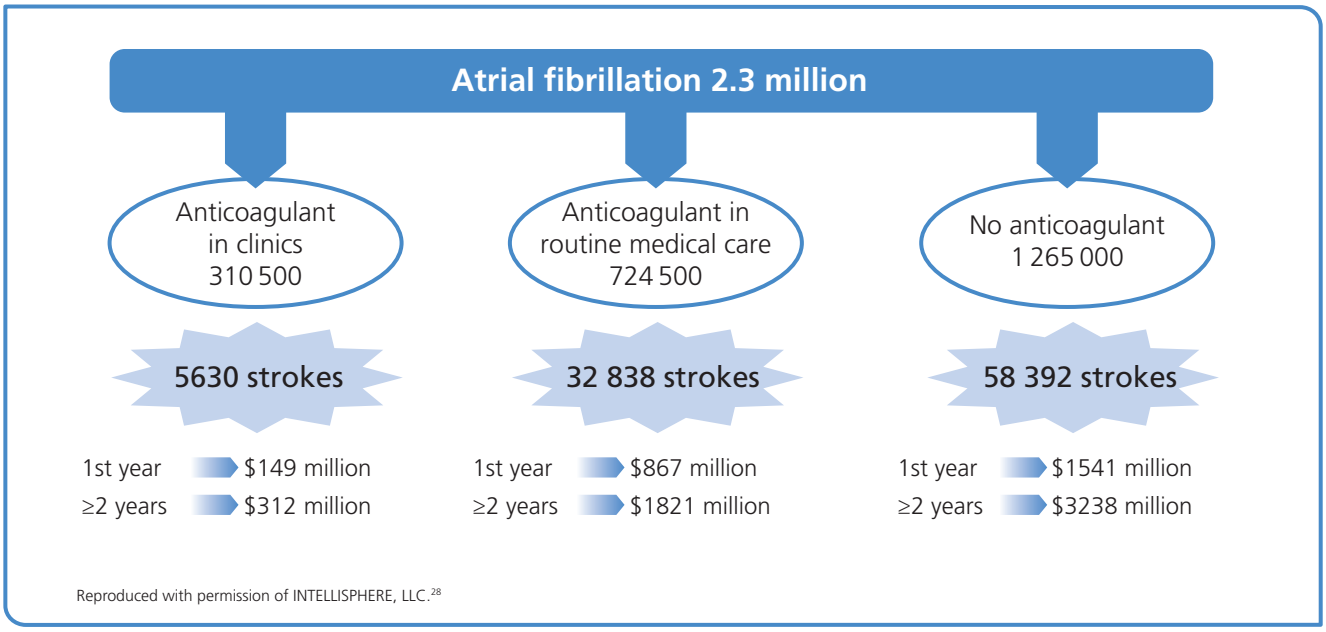
Suboptimal use of VKAs increases costs

- VKA therapy can be cost-effective for the prevention of AF-related stroke, even in elderly patients;[37] however, this depends on how well it is managed
- The cost of stroke per patient with AF in those who were anticoagulated in routine medical care (approximately 70% of patients) was more than double that for patients attending specialized anticoagulation clinics (approximately 30% of patients) ($3710 vs $1485 per patient with AF) in one US model (Figure 2).[38] Much of this extra cost stemmed from managing complications associated with VKA therapy, such as bleeding. It is likely that further strokes resulting from underuse also increased costs
- Thus, it is likely that effective management of VKA therapy in the Asia-Pacific region will be influenced by the availability of anticoagulation clinics

Cost of VKA monitoring

- 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. 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[39]

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



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- Monitoring INR in clinical practice may also incur additional costs to the patient, the carer and society that are not captured in cost-effectiveness studies
  - Cost estimates often do not take into account the indirect costs incurred by the patient and their family (e.g. lost productivity and transport to clinic)
- Further data are needed about the cost of attending anticoagulation clinics in other countries in the Asia-Pacific region. However, access to INR monitoring facilities varies markedly across countries in this region. This issue needs to be addressed before the cost-effectiveness of attending anticoagulation clinics can be assessed

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

- VKAs have their limitations, which contribute to their underuse
- In recent years, the efficacy and safety of the non-VKA oral anticoagulants (OACs) rivaroxaban, dabigatran and apixaban have been tested in large-scale global trials: ROCKET AF, RELY and ARISTOTLE[40–42]
  - Rivaroxaban (Xarelto®, Bayer HealthCare) and dabigatran etexilate (Pradaxa®, Boehringer Ingelheim) have been approved for use and have reimbursement approval for the prevention of AF-related stroke in many countries worldwide[43,44]
- These non-VKA OACs have distinct advantages over VKAs in that they:
  - Have predictable pharmacokinetics/pharmacodynamics. This means that, unlike the VKAs, a given dose of a non-VKA OAC always achieves the same degree of anticoagulation
  - Have few food or drug interactions, in contrast to VKAs
  - Are taken as fixed once-daily (rivaroxaban) or twice-daily (dabigatran) doses
  - Require no routine coagulation monitoring
- The ROCKET AF and RE-LY trials with rivaroxaban and dabigatran, respectively, have shown that these agents are at least as effective as VKAs for the prevention of AF-related stroke. They are also associated with significant reductions in ICH compared with VKA therapy – a particularly feared complication among physicians[40,42]
- Both rivaroxaban and dabigatran were also found to be cost-effective by the UK's National Institute for Health and Clinical Excellence (NICE) 'within the range normally considered a cost-effective use of National Health Service resources'.[45,46] In addition, both anticoagulants have now received reimbursement approval in many countries, including Sweden, France, UK, Canada and Japan, among others
- Although the introduction of agents such as the non-VKA OACs are associated with increased drug costs relative to VKAs, the overall impact on the

healthcare budget may be offset to some extent by the introduction of 'generics' for some key cardiovascular drugs. Furthermore, the improved safety profile of the non-VKA OACs can also be expected to further offset costs versus the VKAs

What can be done: action steps

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

Actions for policy-makers

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

Actions for medical societies and healthcare professionals

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

Actions for patient advocacy groups

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

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

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Conflicts of Interest

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