Atrial Fibrillation-Related Stroke across Europe: A Preventable Problem

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The recommendations in this document are endorsed by the organizations shown below.
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AntiCoagulation Europe
Arrhythmia Alliance – International
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Arrhythmia Alliance Italy
Arrhythmia Alliance Portugal
Arrhythmia Alliance Spain
Arrhythmia Alliance Sweden
ATBV – Gruppo di studio Aterosclerosi, Trombosi, Biologia Vascolare
AF Association – International
AF Association Bulgaria
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AF Association Greece
AF Association Hungary
AF Association Italy
AF Association Norway
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AF Association UK
Bulgaria National Patient Organisation
China Committee of Cardio-Cerebral-Vascular Diseases of GSC
Chinese Society of Cardiology

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www.trombosi.org
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www.afa-es.eu
www.afa-se.eu
www.afa-tr.org
www.atrialfibrillation.org.uk
www.npo.bg
www.cscnet.org.cn
ECAS – European Cardiac Arrhythmia Society
www.ecas-heartrhythm.org
ESZME – Hungarian Association for Stroke Prevention
www.eszme.hu
European Brain Council
www.europeanbraincouncil.org
European Heart Rhythm Association (EHRA)
www.escardio.org/EHRA
European Primary Care Cardiovascular Society
www.epccs.eu
European Society of Neurosonology and Cerebral Hemodynamics
www.esnch.org
European Stroke Conference
www.eurostroke.eu
European Stroke Organisation
www.eso-stroke.org
Feasan – Federación Española de Asociaciones de Anticoagulados
www.anticoagulados.info
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www.ictusfederacion.es
Foundation for Development of Electrophysiology
www.sercedlaarytmii.pl
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Stroke Foundation of Poland
www.fum.info.pl
SZIV SN
www.szivsn.hu
The International FH Foundation
www.fh-foundation.org
World Heart Federation
www.world-heart-federation.org
World Stroke Organization (WSO)
www.world-stroke.org
Atrial fibrillation-related stroke across Europe: a preventable problem
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), an abnormal heart rhythm. The condition occurs with increasing frequency as people get older and is the most common heart rhythm disorder.

♦ 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, and AF-related strokes are more severe than strokes unrelated to AF.

♦ Globally, approximately 15 million people suffer a stroke each year. In Europe, 1.3 million people suffered a stroke in 2010, and approximately one-third of this number were left permanently disabled. The costs associated with stroke are also considerable, and have been estimated previously at approximately 3% of total healthcare expenditure for some countries.

♦ In this booklet, we look at key facts concerning the human and economic cost of this preventable type of stroke in Europe, and how best to prevent it.

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

Atrial fibrillation-related stroke in Europe: the avoidable burden

The clinical burden

♦ In 2010, there were more than 8 million people in Europe who were affected by stroke, with 1.3 million newly diagnosed stroke cases occurring in that same year.

♦ Stroke survivors often have permanent physical and cognitive disabilities; family members can also experience depression and a loss of independence.

The financial burden

♦ The financial burden placed on European countries by stroke is huge. For 2010, the estimated cost of stroke in Europe was €64 billion. Assuming that 15% of these strokes were caused by AF and that AF-related strokes are generally more severe, the cost of AF-related stroke could be at least €10 billion each year.

♦ Approximately two-thirds (66%) of stroke costs were direct healthcare costs; 26% were direct non-medical costs (such as informal care) and approximately 8% were indirect costs (loss of productivity or early retirement).

Figure 1. Cost of stroke (millions) across Europe in 2010.
Stroke costs are also higher in patients with AF compared with costs in patients without AF.

- In the Berlin Acute Stroke Study, the average direct cost of stroke for patients with AF hospitalized for acute stroke (followed up for 1 year) was considerably higher than for patients without AF (€11 799 versus €8817, respectively).

- In a Swedish study of >6500 patients with first-ever stroke,14 patients with AF had an average 3-year inpatient cost of €10 192, which was €818 higher than the average 3-year cost for patients without AF (€9374).

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.15 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.16 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% peryear 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 aspirin17.

- However, clinical trials are ‘controlled’ environments with strict trial conditions and careful anticoagulation monitoring18,19. In real life, VKAs are underused; several studies report anticoagulant use in <50% of AF patients who are at high risk of stroke (Figure 2)20.

- 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).21 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.

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 2.0–3.0.22 VKAs also have an unpredictable and variable dose-response and interact with many different foods, alcohol and drug classes.

- Many physicians overestimate the bleeding risk associated with VKAs and underestimate their benefits, particularly in the elderly.24 Patients themselves may also be unwilling to use them because of fears of side-effects.

- 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.

Suboptimal use of VKAs increases costs

- VKA therapy can be cost-effective for the prevention of AF-related stroke, even in elderly patients; 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...
Figure 2. Patients with atrial fibrillation and prior stroke/transient ischaemic attack: oral anticoagulation levels as a proportion of patients eligible for oral anticoagulation therapy.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>n</th>
<th>Treated with oral anticoagulation therapy</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansen, 2008</td>
<td>Denmark</td>
<td>13,034</td>
<td>70%</td>
<td>30%</td>
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<tr>
<td>Leco, 2008</td>
<td>Sweden</td>
<td>258</td>
<td>90%</td>
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<tr>
<td>Srivastava, 2008</td>
<td>US</td>
<td>90</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Fornari, 2007</td>
<td>Brasil</td>
<td>85</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Andersen, 2007</td>
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<td>1,909</td>
<td>40%</td>
<td>60%</td>
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<tr>
<td>Burgess, 2007</td>
<td>New Zealand</td>
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<td>765</td>
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<td>95%</td>
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<tr>
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<tr>
<td>Guille, 1997</td>
<td>UK</td>
<td>139</td>
<td>10%</td>
<td>90%</td>
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</tbody>
</table>

(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 3). 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.

Cost of VKA monitoring

- The direct cost of routine INR monitoring has been estimated to be approximately €519 in the UK and €513 in Denmark, but can vary substantially depending on country and healthcare system. For example, considerably higher annual costs of ~€1787 for the first year and ~€980 for the second year have been estimated for Swedish primary care.

- Cost estimates often do not take into account the indirect costs incurred by the patient and their family (e.g. lost productivity and transport to clinic). A questionnaire-based study of patients in the SPORTIF trial found that the average cost to patients of attending an anticoagulation clinic varied from €6.90 (France) to €20.50 (Portugal) per visit. Over the course of many years, this can translate into substantial costs.

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

- VKAs have their limitations, which contribute to their underuse.

- In recent years, the efficacy and safety of the non-VKA oral anticoagulants (OACs) rivaroxaban, dabigatran and apixaban have been tested in large-scale global trials: ROCKET AF, RE LY and ARISTOTLE.

- 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 European countries.

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

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’. In addition, both anticoagulants have now received reimbursement approval in many countries, including Sweden, France, UK, Canada and Germany, among others.

Although 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 EU at an estimated annual cost of at least €10 billion. 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 Europe

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 by 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 Europe, 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.42,43
- 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.44,45
- 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.
References


Conflicts of Interest

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Speaker/consultant: AstraZeneca, Bayer, BMS-Pfizer, Daiichi Sankyo, Eli Lilly

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

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